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AIM AND SCOPE

Journal of Dr. Behcet Uz Children's Hospital is a peer-reviewed open-access official scientific publication of the Izmir Children's Health Society and Izmir Dr. Behcet Uz Children's Hospital. The publication frequency of the journal is 3 times a year (April, August, November). Journal of Dr. Behcet Uz Children's Hospital accepts publications in English as of 2020 and published electronically.

Aims and Scope

The journal of Dr. Behcet Uz Children's Hospital is devoted to the continuing education of national and international practicing pediatrics and pediatric surgeons, and to provide a forum for social and scientific communication in the field. Studies that emphasize these aims provide the basis for publication, including original articles, case reports, reviews, annual meetings' abstracts, letters to the editor, review of the recently published books, biographies, and social articles. The journal of Dr. Behcet Uz Children's Hospital accepts only invited review articles.

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Journal of Dr. Behcet Uz Children's Hospital is a double-blind peer-reviewed journal which has been started to be published in 2011.

Articles in the journal are published in content pages and article title pages, as classified according to their types (research, case report, short report, review, letter to editor etc.)

Journal of Dr. Behcet Uz Children's Hospital does not charge any article submission or processing fees, and reviews are prepared due to the invitation of editor.

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Abstract Reports: Researches with small numbers that have preliminary study data and findings which require further studies. References and English abstract required (see Manuscript Preparation section). At most 3000 words in length (8 double spaced pages), additionally English abstract, 15 or less references, 3 tables and/or figures. Ethics committee approval required.

Concepts: Clinical or non-clinical manuscripts about improvement of this field. References and English abstract required. At most 4000 words (16 double spaced pages), additionally Englishabstract (each less than 150 words) and references must be included.

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Evidence based Information: Articles that could answer to the problems of clinical and medical applications. The article should include these sections; clinical vignette, questions and problems, research and selection of the best evidence, detailed examination of the evidence and implementation of the evidence. At most 4000 words (15 double spaced pages), additional English abstract. Authors should also send the copies of the articles to the editor.

Letter to Editor: These are the articles that include opinions and solution advises about the medicine and public health issues, comments about the articles published in journal of Journal of Dr. Behcet Uz Children's Hospital or other journals. At most 1500 words (6 double spaced pages), additionally references should be included.

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References should be provided at the end of the article, under the title "References" and should be numbered and listed according to their order in the text. They should be referred to in parentheses within the text. Complete author citation is required ("et al" is not acceptable). The author(s) are responsible for the accuracy of the references. Journal titles should be abbreviated according to Index Medicus. Refer to the "List of Journals Indexed in Index Medicus" for abbreviations of journal names, or access the list at http://www.nlm.nih.gov/tsd/serials/lji.html. Abbreviations are not used for journals not in the Index Medicus. Only published articles or articles "in press" can be used in references. Authors must add the DOI and/or PMID numbers to the end of each citation. Example of references are given below:

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Hull ML, Escareno CR, Godsland JM, Doig JR, Johnson CM, Phillips SC, Smith SK, Tavaré S, Print CG, Charnock- Jones DS: Endometrial-peritoneal interactions during endometriotic lesion establishment. Am J Pathol 2008;173:700-715. PMID: 18688027, DOI:10.2353/ajpath.2008.071128.

Ferrari A, Casanova M, Bisogno G, Cecchetto G, Meazza C, Gandola L, et al. Malignant vascular tumors in children and adolescents: a report from the Italian and German Soft Tissue Sarcoma Cooperative Group. Med Pediatr Oncol 2002;39:109-114.

Abstract: Heidenreich A, Olbert P, Becker T, Hofmann R. Microsurgical testicular denervation in patients with chronic testicular pain. Eur Urol 2001;39 (suppl 5):126 (abstr.)

Book: Sadler TW. Langman's Medical Embryology, 5th ed., William and Wilkins, Baltimore, 1985. p.224-226.

Book Chapter: Folkman J: Tumor angiogenesis. In Bast Jr RC, Kufe DW, Polock RE,Weichselbaum RR, Holland JF, Frei E (eds). Cancer Medicine. 5th ed. London, B.C. Decker Inc.; 2000. p.132-152.

Online articles: Abood S. Quality improvement initiative in nursing homes: the ANA acts in advisory role. Am J Nurs (serial on the Internet). 2002 Jun (cited 2002 Aug 12); 102 (6): (about 3 p.). Available from: http://www.nap.edu/books/0309074029/html/.

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If the number of authors are less than or equal to 6, then all authors are indicated..

Campbell MR, Fisher J, Anderson L, Kreppel E. Implementation of early exercise and progressive mobility: Steps to success. Crit Care Nurse. 2015;35(1):82-8. doi: 10.4037/ccn2015701.

If the number of authors are more than 6, then the first three authors are indicated.

Aiken LH, Sermeus W, Van den Heede K, Sloane MD, Busse R, McKee M, et al. Patient safety, satisfaction, and quality of hospital care: Cross sectional surveys of nurses and patients in 12 countries in Europe and the United States. BMJ. 2012;344:e1717. doi: 10.1136/bmj.e1717.

If the article has not any DOI number then internet access address (website) is noted.

Pokorny ME, Koldjeski D, Swanson M. Skin care intervention for patients having cardiac surgery. Am J Crit Care. 2003;12(3):535-44. Available from: http://ajcc.aacnjournals.org/content/12/6/535.full.pdf+html?sid=f587c6d5-92a3-4971-8367-f18cd1cd63f0

Supplement:

Ahrens T. Severe sepsis management: Are we doing enough? Crit Care Nurse. 2003;23(Suppl 5):2-15. Available from: http://ccn.aacnjournals.org/content/23/5/S2.full.pdf+html

Book:

Jarvis C. Physical Examination and Health Assessment. 3rd ed. Philadelphia: W.B. Saunders Company; 2000.

If any information about the editor is available:

Breedlove GK, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services; 2001.

A chapter in the book:

Finke LM. Teaching in nursing: the faculty role. In: Billing DM, Halstead JA, editors. Teaching in Nursing: A Guide for Faculty. 3rd ed. USA: Saunders & Elsevier; 2009. p. 3-17.

Translated book:

Ferry DR. ECG in Ten Days [On Günde Temel Elektrokardiyografi]. Kahraman M, translator. İstanbul: Ekbil A.Ş.; 2001.

A chapter in a translated book:

Tolay E. Planlamanın temelleri. In: Robbins SP, Decenzo DA, Coulter M. editors. Yönetimin Esasları: Temel Kavramlar ve Uygulamalar. Öğüt A, translator. Ankara: Nobel Akademik Yayıncılık; 2013. p. 104-29.

Electronic book:

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Aminoff MJ, Greenberg DA, Simon RP. Clinical Neurology. 9th ed. New York: McGraw Hill Medical; 2015. Available from: http://accessmedicine.mhmedical.com/book.aspx?bookID=1194

Electronic report/document:

World Health Organization. World Alliance for Patient Safety Forward Programme 2008-2009. 1st ed. France; 2008. Available from: http://apps.who.int/iris/bitstream/10665/70460/1/WHO_IER_PSP_2008.04_eng.pdf

İzmir Halk Sağlığı Müdürlüğü. Sağlık Bakanlığı Yoğun Bakım Ünitelerinin Standartları. İzmir; 2007. Available from: http://www.ihsm.gov.tr/indir/mevzuat/genelgeler/G_13082007_1.pdf

Dissertations/Theses:

Bayram TY. Üniversitelerde örgütsel sessizlik [master's thesis]. Bolu: Abant İzzet Baysal Üniversitesi, Sosyal Bilimler Enstitüsü; 2010.

Borkowski MM. Infant sleep and feeding: a telephone survey of Hispanic Americans [dissertation]. Mount Pleasant (MI): Central Michigan University; 2002.

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PEER REVIEW, PUBLICATION ETHICS AND MALPRACTICE STATEMENT

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Original Article

Is Multiple Pregnancy Really a Risk Factor? The Results of Fetal Echocardiography in a Tertiary Care Center

Çoğul Gebelik Gerçekten Bir Risk Faktörü mü? Üçüncü Basamak Merkezde Fetal Ekokardiyografi Sonuçları

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ABSTRACT

Objective: The aim of this study was to analyze the frequency and results of congenital heart defects (CHD) in multipl pregnancies by fetal echocardiography. Among these, to evaluate critical congenital heart diseases such as hypoplastic left heart syndrome, interrupted aorta, and pulmonary atresia etc that require care in a tertiary center.

Method: This retrospective cohort study was conducted in pregnant women who admitted for fetal echocardiography. The data of the pregnancy were obtained retrospectively from the hospital records. A total of 9,440 pregnant women were enrolled in this study between January 2016 and September 2019. Two hundred and forty-one of them were multiple pregnancies (232 twins, 7 triplets and 2 quadruplets).

Results: Congenital heart disease rate was 4.31% in singleton pregnancies and 8.7% in multiple pregnancies. The prevalence of CHD was significantly higher in multipl pregnancies (p=0.05). There was no statistically significant difference between the two groups with respect to rate of critical congenital heart disease (p=0.32).

Conclusion: Multiple pregnancies had increased congenital heart defect risk compared with singleton. Therefore, it is important to refer for fetal echocardiography when necessary. Fetal echocardiography is routinely recommended in high-risk pregnancies such as monocarionic twin pregnancies. However, in pregnant women without risk factors for CHD is also seen. Postnatal follow-up of congenital heart disease is important, and early diagnosis of these diseases with fetal echocardiography is important.

Keywords: Congenital heart defect, fetal echocardiography, multipl pregnancy

ÖZ

Amaç: Bu çalışmanın amacı, çoğul gebeliklerde doğumsal kalp hastalığı (DKH) sıklığını fetal ekokardiyografi ile değerlendirmek ve sonuçlarını incelemektir. Bunlar arasında hipoplastik sol kalp sendromu, kesintili aort ve pulmoner atrezi vb. gibi üçüncü basamak bir merkezde bakım gerektiren kritik DKH'yi değerlendirmektir.

Yöntem: Bu retrospektif kohort çalışması, fetal ekokardiyografi için başvuran gebelerde gerçekleştirildi. Gebelerin verileri geriye dönük olarak hastane kayıtlarından elde edildi. Ocak 2016 ile Eylül 2019 arasında toplam 9.440 gebe çalışmaya alındı. Bunların 241'i çoğul gebelikti (232 ikiz, 7 üçüz ve 2 dördüz).

Bulgular: Doğuştan kalp hastalığı oranı tekil gebelerde %4,31 ve çoğul gebelerde %8,7 idi. Çoğul gebeliklerde doğuştan kalp hastalığı prevalansı anlamlı olarak daha yüksekti (p=0,05). Kritik doğuştan kalp hastalığı oranı açısından iki grup arasında istatistiksel olarak anlamlı fark yoktu (p=0,32).

Sonuç: Çoğul gebelikler, tekil gebeliklere göre daha yüksek DKH riskine sahipti. Bu nedenle gerektiğinde fetal ekokardiyografiye başvurmak önemlidir. Monokariyonik ikiz gebelikler gibi yüksek riskli gebeliklerde rutin olarak fetal ekokardiyografi önerilmektedir. Ancak doğuştan kalp hastalıkları risk faktörü olmayan gebelerde de görülmektedir. Doğuştan kalp hastalığının doğum sonrası takibi önemlidir ve bu hastalıkların fetal ekokardiyografi ile erken teşhisi önemlidir.

Anahtar kelimeler: Doğumsal kalp hastalığı, fetal ekokardiyografi, çoğul gebelik

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INTRODUCTION

Congenital heart defects are the most common birth defects and the most important cause of anomaly-related mortality during infancy [1-3]. Recent developments in fetal echocardiography has made feasible and highly accurate prenatal diagnosis of congenital heart disease possible in appropriate settings [4,5].

Multiple births account for 1-2% of all pregnancies, and its incidence has been increasing gradually, possibly as a consequence of increased usage of assisted reproductive technologies [6]. The rate of congenital malformations was reported to be higher in twin pregnancies compared with single pregnancies [7-10]. Congenital heart defects are the most common congenital anomalies with an incidence rate of one in 8:1000 live births [2]. The incidence of congenital heart defects in multiple births was reported as one in 20:1000 live births [5]. Several studies reported 4 to 9-fold increased risk of heart malformations in monozygotic twin pregnancies [10-13].

This study aims to evaluate the prevalence of congenital heart defects in singleton versus multiple pregnancies. We also aimed to evaluate the type of congenital heart disease and the neonatal outcome in our cohort of patients.

MATERIALS and METHODS

The study was a retrospective analysis of pregnant patients referred to the pediatric cardiology unit of our hospital, from January 2016 to September 2019 for fetal echocardiography. The study was approved by the University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital Clinical Research Ethics Committee (approval number: 11/15, date: 14.09.2020. All participants had provided their written informed consent during the aforementioned time interval. For all cases, the following parameters were retrieved, and recorded from our database: the ages of the patients, gestational week, number of fetuses, chorionicity, fetal echocardiogram and postpartum echocardiography results. Infants of mothers with missing information were excluded. Cases who were diagnosed after the deadline of the study as patent foramen ovale and patent ductus arteriosus were not included. Data on chorionicity was based on the prenatal ultrasonographic diagnoses. Our primary outcome in this study was the total number of patients with congenital heart disease which were seen on fetal echocardiograms of multiple pregnancies. Secondary outcomes as the number of critical congenital heart disease in singleton and multiple pregnancies were also evaluated. The group of critical congenital heart diseases included hypoplastic left heart syndrome, common arterial trunk, coarctation of the aorta, interrupted aortic arch, pulmonary atresia with intact septum, tetralogy of Fallot, total anomalous pulmonary venous return, d-transposition of great arteries, tricuspid atresia, double outlet right ventricle, Ebstein's anomaly and single ventricle.

Fetal Echocardiography

Fetal echocardiographies were routinely performed on patients who applied to perinatology outpatient clinics. All of the fetal echocardiography examinations were performed by four experienced pediatric cardiologists in our center. Fetal echocardiographies were performed in all cases between 18 to 37 gestational weeks. Fetal heart scans were performed with the patients in supine position, and tilted 15º to the left. The study patients had a detailed transabdominal fetal echocardiography with a full assessment of cardiovascular structural anatomy and function according to the guidelines of the American Institute of Ultrasound in Medicine [14].

The following echocardiography machines were used.

Philips Affiniti 50 (Philips Healthcare, Andover, Netherlands) equipped with C5-1 MHz transabdominal curvilinear transducers or;

Philips Epiq C7 (Philips Medical Systems, Bothell, WA, USA; 2014) equipped with C5 MHz transabdominal curvilinear transducers.

A detailed and complete echocardiographic examination was performed in every case, including biometric measurements along with a thorough and sequential scanning and identification of each view including 4-chamber view, 3-vessel view, trachea and 3-vessel view, outflow tract view, and aortic and ductal arches view. All ultrasonographers strictly followed the standard guidelines for scanning and diagnosis of heart malformations.

Statistical Analysis

All statistical analyses were performed using SPSS 21.0 (SPSS Inc., Chicago, IL); $p<0.05$ was considered statistically significant. Continuous data were expressed as mean value ± standard deviation. Numbers and percentages of congenital heart lesions in singleton and

multiple pregnancy groups were calculated. Comparison between the two groups were performed using chi-square test.

RESULTS

Fetal echocardiography was performed in 9,440 cases including 241 multiple and 9,199 singleton pregnancies. The group of multiple pregnancies consisted of twin (96.3%), triplet (2.9%), and quadruplet (0.8%) pregnancies. The mean maternal age of the patients was 30.5±5.8 years (16-47 years), and the mean gestational age at the time of referral was 22.3±3.8 weeks. A total number of 418 cases with congenital heart defects including 397 singletons (4.31%). and 21 twins (8.7%) had been delivered during the study period: The prevalence of congenital heart defects was significantly higher in twin pregnancies (p=0.005). There was no statistically significant difference between the two groups with respect to rate of critical congenital heart disease (p=0.32). The most common cardiac lesion identified in both groups was ventricular septal defect. Cardiac lesions which were identified in singleton and twin pregnancies are summarized in Table 1, 2. The relation between chorionicity and the presence of congenital heart defects is shown in Table 3.

Trisomy 21 was detected in two cases with twin pregnancies and intrauterine death developed in 10 fetuses. Of the twins with prenatally identified congenital heart defects, 13 patients were born in our center. Prenatal diagnosis of twins using fetal echocardiography was all the same except in one case who had hypoplastic left heart syndrome which was originally had received

Table 1. Cardiac lesions identified in single pregnacy

CHD	**VSD**	**AVSD**	**CoA**	**HLHS**	**UH**	**DORV**	**TOF**	**ASD**	**VSD-PA**
n (%)	101 (1.1)	56 (0.6)	35 (0.4)	33 (0.4)	26 (0.3)	25 (0.3)	23 (0.2)	17 (0.2)	16 (0.2)
CHD	**PS**	**AS**	**TGA**	**TA**	**TAPVD**	**EA**	**EC**	**APV**	**Normal/Total**
n (%)	15 (0.2)	11 (0.1)	10 (0.1)	10 (0.1)	8 (0.1)	6 (0.1)	4 (<0.1)	1 (<0.1)	8,802 (95.7)/9,199 (100)

CHD: Congenital heart disease, VSD: Ventricular septal defect, AVSD: Atrioventricular septal defect, CoA: Coarctation of aorta, HLHS: Hypoplastic left heart syndrome, UH: Univentricular heart, DORV: Double outlet right ventricle, TOF: Tetralogy of Fallot, ASD: Atrial septal defect, VSD-PA: Pulmonary atresia with ventricular septal defect, PS: Pulmonary stenosis, AS: Aortic stenosis, TGA: Transposition of great arteries, EA: Ebstein's anomaly, TA: Truncus arteriosus, TAPVD: Total anomalous pulmonary venous return, APV: Aortopulmonary window, EC: Ectopia cordis

Table 2. Cardiac lesions identified in multipl pregnancy

CHD	**DCDA (n, %)**	**MCDA (n, %)**	**MCMA (n, %)**	**Twins (any chorionicity)**	**Triplet, quadriplet (n, %)**	**Total (n, %)**
VSD	5 (3.9)	1 (1.4)	2 (22.7)	-	1 (12.5)	9 (3.7)
HLHS	1 (0.8)	1 (1.4)	1 (11.1)	-	-	3 (1.2)
DORV	1 (0.8)	1 (1.4)	-	-	-	2 (0.8)
TOF	1 (0.8)	1 (1.4)	-	-	-	2 (0.8)
AVSD	2 (1.6)	-	-	-	-	2 (0.8)
PS	-	1 (1.4)	-	-	-	1 (0.4)
UH	-	1 (1.4)	-	-	-	1 (0.4)
AS	-	1 (1.4)	-	-	-	1 (0.4)
Normal	118 (92.2)	62 (89.9)	6 (66.7)	27	7 (87.5)	220 (91.4)
Total	128 (100)	69 (100)	9 (100)	27	8 (100)	241 (100)

CHD: Congenital heart disease, DCDA: Dichorionic, diamniotic, MCDA: Monochorionic/diamniotic, MCMA: Monochorionic-monoamniotic, VSD: Ventricular septal defect, HLHS: Hypoplastic left heart syndrome, DORV: Double outlet right ventricle, TOF: Tetralogy of fallot, AVSD: Atrioventricular septal defect, PS: Pulmonary stenosis, UH: Univentricular heart, AS: Aortic stenosis

Table 3. CCHD distribution in the groups

	CCHD (n)	**CHD (n)**	**p**	**Total CHD (n)**	**Total patient**
Single pregnacy	193 (2.09)	204 (2.21)	0.32	397 (4.31)	9199
Multipl pregnancies	8 (3.31)	13 (5.3)	0.32	21 (8.71)	241

CCHD: Critical congenital heart disease, CHD: Congenital heart disease

the diagnosis of single ventricle. Of these cases, one with unbalanced atrioventricular septal defect died due to sepsis, two cases with hypoplastic left heart syndrome exited after stage 1 repair.

DISCUSSION

In this retrospective-cohort study, the prevalence of congenital heart defects was significantly higher in multiple pregnancies when compared to singleton pregnancies. The rate of congenital heart defects was 8.7% in multiple and 4.31% in singleton pregnancies. Herskind et al. [15] studied 25-year data of 41,525 twin pregnancies in Denmark. In their study the prevalence of congenital heart defects was 1.4% in twin, and 0.87% in 74,773 singleton pregnancies, and the authors concluded that twin pregnancies increased the rate of congenital heart defects. In our study, the prevalence of congenital heart defects in twin pregnancies was higher than those reported in prior population- based studies. A possible explanation for this difference might be that our population consisted of patients who were referred to a tertiary care center- who had fetal echocardiography indications.

Best and Rankin [6] studied the prevalence of congenital heart defects in twin and singleton pregnancies in North England between 1998-2010, and found that congenital heart defects were significantly more prevalent in twin pregnancies with a rate of 1.3%, and congenital heart defects were more common in monochorionic twins compared to dichorionic twins. In our study, the prevalence rates of congenital heart defects were 11.7% in monochorionic and 10.1% in dichorionic twins. In a meta-analysis, Bahtiyar et al. [12] found that the prevalence of congenital heart defects in monochorionic/diamniotic gestations was nearly nine-fold higher and 40 patients with congenital heart defects were found in 830 twin pregnancies. The current study confirms that monochorionic/diamniotic twin pregnancies were associated with congenital heart defects which further supports the idea that fetal echocardiography should be necessary for all monochorionic/diamniotic twin pregnancies. Li et al. [16] showed that in 2 pairs of the twins, the two fetuses had the same kind of CHD. They also noted that of 12 patients, 4 were in high and 8 in low-risk categories. None of the twins in our study had the same heart disease.

There is no definite explanation why the prevalence of congenital heart defects is higher in multiple pregnancies. There are, however, possible explanations regarding genetic and hemodynamic aspects [17-19]. One theory suggests that the unequal division of cells in monozygotic twins as a possible explanation. Another possible explanation for this is that genetic basis of several cardiac anomalies may cause discordant manifestations in different patients. Hillebrand et al. [20] reported a case of twins with 22q11 deletion, one of them had congenital heart defects and other one aortic interruption, ventricular septal defect and atrial septal defect. Several studies have shown that multiple pregnancies significantly worsen the performance of ultrasound in pregnancy. In the study of Paladini et al. [21], diagnostic performance of fetal echocardiography in experienced center was good with a sensitivity of 88.8% and specificity of 99.8 percent.

Study Limitations

The current study has several limitations. We only studied fetal echocardiography records of our tertiary care center. Further work is required to establish the prevalence of multiple pregnancies and congenital heart defects in population-based studies. Another weakness of this study, is that we did not have information on whether the patient had used assisted reproductive technologies.

CONCLUSION

The main goal of the current study was to determine the prevalence of congenital heart defects in multiple pregnancies. This study has revealed that the risk of congenital heart defects increases in multiple pregnancies compared with singleton pregnancies. Our small sample size was also a limitation of this study.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital Clinical Research Ethics Committee (approval number: 11/15, date: 14.09.2020).

Informed Consent: Since our study had a retrospective design, informed consent was not obtained from the patients.

Peer-review: Externally and internally peer-reviewed.

Author Contributions

Surgical and Medical Practices: T.D., A.R.B., H.G.P., A.Ş., N.N., C.K., Concept: T.D., B.G., C.K., Design: T.D., B.G., A.R.B., H.G.P., A.Ş., Data Collection and/or

Processing: T.D., A.R.B., H.G.P., A.Ş., C.K., Analysis and/or Interpretation: H.G.P., C.K., Literature Search: B.G., N.N., Writing: T.D., B.G., A.Ş.

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Original Article

Assessment of Intravenous Immunoglobulin Indications in Pediatric Intensive Care

Çocuk Yoğun Bakımda İntravenöz İmmünoglobulin Endikasyonlarının Değerlendirilmesi

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ABSTRACT

Objective: Intravenous immunoglobulin (IVIg) is one of the most common biologic agents used in daily intensive care practice. Our aim in this study was to evaluate IVIg indications and side effects in patients hospitalized in the pediatric intensive care unit.

Method: The data of 116 patients who received IVIg treatment between 2014-2018 in a tertiary level pediatric intensive care unit were retrospectively evaluated.

Results: The patient group with the highest use of IVIg was found to have sepsis. The highest dose was detected in patients with Steven Johnson syndrome and the highest total dose was detected in patients with secondary immunodeficiency. Use of IVIg in off-label diseases was found more than use by indication.

Conclusion: IVIg is a life-saving treatment in selected patients and clinical conditions. In our study, the most common disease group in which IVIg was used and concomitant highest mortality was found to be sepsis. In off-label diseases, especially in sepsis, the use of IVIg can be reduced with alternative treatments.

Keywords: Intravenous immunoglobulin, pediatric intensive care, sepsis

ÖZ

Amaç: İntravenöz immünoglobulin (İVİg), günlük yoğun bakım pratiğinde kullanılan en yaygın biyolojik ajanlardan biridir. Bu çalışmada amacımız çocuk yoğun bakım ünitesinde yatan hastalarda İVİg endikasyonlarını ve yan etkilerini değerlendirmektir.

Yöntem: Üçüncü basamak çocuk yoğun bakım ünitesinde, 2014-2018 yılları arasında İVİg tedavisi almış 116 hastanın verileri retrospektif olarak değerlendirildi.

Bulgular: İVİg kullanımının en fazla olduğu hasta grubu sepsis olarak bulundu. En yüksek doz steven johnson sendromu hastasında, toplam en yüksek doz ise sekonder immün yetmezlikli hastalarda saptandı. Endikasyon dışı hastalıklarda İVİg kullanımı, endikasyon ile kullanımdan daha fazla saptandı.

Sonuç: İVİg, seçilmiş hastalarda ve klinik koşullarda hayat kurtaran bir tedavidir. Çalışmamızda en sık İVİg kullanılan ve mortalitenin en fazla olduğu hastalık grubu sepsis olarak bulunmuştur. Endikasyon dışı hastalıklarda, özelikle sepsiste, alternatif tedaviler ile İVİg kullanımı azaltılabilir.

Anahtar kelimeler: İntravenöz immünoglobulin, çocuk yoğun bakım, sepsis

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INTRODUCTION

Intravenous immunoglobulin (IVIg) preparations are biological products derived from human plasma used for their replacement and immunomodulatory effects on the immune system. IVIg is a biological agent containing a high rate (>95%) of polyclonal immunoglobulin G (IgG) obtained from plasma taken from a large number of healthy donors [(1)]. Igs are the main or supportive treatment option in the prevention and treatment of some post-transplant diseases, especially in primary immunodeficiencies, and in neurological and autoimmune-inflammatory

diseases [2]. In addition, with the discovery of its anti-inflammatory and immunomodulatory effects, it has been shown to be protective or therapeutic in many diseases [3]. Despite its increasing use, IVIg is known to be administrated in some diseases with a low level of evidence. It should be used with caution in selected cases due to the difficulties encountered in obtaining IVIg and its cost, as well as its side effects. In this study, we have evaluated IVIg indications, doses and side effects in patients hospitalized in our pediatric intensive care unit.

MATERIALS and METHODS

Study Design

The study was conducted retrospectively with the data of patients hospitalized in a 24-bed tertiary level pediatric intensive care unit between January 2015 and January 2019 in a training and research hospital. The study was approved by the University of Hatay Mustafa Kemal University Ethics Committee (approval number: 27, date: 12.11.2020).

Study Population

Patients aged between 1 month and 18 years who received IVIg treatment in the pediatric intensive care unit were included whereas patients younger than one month and older than 18 years of age, and patients who were discharged or died within the first 24 hours, and those with missing data required for the study were excluded from the study.

The medical records of the patients who received IVIg treatment during intensive care unit hospitalization were retrospectively reviewed, and demographic data, hospitalization diagnoses, number and doses of IVIg treatment received, side effects and prognosis were recorded. Informed consent was obtained from the families of the patients.

The primary endpoint of the study was length of stay, and the secondary endpoint was mortality. Side effects associated with IVIg infusion are classified either as acute and delayed reactions during infusion or as mild/moderate/severe reactions within the clinical classification.

Acute and delayed reactions are classified as follows;

1. Acute reactions: Headache, nausea, myalgia, fever, chills and chest pain, skin findings such as rash redness, and signs of anaphylaxis.

2. Delayed reactions: Migraine-type headache, aseptic meningitis, kidney injury, thrombotic events, hemolysis, neutropenia, transfusion-associated acute lung injury.

Side effects are also clinically classified as mild, moderate or severe as follows;

1. Mild reactions: These include headache, rash, muscle aches, chills, feeling sick, itching, urticaria, anxiety, dizziness, unsteadiness or nervousness. It can be controlled by reducing the infusion rate.

2. Moderate reactions: Includes mild reactions that worsen or other symptoms such as chest pain or wheezing that require discontinuation of the infusion.

3. Severe reactions: These include persistent or worsening moderate reactions or other symptoms such as tightness in the throat, severe headache and chills, severe shortness of breath or wheezing, severe dizziness or fainting, chest pressure or collapse. Severe reactions require medical attention by stopping the drug infusion.

All medications used in our study contained 5% IVIg concentration, at least ≥95% of IgG and additionally maltose as a stabilizing agent. After IVIg solutions were diluted 1:1 with 5% dextrose, it was started at a rate of 0.02 mg/kg/min and was administered at a rate of 0.08 mg/kg/min by increasing the dose if no side effects were observed within 15-30 minutes. No routine premedication was applied to the patients before IVIg administration.

Statistical Analysis

The data were transferred to the SPSS 22.0 program. Distributions of numerical variables were analyzed using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Mean ± standard deviation or median/interquartile range (IQR) was used as a measure of distribution. Since the numerical data were not normally distributed, non-parametric tests were applied. The Mann-Whitney U test was used to compare the means of two independent groups. Results with a p-value below 0.05 were considered statistically significant.

RESULTS

One hundred and sixteen of 130 patients who received IVIg during the study period were included in the study. Ten patients died within the first 24 hours, and 4 more patients were excluded from the study because their medical data were missing. Sixty (51.7%) of 116 patients were male and 56 (48.3%) were female.

Average age and weight were 23 (IQR: 65) months and 11.55 (IQR: 18.5) kilograms, respectively. Sepsis was the most common (23.3%, n=27) in ten disease groups. According to the primary disease, a total of 56 (48.2%) patients [primary immunodeficiency, secondary immunodeficiency, idiopathic thrombocytopenic purpura (ITP), Kawasaki disease] received IVIG with indication, while the remaining 60 (51.7%) patients (sepsis, myocarditis, encephalitis, Guillain Barre syndrome, acute disseminated encephalomyelitis (ADEM): Steven Johnson syndrome (SJS) was found to have received IVIg with evidence-based methods without any indication.

Respiratory distress, sepsis and shock, neurological diseases and renal problems were found to be the most common reasons for admission to the intensive care unit in patients with primary and secondary immunodeficiency, respectively.

The demographic data of the patients are shown in Table 1, and the use of IVIg by indication and evidence category is shown in Table 2.

Side effects were observed in 17 patients in our study (14.65%). There was no significant difference between genders in terms of side effects (p=0.137). The patient group with the most common side effects were those with primary immunodeficiency. In our study, the most common side effects were flushing and rash observed in four patients, while fever was the second most common and observed in three patients. Mild hypotension was observed in two patients and chest pain observed in one adolescent patient. Side effects of diseases are given in Figure 1.

Table 2. Use of IVIg by indication and evidence category

Indication	Number of cases (n, %)	Level of evidence
FDA-approved indications		
Primary immundeficiency	26	Iıb
Agammaglobulinemia	4	Iıb
CVID	6	III
Hiper IgM	3	III
Hiper IgE	3	III
IgG subclass deficiency	10	
ITP	-	Ia
Kawasaki disease	-	Ia
Evidence-based indications		
Sepsis	27	III
Seconder immundeficiency	25	
Acute lymphoblastic leukemia	11	IV
Acute myeloid leukemia	8	IV
Lymphomas	4	IV
Neuroblastoma	2	IV
Encephalitis	15	III
Myocarditis	13	III
Guillain Barre syndrome	2	Ib
ADEM	2	III
SJS	1	Iıa

IVIg: Intravenous immunoglobulin, CVID: Common variable immun deficiency, ITP: Immune thrombocytopenic purpura, ADEM: Acute disseminated encephalomyelitis, SJS: Steven Johnson syndrome, IgG: Immunoglobulin G, FDA: The United States Food and Drug Administration

Table 1. Demographic and clinical findings

Parameter	Age (month)	Weight (kg)	n (%)
Primary disease			
Sepsis*	8 (18)	7.25 (7.1)	27 (%23.3)
Primary immunodeficiency*	15.50 (29)	9.5 (8.87)	26 (%22.4)
Secondary immunodeficiency*	60 (116)	30 (23.5)	25 (%21.6)
Encephalitis*	49 (99)	17.65 (25.50)	15 (%12.9)
Myocarditis*	6 (32)	6.25 (11.25)	13 (%11.2)
ITP**	21 (7-25)	13.90 (8.1-14.5)	3 (%2.6)
Kawasaki dissease**	23.50 (21-26)	11.8 (10.6-13)	2 (%1.7)
Guillain Barre syndrome**	83.5 (47-120)	28.25 (17.5-39)	2 (%1.7)
ADEM**	67 (62-72)	28 (27-29)	2 (%1.7)
SJS	96	25	1 (%0.9)

*Median (IQR): Interquartile range, **Median (minimum-maximum), age and weight given as Steven Johnson syndrome is one patient. ITP: Immune thrombocytopenic purpura, ADEM: Acute disseminated encephalomyelitis, SJS: Steven Johnson syndrome

Considering the mortality rates, 14 patients were found to have died (12.06%). The most common mortality was seen in sepsis patients (6 exitus), primary immunodeficiency (4 exitus), secondary immunodeficiency (3 exitus), and myocarditis (1 exitus) patients, respectively.

The most IVIg was used for the patients with SJS, the second most common reason to use IVIg was Guillain Barre syndrome and the third was ADEM. There were a total number of 5 patients in these three disease groups. The disease group with the highest amount of IVIg use, in general, was found to be secondary immunodeficiencies. The second most common disease group was found to be encephalitis. The lowest dose used in our study was 400 mg/kg, while the highest dose was 1,000 mg/kg (Table 3).

DISCUSSION

While IVIg was first used in patients with primary immunodeficiency in 1981, it is now widely used in the treatment of many autoimmune diseases and systemic inflammatory diseases [4].

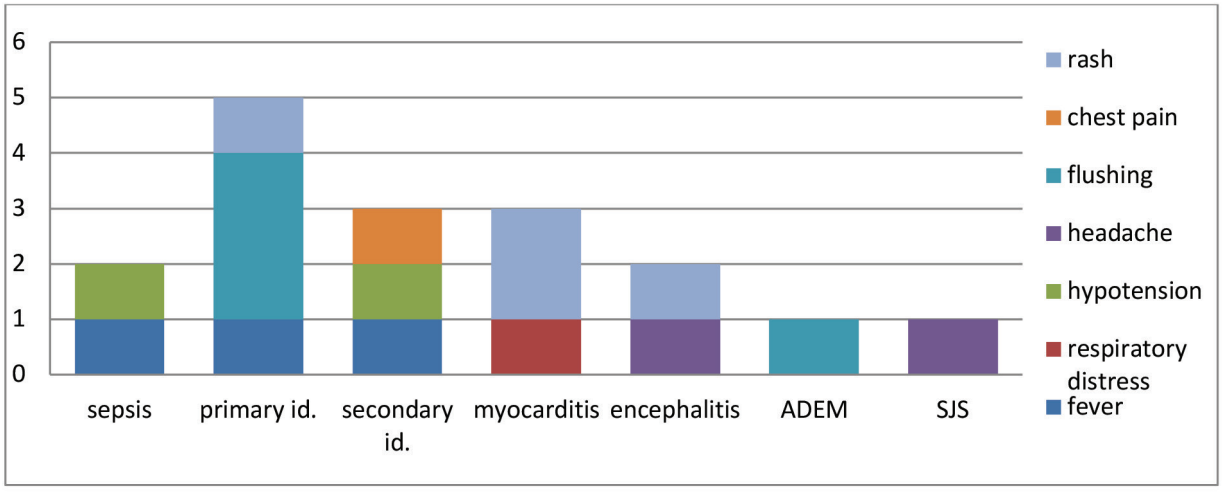

Figure 1. Side effects according to diseases

Primary id: Primary immundeficiency, Secondary id: Secondary immundeficiency, ADEM: Acute disseminated encephalomyelitis, SJS: Steven Johnson syndrome

Table 3. Total amount of IVIg used by disease groups

Parameter	Number of cases (n)	IVIg dose (mg/kg) (minimum-maximum)	Number of doses of IVIg (n) (minimum-maximum)	Total amount of IVIg (grams) [median (IQR)]
Primary disease				
Sepsis	27	400-1000	1-2	6.5 (5.7)
Primary immundeficiency	26	400-800	1-5	10 (15.6)
Secondary immundeficiency	25	400-600	1-5	30 (41.9)
Encephalitis	15	1000	1-2	31.6 (48)
Myocarditis	13	1000	1-2	12.6 (11.6)
ITP	3	1000	1-2	17.4 (8.1-25)*
Kawasaki disease	2	2000	1	18.3 (10.6-26)*
Guillain Barre syndrome	2	400	5	56.5 (35-78)*
ADEM	2	400	5	56 (54-58)*
SJS	1	400	5	80*

IVIg: Intravenous immunoglobulin, IQR: Interquartile range, ITP: Immune thrombocytopenic purpura, ADEM: Acute disseminated encephalomyelitis, SJS: Steven Johnson syndrome, Due to the low number of cases for ITP, Kawasaki disease, Guillain Barre, ADEM and SJS, minimum-maximum values were given instead of IQR for the total amount of IVIg

The effects of IVIg include complex mechanisms [5]. It shows its main effect by destroying nonspecific Fc receptors in the mononuclear phagocytic system or by preventing the binding of immune complexes to Fc receptors in cells [6]. In addition, it prevents the activation of the cascade by interacting with complement and cytokines, decreases the dendritic cell effect, prevents T and B-lymphocyte activation and differentiation [7,8].

IVIg indication is basically divided into two categories as evidence-based and non-evidence based [9]. Based on the evidence, IVIg use has been granted by the FDA (The United States Food and Drug Administration) for the following seven diseases. These diseases are listed as follows;

1. Primary immunodeficiency treatment,
2. Prevention of recurrent infections caused by B-cell chronic lymphocytic leukemia and bacterial infections in patients with hypogammaglobulinemia,
3. Prevention of coronary artery aneurysms in Kawasaki disease,
4. Prevention of infections, pneumonia and acute graft versus host disease after bone marrow transplantation,
5. Reducing severe bacterial infection in human immunodeficiency virus-infected children,
6. Increasing the number of platelets in ITP, preventing or controlling bleeding,
7. Chronic inflammatory demyelinating polyneuropathy.

Apart from FDA approved indications, IVIg is also used in the treatment of diseases for which there is some uncertain evidence of its benefit [10]. For example, IVIg has been shown to increase left ventricular functions in pediatric patients with fulminant myocarditis [11]. It is thought to be beneficial by stopping spasms, unconsciousness, shortening the duration of neuropathic symptoms and fever in viral encephalitis, and reducing seizures in autoimmune encephalitis [12,13]. In studies evaluating the use of IVIg, it has been reported that IVIg is used as a treatment option in non-indicative diseases at a rate of 14% to 47% due to its clinical benefits, and its use has increased from past to present [14]. Similar to our study, in a recent study conducted retrospectively with 301 patient data, it was reported that only 56 patients received IVIg with FDA-approved indications, and other patients were given IVIg with low-level of evidence indications [15]. Current studies show that the use of IVIg increases in all disease groups, especially in off-label diseases. In our study, we found that the most common IVIg was used in the sepsis patients (n=27, 23.3%), and similar to the literature data, the use of off-label IVIg was more often than its labeled use. In addition, sepsis was the second most common reason for intensive care hospitalization in primary and secondary immunodeficiency patients. This was explained by the fact that our hospital is the largest pediatric intensive care clinic in the region, and that patients with a specific diagnosis were referred to our hospital. Table 2 presents the diseases in which IVIg is used according to indication and evidence category.

It is known that IVIg in sepsis increases passive immunity through neutralization of bacterial toxins, increasing opsonization of bacteria and inhibition of immune cell proliferation and inflammatory cytokines [16]. It has been reported that IVIg treatment in patients with sepsis and septic shock reduces the course of advanced treatment methods in patients hospitalized in the intensive care unit or is used as a rescue therapy [17]. Although IVIg treatment is not recommended routinely in the treatment of sepsis in children, the current sepsis guideline leaves its use in selected patients, even with a low level of evidence, to the preference of the clinician [18].

It is clinically important to determine which patients will generally benefit most from IVIg therapy in patients with sepsis. However, studies investigating immunomodulatory treatment approaches in the treatment of sepsis generally do not specify a definite classification of suitable patients [19,20]. In our study, IVIg treatment was applied to severe sepsis patients who developed more than two organ dysfunctions while they were hospitalized with the diagnosis of sepsis. In these patients, due to the severity of inflammation caused by sepsis, the development of multiorgan failure is common and the high mortality rates associated with this multiorgan failure, therefore, IVIg treatment was applied considering that they could benefit from this treatment due to its anti-inflammatory properties.

It is thought that lymphopenia developing in septic and therefore Ig deficiency is associated with increased mortality and the mortality of septic shock is more than 50% [21]. In a meta-analysis from 8 studies involving 492 patients using IVIg for the adjuvant treatment of bacterial sepsis or septic shock, IVIg treatment was reported to be associated with a significant reduction in mortality [22]. In our study, mortality was 22.2% in septic patients who received IVIg treatment. Compared to these data,

although the mortality rate in sepsis patients is low in our study, the effect of IVIg to this rate cannot be clearly demonstrated.

Although the dose and duration of IVIg treatment varies depending on the disease, it can be used as replacement therapy (low dose: 200-400 mg/kg) and immunomodulator-anti-inflammatory therapy (high dose: 1-2 g/kg) [23]. Considering the amount of IVIg used according to disease groups in our study (Table 3), it was seen that the highest amount of IVIg was used in Steven Johnson's patient and the highest total amount was used in secondary immunodeficiency patients. This situation was found to be related with the high number and weight of patients with secondary immunodeficiency. Although the SJS group received a very high dose of IVIg, there was only one patient in this disease specific group. The minimum and maximum IVIg doses used in our study were found to be 400-1000 mg/kg.

IVIg therapy is generally a relatively safe treatment with mild side effects [24]. Although numerous clinical studies have shown that Ig is effective and well tolerated, various side effects have also been reported. Generally, mild to moderate reactions occur in 5% to 15% of infusions [25]. Side effects may develop due to patient-induced factors or the content of the IVIg preparation. Most can be controlled by slowing the infusion rate. In addition, the dose and concentration of IVIg and the daily dose should be carefully adjusted [26]. In our study, flushing and rash were the most common side effects in four patients, while fever which was seen in three patients was the second most common side effect. There was mild hypotension in two patients and a feeling of chest pain in one adolescent. When IVIg infusion was interrupted, the complaints regressed. These complaints seen in three patients did not recur when the treatment was continued by reducing the infusion rate. electrocardiogram was normal in these patients due to chest pain. When the infusion was interrupted or the infusion rate was decreased in patients who developed side effects, the indicated side effects regressed.

Knowing what mild to serious side effects to expect in the application of immune globulin therapy can prepare both the patients and the clinicians for treatment changes to reduce their effects [27]. In addition, while the mortality was higher in the study group than our intensive care overall mortality rate, this was attributed to the fact that the study was conducted in the most critically ill patients.

IVIg is used frequently in pediatric intensive care, in cases of open and unclear indications. Regulations should be made for access to IVIg in the indication list within the scope of national health planning and the conditions required for IVIg use should be explained. The criteria for clinical use of IVIg should be more clearly defined. There is a need for up-to-date protocols developed for clinicians to help determine the appropriate IVIg use and indications.

Targeted treatment of patients who would potentially benefit from IVIg therapy, based on evidence-based criteria, should be made in a non-discriminatory approach. Unfortunately, with the available data it is difficult to interpret a reliable and validated assessment of cost-effectiveness in relation to total treatment costs for diseases using labeled and off-labeled IVIg.

The continued substantial annual growth in IVIg use, its relatively high cost, and difficulty in procuring require health policy to remain consistent with an evidence-based approach to IVIg use. In order to confirm the rationale for the use of IVIg presented in this study and to target the treatment to the right patient group, at the right time, at the appropriate dose and in an optimal period, detailed studies are needed to investigate the effect of IVIg on mortality and length of stay on a disease basis which may preferably compare alternative treatments and cost-effectiveness.

CONCLUSION

IVIg is a life-saving treatment in selected patients and clinical conditions. However, the necessary indications should be selected carefully due to the side effects and cost. Treatment guidelines can be updated by the use of other immunomodulatory treatments such as corticosteroids and plasma exchange in sepsis, encephalitis and myocarditis where IVIg is frequently used, and by determining the effectiveness of these alternative therapies.

Ethics

Ethics Committee Approval: The study was approved by the University of Hatay Mustafa Kemal University Ethics Committee (approval number: 27, date: 12.11.2020).

Informed Consent: Informed consent was obtained from the families of the patients.

Peer-review: Externally and internally peer-reviewed.

Author Contributions

Surgical and Medical Practices: F.S., G.A., Concept: F.S., H.A., Design: H.A., Ö.S.S., Data Collection and/or Processing: F.S., Ö.S.S., Analysis and/or Interpretation: F.S., G.C., Literature Search: F.S., G.A., H.A., Writing: F.S., G.A., G.C., Ö.S.S., H.A.

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Original Article

Does the Cartilaginous Index Affect Acetabular Development in Developmental Dysplasia of the Hip? A Radiographic Study on Patients with Long-term Follow-up

Kıkırdak Asetabüler Indeksin Kalça Gelişimine Etkisi. Uzun Dönem Takipli Hastalarda Radyolojik Çalışma

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ABSTRACT

Objective: Developmental dysplasia of the hip is one of the most common infantile diseases. Estimating the roles of factors affecting the development of dysplastic hip is essential in determining the treatment outcomes. In this study, we investigated if the cartilaginous acetabular index (CAI), osseous acetabular index, or their difference (delta angle) affect acetabular development in the long- term follow-up.

Method: Thirty-five hips of 30 patients are included in the study. The mean age of the patients was 15.71±6.37 (3-31) months. All patients were treated using a medial approach. The mean follow-up was 149.91±51.43 (60-262) months. Five hips were excluded due to the development of avascular necrosis.

Results: Any statistically significant difference was not found in the evaluation of the correlation between CAI, osseous acetabular index, or delta angle measurements in terms of acetabular development. The acetabular growth in the first year following the reduction was statistically significant ($p<0.001$), while, the acetabular development for the following years were not found to be statistically significant ($p>0.05$).

Conclusion: CAI, osseous acetabular index, and delta angles do not directly affect acetabular development rate. However, most of the acetabular development occurs during the first year after concentric reduction in children younger than 24 months.

Keywords: Acetabular development, dysplasia of the hip, DDH, medial approach, the cartilaginous acetabular index, child

ÖZ

Amaç: Gelişimsel kalça displazisi infant çağının sık görülen hastalıklarındandır. Hastalığın takip ve tedavi sürecinin değerlendirilmesinde, kalça gelişimine etkileyen faktörlerin bilinmesinin önemi büyüktür. Bu çalışmada, başlangıçta ölçülen kıkırdak asetabüler indeks (KAİ) değerinin, hem tek başına hem de asetabüler indeks değeri ile farkının kalça gelişimine etkisi uzun dönem takip edilen hastalarda, radyografik olarak değerlendirildi.

Yöntem: Çalışmaya otuz hastanın otuz beş kalçası dahil edildi. Hastaların ortalama yaşı 15,71±6,37 (3-31) aydı. On üç kalçaya sınırlı medial girişim, 22 kalçaya ise medial girişim uygulandı. Ortalama takip süresi 149,91±51,43 (60-262) aydı. Beş kalça takipler sırasında avasküler nekroz gelişmesi nedeniyle değerlendirme dışı bırakıldı.

Bulgular: Yıllık asetabüler gelişim ile başlangıçta ölçülen KAİ değeri arasında istatistiksel olarak önemli bir ilişki izlenmedi ($p>0,05$). Redüksiyonu takip eden ilk yılın sonunda görülen kalça gelişimi istatistiksel olarak anlamlı saptandı ($p<0,001$). Takip eden yıllardaki asetabüler gelişim istatistiksel olarak anlamlı bulunmadı ($p>0,05$).

Sonuç: KAİ değeri, kalça gelişimini direk olarak etkilememektedir. Bununla birlikte asetabüler gelişim, 24 aydan küçük çocuklarda konsantrik redüksiyonu takip eden ilk yıl içerisinde en yüksek oranda gerçekleşmektedir.

Anahtar kelimeler: Asetabüler gelişim, gelişimsel kalça displazisi, GKD, medial yaklaşım, kıkırdak asetabüler indeks, çocuk

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INTRODUCTION

Although early concentric reduction of the femoral head in the treatment of the developmental dysplasia of the hip (DDH) is an essential factor for acetabular development in infants, higher initial acetabular index (AI) values negatively affect the treatment outcomes [1,2]. Infant acetabulum consists mainly of cartilage tissue. It isn't easy to assess cartilage acetabulum by plain radiographs, and generally, arthrographic imaging, ultrasound, or magnetic resonance imaging (MRI) is being used for this evaluation.

The cartilaginous acetabular index (CAI) can be measured by MRI and arthrographic imaging. Measurement of CAI is also essential for the evaluation of acetabular development [3,4]. The cartilaginous coverage of the acetabulum was also assessed as a predictor of residual hip dysplasia. Many researchers assessed CAI as a potential predictor for decision-making about the need for an acetabuloplasty [4-8].

In the present study, we retrospectively evaluated the development of dysplastic infant hips, which have been treated successfully. We aimed to determine whether the CAI is correlated with acetabular development.

MATERIALS and METHODS

Thirty-five hips of 30 patients treated with the diagnosis of DDH were evaluated retrospectively. Twenty-nine (96.7%) patients were girls and eighteen of the 35 hips were left-sided. Five patients had bilateral DDH. The mean age of the patients was 15.71±6.37 (3-21) months. All patients were treated using a medial approach. The mean follow-up period was 149.91±51.43 (60-262) months.

Our treatment algorithm for DDH is to firstly apply a limited medial approach [9]. Following the skin incision, adductor longus and iliopsoas tenotomies were made. The hip was then reduced, and with one ml contrast material (UROGRAFIN®, Bayer AG Leverkusen/Germany) was injected into the hip joint, and arthrography was performed. According to the arthrographic assessment of Tönnis, the procedure would be completed for type 1 patients who underwent concentric hip reduction. While Type 2 and 3 DDH patients undergo a complete medial approach procedure, including capsulotomy, ligamentum teres excision, transverse acetabular ligament transection, and gentle pulvinar removal [10].

During the postoperative period, hip spica cast was applied for all of the patients with the patient in the 'human position' to be kept for three months and the hips were stabilized in abduction braces with a 90°-100° flexion and 40°-45° abduction for a further three months. Follow-up visits were made at postoperative 6th week, third and sixth months, first-year, then annually. Five hips were excluded from the study during the follow-ups due to the development of avascular necrosis.

On the pre-operatively obtained pelvic anteroposterior radiographs, AI angles were measured (Figure 1). CAI was measured from intraoperatively made artrographic images (Figure 2). The difference between AI and CAI values was accepted as cartilaginous acetabular thickness and described as the "delta angle" for statistical assessment.

Annual measurements were made on the anteroposterior pelvic radiographs for five years. Wiberg's CE angle and Sharp's acetabular angle were measured on the most recent anteroposterior pelvic radiographs of the patients. These measurements were evaluated according to reference values for age and gender [11,12]. The most recent pelvic radiographs of the patients were used for the decision of maturation. Because of the irregularity of the patients' visits during the follow-up period, the acetabular development was assessed only for the first five years.

This study was the research thesis of Mert Filibeli. The study was approved by the University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital

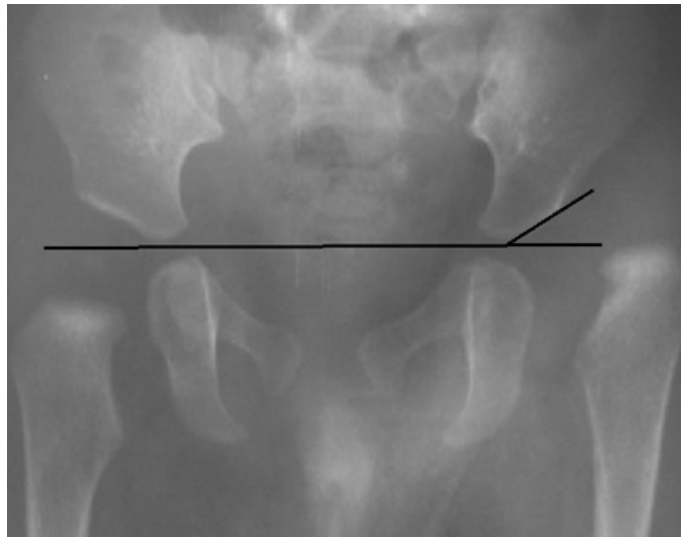

Figure 1. Pre-operative measurements of acetabular indices

Clinical Research Ethics Committee (approval number: 3, date: 05.12.2016).

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, ver. 23.0 (IBM Corp, Armonk, New York, USA). The normality of distribution among the groups was assessed using the Shapiro-Wilk test. The p-values greater than 0.05 were accepted as an indication for a normal distribution, and statistical analyses were continued with parametric tests. If the p values were <0.05, non-parametric tests were used for statistical analyses. To compare the improvement of AI values during postoperative years, we used the Bonferroni test. The factors affecting the improvement in acetabular indices progress over the years such as surgical technique, CAI, delta angle were analyzed using covariance analysis (ANCOVA). To conduct an efficient ANCOVA analysis, the patients were divided into groups. According to the surgical technique and labrum status, the patients were divided into two groups as limited and complete medial approach; normal and inverted labrum, respectively. The cut-off value for CAI was accepted as 20° [4], and accordingly patients were divided into two groups. Lastly, the patients were divided into two groups relative to the 30° cut-off value of delta angle.

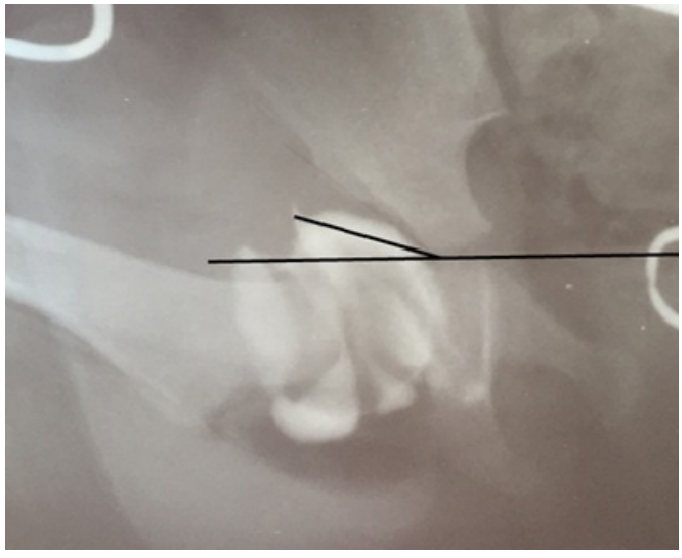

Figure 2. Measurements of the cartilaginous acetabular indices

RESULTS

The mean pre-operative AI angle was 39.2°±4.52 (30-48). The mean CAI, and delta angles were 16.1°±6.94 (4-30), and 23.17°±8.29 (2-40) respectively.

An ANCOVA test was conducted to compare the effects of the CAI, delta angle, labrum status, and surgical technique on the acetabular development in five years while controlling the AI. There was no statistical significance. The F and p values of the analysis are given in Table 1.

No statistically significant difference was found in evaluating the correlation between CAI angle measurements and annual acetabular development (p>0.05).

The mean AI values following reduction are shown in Figure 3.

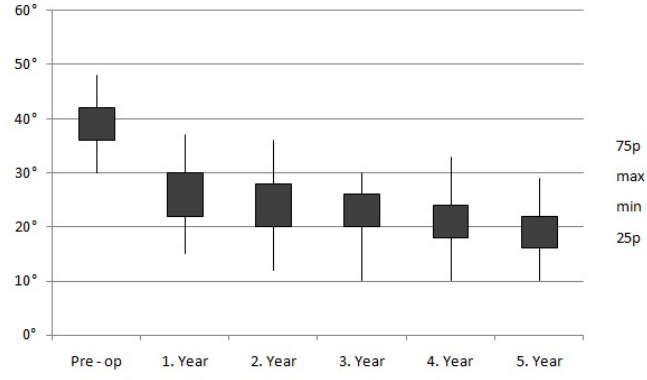

Figure 3. The mean acetabular index values in the first five years

max.: Maximum, min.: Minimum

Table 1. The results of ANCOVA on the acetabular development in five years

	CAI	Delta angle	Surgical technique	Labrum status
1. year	F (1.27)=0.33, p=0.25	F (1.27)=0.07, p=0.79	F (1.27)=0.80, p=0.38	F (1.27)=0.18, p=0.68
2. year	F (1.27)=0.80, p=0.78	F (1.27)=0.28, p=0.60	F (1.27)=0.99, p=0.33	F (1.27)=0.19, p=0.18
3. year	F (1.27)=0.10, p=0.75	F (1.27)=0.00, p=0.99	F (1.27)=0.56, p=0.46	F (1.27)=1.10, p=0.31
4. year	F (1. 27)=0.24, p=0.63	F (1.27)=0.02, p=0.89	F (1.27)=0.10, p=0.75	F (1.27)=1.33, p=0.26
5. year	F (1.27)=0.14, p=0.71	F (1.27)=0.00, p=0.97	F (1.27)=0.20, p=0.66	F (1.27)=1.26, p=0.27

CAI: Cartilaginous acetabular index, ANCOVA: Analyzed using covariance analysis

When the patients' acetabular development in the first five years was compared using multi-directional analysis of variance (Bonferroni), the change over the years was statistically significant (p<0.01) (Table 2).

The multivariate analysis of Bonferroni was used to assess the improvement of the AI over the years. The mean annual differences in acetabular indices in the postoperative first [13.51±5.85 (1-24)], second [2.34±2.76 (0-12)], third [2.11±2.01 (0-8)], fourth [2.11±2.01 (0-8)], ane fifth [1.28±1.58 (0-6)]. The improvement in the first year following the reduction was statistically significant (p<0.001), while the changes between the following years in terms of androgen insensitivity syndrome were not (p>0.05) (Table 3).

No statistically significant difference was found between patients whose age at the operation were younger, and older than 12 months in terms of acetabular development (Table 4).

DISCUSSION

The aim of DDH treatment is to get a concentric and stable reduction of the hip [13-15]. In our study, we evaluated the hips treated with the medial approach

Table 2. The improvement of the acetabular indices over the years (Bonferroni)

	Acetabular index according to years*	Mean difference	Standard error**	p-value	95% CI	
					Bottom	Top
Pre-op	1	12.471*	0.991	0.000	9.334	15.607
	2	14.706*	0.963	0.000	11.658	17.754
	3	16.794*	0.885	0.000	13.993	19.596
	4	18.353*	0.903	0.000	15.494	21.212
	5	19.765*	0.899	0.000	16.921	22.608
1. year	Pre-op	-12.471*	0.991	0.000	-15.607	-9.334
	2	2.235*	0.468	0.001	0.753	3.717
	3	4.324*	0.479	0.000	2.808	5.839
	4	5.882*	0.604	0.000	3.971	7.794
	5	7.294*	0.671	0.000	5.171	9.417
2. year	Pre-op	-14.706*	0.963	0.000	-17.754	-11.658
	1	-2.235*	0.468	0.001	-3.717	-0.753
	3	2.088*	0.349	0.000	0.984	3.193
	4	3.647*	0.506	0.000	2.045	5.249
	5	5.059*	0.562	0.000	3.282	6.836
3. year	Pre-op	-16.794*	0.885	0.000	-19.596	-13.993
	1	-4.324*	0.479	0.000	-5.839	-2.808
	2	-2.088*	0.349	0.000	-3.193	-0.984
	4	1.559*	0.336	0.001	0.497	2.621
	5	2.971*	0.423	0.000	1.631	4.31
4. year	Pre-op	-18.353*	0.903	0.000	-21.212	-15.494
	1	-5.882*	0.604	0.000	-7.794	-3.971
	2	-3.647*	0.506	0.000	-5.249	-2.045
	3	-1.559*	0.336	0.001	-2.621	-0.497
	5	1.412*	0.296	0.001	0.476	2.348
5. year	Pre-op	-19.765*	0.899	0.000	-22.608	-16.921
	1	-7.294*	0.671	0.000	-9.417	-5.171
	2	-5.059*	0.562	0.000	-6.836	-3.282
	3	-2.971*	0.423	0.000	-4.31	-1.631
	4	-1.412*	0.296	0.001	-2.348	-0.476

*Acetabular index according to years. **Standard error, CI: Confidence interval

and ended up with Severin type 1 hips after the follow-up of the patients up to the skeletal maturity. By including only the Severin type 1 hips in the study, we aimed to investigate the factors affecting the acetabular development independent from complicated hips. According to our findings, the acetabular development occurred largely in the first postoperative year following the reduction. There were no statistically significant factors affecting the acetabular development except the concentric reduction.

Some studies have investigated the relationship between the CAI and the acetabuler development. Different cut-off values and age limitations for CAI were suggested to be used for deciding acetabuloplasty [4,7,16,17]. In our study, initial AI or CAI values were of no statistical significance on the acetabular development. However, in our institute, we don't routinely perform MRI or arthrography on patients with DDH for only assessing development at a young age.

As many studies have shown, the acetabulum develops rapidly in the first year following reduction [18-21]. Our results demonstrate statistical significance in the first year's acetabular development. Albeit at a decreasing rate, and without any statistical significance

Table 3. Analysis of the annual differences in acetabular indices (Bonferroni)

	Acetabular development	Mean difference	Standard error	p-value	95% CI	
					Bottom	Top
1. year	2	11.171	1.184	0.000	7.616	14.727
	3	11.400	1.078	0.000	8.164	14.636
	4	12.000	1.021	0.000	8.936	15.064
	5	12.229	1.082	0.000	8.979	15.478
2. year	1	-11.171	1.184	0.000	-14.727	-7.616
	3	0.229	0.661	1.000	-1.756	2.213
	4	0.829	0.573	1.000	-0.892	2.549
	5	1.057	0.502	0.427	-0.450	2.564
3. year	1	-11.400	1.078	0.000	-14.636	-8.164
	2	-0.229	0.661	1.000	-2.213	1.756
	4	0.600	0.453	1.000	-0.760	1.960
	5	0.829	0.441	0.686	-0.494	2.151
4. year	1	-12.000	1.021	0.000	-15.064	-8.936
	2	-0.829	0.573	1.000	-2.549	0.892
	3	-0.600	0.453	1.000	-1.960	0.760
	5	0.229	0.442	1.000	-1.097	1.555
5. year	1	-12.229	1.082	0.000	-15.478	-8.979
	2	-1.057	0.502	0.427	-2.564	0.450
	3	-0.829	0.441	0.686	-2.151	0.494
	4	-0.229	0.442	1.000	-1.555	1.097

CI: Confidence interval

Table 4. Alysis of acetabular development regarding age at the procedure

	<12 months	>12 months	p-value*
1. year	12.66±8.38 (1-24)	13.80±4.87 (4-24)	0.78
2. year	2.88±2.02 (0-7)	2.15±2.98 (0-12)	0.14
3. year	1.88±1.96 (0-5)	2.19±2.05 (0-8)	0.83
4. year	1.77±1.64 (0-4)	1.42±2.06 (0-6)	0.42
5. year	1.88±1.83 (0-6)	1.07±1.46 (0-5)	0.17

*Mann-Whitney U test

acetabular development was maintained over the years. These findings favor Ponseti and Harris's reports related to acetabular development [19,20]. All the AI values at the age of three were <32°, and all the hips completed their normal development, supporting the study of Shin et al. [17].

Ponseti [19] reported that the inverted labrum did not act as an obstacle for the reduction following iliopsoas tenotomy and capsulotomy. On the other hand, Ge et al. [22] evaluated the labrum one year after hip reduction surgeries using magnetic resonance imaging. They reported that the inversion of the anterior part affected the development of the hips, while the inversion of the posterior part affected only the quality of reduction[22]. Contrary to Miyake et al.'s [16] study, labrum status was not associated with the acetabular development in the present research. In our clinic we do not routinely interfere with the labrum during open reduction procedures.

The potential of acetabular development drops after four years of age. The age at the reduction affects the development of hips. Favorable and unfavorable treatment outcomes have been reported in various studies for procedures performed after 12 months of age is [20-32]. The present study reports that the age at the operation did not statistically significantly affect the treatment success rates. The oldest of the patients at the surgery was 31 months of age. We suggest that the medial approach could be an appropriate procedure for patients older than 12 months and as suggested by many authors, we recommend follow-up all the patients up to the skeletal maturity [23-28].

Study Limitations

The number of patients and the measurements made by only one researcher are the main limitations of this study. The most recent pelvic radiographs of the patients have been used for the decision of maturation. Because of the irregularity of the patients' visits during the follow-up period, the acetabular development was assessed only for the first five years. The patients were followed up for almost 13 years which constituted the strength of our study.

CONCLUSION

In conclusion, the results of the present study have shown that concentric and stable reduction are the main factors affecting the development of dysplastic acetabulum. For such hips, acetabular development occurs during the following years at a decreasing rate, and most of the acetabular development is seen in the first year. The CAI should be evaluated carefully as a predictor for the development of infants' dysplastic acetabulum.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital Clinical Research Ethics Committee (decision no:3, date: 05.12.2016).

Informed Consent: Since our study had a retrospective design, informed consent was not obtained from the patients.

Peer-review: Externally peer-reviewed.

Author Contributions

Surgical and Medical Practices: H.A., M.F., A.T., Ö.K., Concept: H.A., M.F., A.T., Ö.K., Design: H.A., M.F., A.T., Ö.K., Data Collection and/or Processing: H.A., M.F., A.T., Ö.K., Analysis and/or Interpretation: H.A., M.F., A.T., Ö.K., Literature Search: H.A., M.F., A.T., Ö.K., Writing: H.A., M.F., A.T., Ö.K.

Conflict of Interest: The authors have no conflict of interest to declare.

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Original Article

The Effect of Screen Addiction and Attention-Deficit Hyperactivity Disorder on Insulin Resistance in Children

Çocuklarda Ekran Bağımlılığı ve Dikkat Eksikliği ve Hiperaktivite Bozukluğunun İnsülin Direnci Üzerine Etkisi

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ABSTRACT

Objective: Among screen-addicted children, there is a risk of insulin resistance (IR), obesity, hypertriglyceridemia and diabetes mellitus type 2 due to decreased physical activity and irregular eating habits. Most recently, relations of screen addiction (SA) and attention-deficit hyperactivity disorder (ADHD) with obesity have been reported. Herein, we aimed to investigate the presence of IR and dependent factors in screen-addicted children with and without obesity.

Method: A total of 108 children in the age range of 11-17 years were included in the study. Cases were divided into three groups according to ADHD and SA scale scores. In these three groups, there were equal numbers of obese and non-obese patients. Homeostasis model assessment for insulin resistance (HOMA-IR) of the patients was assessed at baseline. Body fat analysis was performed with TANITA BC-420 MA body composition analyzers. All cases wore pedometers for 3 days to determine their basal metabolic rates (BMR) during active and sedentary periods. Carbohydrate, fat and calorie consumption was calculated using a professional nutrition program.

Results: There were no statistically significant differences between the SA and non-SA groups on the energy consumption, BMR and fat mass and dietary contents. There was no effect of ADHD and SA on HOMA-IR values.

Conclusion: We did not find any association between SA and IR. Also dependent factors were similar between groups. New studies are needed to determine how SA affects obesity.

Keywords: Insulin resistance, screen addiction, attention deficit hyperactivity disorder, HOMA-IR

ÖZ

Amaç: Ekran bağımlılığı (EB) olan çocuklar, azalmış fiziksel aktivite ve bozulmuş beslenme düzenine bağlı olarak insülin direnci (İD), obezite, hiperlipidemi ve tip 2 diabetes mellitus açısından yüksek risk altındadırlar. Yakın zamanda yapılan çalışmalarda EB ve dikkat eksikliği hiperaktivite bozukluğunun (DEHB) obezite ile ilişkisi gösterilmiştir. Bu çalışmamızda, EB olan çocuklarda (obez olan veya olmayan) İD varlığını ve etkili faktörleri göstermeyi amaçladık. DEHB, EB ile birliktedir. EB olan çocuklarda aktivite azalmıştır ve buna bağlı olarak İD vardır.

Yöntem: Çalışmaya 11-17 yaş aralığında 108 çocuk alındı. Olgular DEHB ve EB açısından ölçekler ile değerlendirilerek üç gruba ayrıldı. Bu üç grupta eşit sayıda obez ve obez olmayan olgu bulunmaktaydı. İD'yi değerlendirmek için insülin direncinin homeostatik modeli değerlendirmesi (HOMA-IR) değerleri hesaplandı. Vücut yağ analizleri TANITA BC-420 MA vücut kompozisyon analizatörü ile yapıldı. Tüm olgulara 3 gün süre ile "Armband Sense Wear" pedometer takılarak bazal metabolik hız (BMH), aktivite ve istirahat süreleri kaydedildi. Karbonhidrat, yağ ve kalori tüketimi özel beslenme programı (BEBIS) ile hesaplandı.

Bulgular: Ekran bağımlılığı olan ve olmayan gruplar arasında enerji tüketimi, BMH ve vücut yağ kitlesi ve diyet içeriği benzerdi. DEHB ve ekran bağımlılığının, HOMA-IR üzerine etkisi saptanmadı.

Sonuç: EB ile İD arasında ilişki saptanmadı. Bağımlı faktörler gruplar arasında benzerdi. Ekran bağımlılığının obezite ile ilişkisini ve nedenlerini ortaya koymak için daha çok çalışmaya ihtiyaç vardır.

Anahtar kelimeler: İnsülin direnci, ekran bağımlılığı, dikkat eksikliği ve hiperaktivite bozukluğu, HOMA-IR

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INTRODUCTION

Screen addiction (SA) is the limitless and uncontrolled use of television, computer, smart phone and the other screen devices. It is more comprehensive version of the internet addiction that is under discussion all over the world. A large body of evidence shows that SA is always comorbid with other psychiatric conditions, especially attention-deficit hyperactivity disorder (ADHD) [1]. Among screen- addicted children, there is a risk of insulin resistance (IR) and IR related conditions i.e. obesity, hypertriglyceridemia and diabetes mellitus (DM) type 2 due to decreased physical activity and irregular eating habits [2,3]. Numerous studies have examined the relationship between sedentary lifestyle and obesity. Usage of screen devices and screen time are thought to be associated with obesity and long-term health problems [3].

IR, is defined as decreased tissue response to insulin-mediated cellular actions. The term "IR" as generally applied, refers to whole-body reduced glucose uptake in response to physiological insulin levels and its consequent effects on glucose and insulin metabolism.

The major acquired factors leading to IR are sedentary lifestyle brought about by industrialization and innovations in technology, unhealthy eating habits, and obesity. The most widely diagnostic method in clinical practice is homeostasis model assessment for ınsulin resistance (HOMA-IR) [4-6].

Our study aims to investigate the presence of IR and its possible causes in screen-addicted children.

MATERIALS and METHODS

The study was conducted between March 2013 and August 2014 with 36 pubertal children between 11-18 years of age, and diagnosed as SA and ADHD (group 1) by the department of child and adolescent psychiatry. Children with a chronic illness or those taking any medication(s) were excluded from the study. The control group consisted of children and adolescents with non-screen- addicted ADHD (group 2) and those that did not receive the diagnoses of ADHD and SA (group 3). Each group contained equal numbers of obese and non-obese children.

The study was approved by the Ege University Faculty of Medicine Ethics Committee (approval number: 13-2/47, date: 20.02.2013). Written informed consent was obtained from all participants and their parents. Clinical examination, weight and height measurements of the cases were performed by the same investigator. Height was measured to the nearest centimeter using a rigid stadiometer. Weight was measured unclothed to the nearest 0.1 kg using a calibrated balance scale. Body mass index (BMI) was calculated by dividing the weight in kilograms by the square of the height in meters (m^2). Percentiles and Z-scores of weight, height and BMI were determined by using data of Turkish children according to their age and sex [7]. The children with a BMI equal or greater than the +2 standard deviations (SD) for age and sex were considered as obese.

Participants' activity and duration of their resting periods were recorded with the "Armband Sense Wear", body fat-muscle-bone analysis was done using TANITA BC-420 MA Body Composition Analyzer. Participants' food intake for 3 consecutive days was recorded by themselves. Energy, protein, fat and carbohydrate intake were analyzed using a professional nutrition information program, BEBIS. IR was evaluated by HOMA-IR (calculated based on preprandial blood glucose and insulin levels). Acceptable range of HOMA-IR is below 2.7 and any level greater than 2.7 was considered as presence of IR [5,8].

Statistical Analysis

Statistical analyses of the data were performed using SPSS v20.0 for Windows (IBM Corp., Armonk, NY, USA). Distribution of data was evaluated using the Kolmogorov-Smirnov test. For comparison of more than two groups, one-way ANOVA or Kruskall-Wallis test was used according to normal or non-normal distribution of the data. If a significant difference was found in the comparison of more than two groups, Mann-Whitney U test with Bonferroni correction or post-hoc Tukey test was performed to determine where the differences truly originated from. Numerical data were expressed as median (25-75th percentile) or mean ± SD based on 95% confidence interval. The value of $p<0.05$ was considered to be statistically significant.

RESULTS

Mean age of the patients was 13.7±1.95 years. Mean weight, weight SDS, height and height SDS of the patients were 66±21 kg (30-120 kg), 1.2±1.8 (-3.3-+4.6), 159.3±9.9 cm (141.5-184 cm), 0.11±1 (-2.3-+2.5), respectively. Mean BMI, and BMI SDS of all cases were 25.8±7 kg/m^2 (14.9-40 kg/m^2) and 1.17±1.88 (-3.49-3.81), respectively. There were equal number of obese and non-obese children in all of these three groups. Anthropometric data and results of body fat analysis of all participants are given

in Table 1. Family history of IR and its complications (obesity, hypertension, DM type 2) was revealed in 41 cases. In the obese cases, the incidence of familial IR was significantly higher (p<0.05). Body fat composition was higher in the obese group as expected. There was no significant difference among the groups as for body fat composition (Table 1).

Basal metabolic rates (BMR), energy consumption, number of steps per day, activity, resting and sleeping periods and nutrient intakes of all the groups are shown in Table 2. Mean BMR of obese and non-obese cases were 1.5±0.3 and 1.74±0.27, respectively (p<0.05). There was no significant difference among three groups in terms of BMR, daily energy consumption, number of steps, resting, sleeping and activity durations (Table 2). Daily active energy consumption was lower in group 3.

Eighty-nine participants had completed the dietary list. Carbohydrate, fat, protein and energy intakes

Table 1. Anthropometric data and body fat analysis of participants

Parameters	Group 1 SA (+) ADHD (+)	Group 2 SA (-) ADHD (+)	Group 3 SA (-) ADHD (-)	p
Sex (n)	36	36	36	0.017[a]
Male	27 (75%)	25 (69.4%)	16 (44.4%)	
Female	9 (25%)	11 (30.5%)	20 (55.5%)	
Age (years)	13.51 (12.5-14.5)	13.80 (11.9-16.2)	13.86 (11.6-16.1)	0.723[b]
Weight (kg)	67.9±22.7	64.3±21.1	66.9±20	0.764[b]
Height (cm)	160.3±8.4	160.2±11.3	157.5±9.8	0.394[b]
Weight SDS	1.26±1.73	1.12±1.89	1.4±2.09	0.818[b]
Height SDS	0.12±0.86	0.24±1.06	-0.02±1.07	0.526[b]
BMI SDS	1.76 (-0.49-2.51)	1.43 (-1.18-2.65)	1.74 (0.53-2.85)	0.511[c]
Body fat ratio (%)	30.6 (13.7-36.4)	23 (11-39.5)	33.3 (15-42.8)	0.464[c]
Body fat mass (kg)	21.9 (2.1-30)	19.2 (2.5-30.1)	19.1 (1.5-36.6)	0.716[c]

ADHD: Attention-deficit hyperactivity disorder, SA: Screen addiction, Data were presented as mean ± SD or median (25-75th percentiles), [a]chi-square, [b]One-way-ANOVA, [c]Kruskal-Wallis

Table 2. BMR, activity and resting periods and nutrient intakes of the subgroups

	Group 1 SA (+) ADHD (+)	Group 2 SA (-) ADHD (+)	Group 3 SA (-) ADHD (-)	p
BMR	1.6 (1.4-2)	1.5 (1.4-1.7)	1.4 (1.3-1.5)	0.080[b]
Energy consumption (kcal)	2,399±895	2,450±1,003	2,385±567	0.585[a]
Number of steps	8,926±3,804	8,273± 3,669	8,989±3,499	0.579[a]
Resting duration (hr)	8.9 (7-9.6)	8.9 (7.6-9.5)	8.1 (7-9.1)	0.953[b]
Sleep duration (hr)	7.1 (5.5-7.8)	7.1 (6.5-7.9)	6.9 (5.7-7.7)	0.455[b]
Daily active energy consumption (kcal)	576 (356-976)	422 (298-666)	356 (251-636)[cf]	0.037[b]
Duration of physical activity (hr)	1.77 (1.2-4)	1.49 (1-2.2)	1.15 (0.8-1.9)	0.061[b]
Energy intake (kcal)	1,870 (1,720-2,223)	1,732 (1,431-2,237)	1,839 (1,335-2,125)	0.334[b]
Protein intake (g)	74 (55.9-85.2)	66.6 (54.3-81.6)	55 (47.3-79.3)	0.052[b]
Fat intake (g)	77.1 (62.3-101.9)	69.9 (57.4-104.2)	70.3 (59.7-93.4)	0.407[b]
Carbohydrate intake (g)	210 (181-309)	197 (161-241)	214 (139-268)	0.440[b]
Energy intake per weight (kcal)	28.8 (21.7-42.7)	28.3 (19-49.3)	25 (16.3-31.5)	0.223[b]
Protein intake per weight (g)	1.07 (0.74-1.43)	1.12 (0.78-1.93)	0.84 (0.60-1.23)[cf]	0.026[b]
Fat intake per weight (g)	1.17 (0.76-1.52)	1.14 (0.74-2.33)	1.06 (0.80-1.33)	0.333[b]
Carbohydrate intake per weight (g)	3.17 (2.27-5.93)	3.18 (2.51-4.83)	2.92 (1.75-3.53)	0.230[b]

SA: Screen addiction, ADHD: Attention-deficit hyperactivity disorder, kcal: kilocalorie, g: grams, hr: hours, Data were presented as mean ± standard deviation or median (25-75th percentiles), [a]One-Way-ANOVA, [b]Kruskal-Wallis test, [c]Mann-Whitney U test with Bonferroni correction (p<0.017), post-hoc test to determine the predominance for non-parametric three group comparisons

of 89 participants are shown in Table 2. There was no significant difference between total nutrient intakes of the groups. Energy, fat and carbohydrate intake per weight were similar between groups, on the other hand, protein intake per weight was lower in the group 3.

Mean HOMA-IR of the patients was 3.45±2.71 (0.62-16.46). Median HOMA-IR values of the groups were similar (Table 3).

DISCUSSION

Most recently relations of SA and ADHD with obesity have been reported. To our knowledge, this is the first study that investigates the association between SA and IR and the dependent factors.

BMR is the energy consumption at resting. BMR increases with physical activity, weight loss and healthy eating while decreases with sedentary lifestyle, aging and obesity. Recent studies in obese children suggest that BMR is negatively correlated with obesity [9]. Klesges et al. [10] showed that BMR was lower while watching TV rather than resting. Also recent studies have shown that BMR is lower in girls [9,11]. Contrary to these evidence, we have shown that ADHD and SA did not significantly affect BMR. These results should be considered along with the gender difference between the subgroups.

According to some authors, more frequent use of internet may cause lower physical activity and higher rates of overweight [12]. In another study, Mihrshahi et al. [13] has shown that the association between screen time and obesity also concerns decreased physical activity. In addition, many studies have shown that decreased physical activity and increased ST induce overweight [14]. Ebenegger et al. [15] has shown that ADHD rating scale scores were related to higher physical activity and prolonged screen time. In support of their findings, in our study, the active energy consumption was higher in ADHD cases regardless of the presence of SA.

There are numerous studies about the effects of screen time on sleep. According to these studies, screen time reduces the duration and quality of sleep and it is a risk factor for obesity [13,16-19]. However, in our study, there was no significant difference in sleep durations among the groups. The number and gender difference between subgroups may reveal this result. In addition, numerous studies examining the lifestyle of children with ADHD have shown that children with ADHD sleep less at night [20,21]. Various studies have revealed that obesity is related with decreased sleep duration and poor sleep quality [22]. Buxton and Marcelli [23] demonstrated that sleeping less than 7 h per night causes 6% increase in obesity risk of adults. However, psychopathologies or other factors that may lead to sleep disorders have not been analysed.

Obesity is a clinical situation that manifests with increased fat mass due to higher energy intake than consumed. Clinical studies have shown the existence of an association between obesity and higher fat and carbohydrate consumption [24,25]. In our study energy, carbohydrate, fat, protein intake per kg were observed lower in obese group. It was thought that this may be due to lower food intake with auto-control and/or showing less food intake with guilt/shame. This is in agreement with some other studies indicating that self-recorded dietary lists can not reflect the reality [26,27].

Epidemiologic studies have revealed that eating disorders of the children with ADHD lead to obesity in despite their increased physical activities [28-30]. As important etiologic factors in obesity, skipping meals, binge eating, higher intake of fast-food, and calorie-rich foods are frequently observed in ADHD children due to impulsitivity [2,31]. In our study; energy, fat and carbohydrate intakes of the groups were similar. Protein intake per weight of the group 3 was at the lowest level.

Current evidence suggests that screen media exposure leads to obesity in children and adolescents through overeating in front of the screen, exposure to low nutrient food with high calorie intake, and consumption of various beverages [32]. Epidemiologic studies reveal that children who consume more screen media also consume fewer fruits and vegetables and more energy dense snacks, drinks and fast food [33,34]. A number of studies showed that SA children receive higher percentage of their energy from fats and have a higher total energy intake [35-37]. There was no difference

Table 3. HOMA-IR values of the groups (median + IQR)

	Group 1 SA (+) ADHD (+)	Group 2 SA (-) ADHD (+)	Group 3 SA (-) ADHD (-)	p
HOMA-IR	2.66 (1.64-5.06)	2.14 (1.21-3.27)	3.45 (1.72-5.62)	0.081

HOMA-IR: Homeostasis model assessment for insulin resistance, IQR: Interquartile range, SA: Screen addiction, ADHD: Attention-deficit hyperactivity disorder, Data were presented as median (25-75th percentiles), Kruskal-Wallis test

in terms of dietary habits between groups in this study. As a limitation, we did not analyze the dietary lists of the patients in terms of their fruit, vegetable and snack contents.

Inheritance, metabolism, eating habits and physical activity affect the body fat composition. It has been observed in reviews that body fat composition of the children is affected by gender and age [38]. In a national study, relatively higher body fat composition was found in girls and at postpubertal ages which was also positively corelated with weight. Must and Tybor [39] showed that sportive activities decreases the body fat mass. Similarly, in numerous studies no association can be found with screen time and body fat mass [40-45]. In our study, body fat composition was significantly higher in obese group as expected but there was no significantly difference between three groups. Our results have shown that SA and ADHD does not affect the body fat composition which can be also related to the similar number of obese children in the groups.

HOMA-IR values increase in line with obesity and sedentary lifestyle [46]. Our results confirm the presence of higher HOMA-IR values in the obese group. To our knowledge, the relation between SA and IR has not been investigated yet, but a study about screen time and HOMA-IR showed increases in HOMA-IR values with screen time [2]. While the comorbidity between ADHD and obesity has been extensively studied [47-49], the possible association with IR has received less attention. We could not find any affect of SA and ADHD on HOMA-IR which can be due to the differences between subgroups in terms of number/gender/pubertal stages or similar BMI values between the groups.

Study Limitations

Our study has some limitations. Firstly, this study included a small number of subjects and therefore our results require confirmation in a larger cohort. Secondly, HOMA-IR levels may vary due to gender differences between the groups. Likewise, pubertal stages of the subjects may affect the HOMA-IR levels but we did not evaluate the pubertal stages of the study participants. Thirdly, in our study there was similar number of obese children in the groups. The other limitation was that HOMA-IR values were used as surrogate measures of insülin resistance Still, though impractical more sensitive measures of insülin resistance could be used instead.

CONCLUSION

We did not find any association between SA and IR. Also dependent factors were similar between groups. Further studies are needed to determine the effects of SA on obesity.

Ethics

Ethics Committee Approval: The study was approved by the Ege University Faculty of Medicine Ethics Committee (approval number: 13-2/47, date: 20.02.2013).

Informed Consent: Written informed consent was obtained from all participants and their parents.

Peer-review: Externally peer-reviewed.

Author Contributions

Surgical and Medical Practices: Ö.K., E.Ş., S.Ö., Concept: Ö.K., Ş.D., B.Ö., Design: Ö.K., Ş.D., B.Ö., Data Collection and/or Processing: Ö.K., E.Ş., Analysis and/or Interpretation: Ö.K., Y.A.A., S.Ö., D.G., Literature Search: Ö.K., Ş.D., D.G., Writing: Ö.K., Ş.D., D.G.

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Original Article

Evaluation of the Genetically Diagnosed Mitochondrial Disease Cases with Neuromuscular Involvement

Nöromusküler Tutulum Gösteren Genetik Tanılı Mitokondriyal Hastalık Tanılı Olgularımızın Değerlendirilmesi

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ABSTRACT

Objective: Due to the fact that mitochondrial diseases can involve different organ systems, neuromuscular involvement is frequently observed and has a substantial place in clinical practice. In this study, the clinical, radiological, electrophysiological and imaging features of the patients with mitochondrial disease with neuromuscular involvement were investigated.

Method: The clinical, radiological and genetic features of 16 patients with genetically diagnosed mitochondrial disease followed in the Departments of Pediatric Neurology and Pediatric Metabolism and Nutrition in Dokuz Eylül University Faculty of Medicine were retrospectively evaluated.

Results: The cases were between 3-17 years of age (mean: 8.8±4.2 years). 44% (n=7) of the cases were male. Clinical findings started at a mean age of 30 months (2-132 months). There was consanguineous marriage in 81% (n=13) of the cases. Leigh syndrome (LS), Charcot-Marie-Tooth disease (CMT) 2A, and CMT disease-axonal-type 2K were diagnosed in 5, 4, 2 cases, respectively. Alpers syndrome, combined oxidative phosphorylation deficiency-13, megalencephaly without cystic leukoencephalopathy, mt.9804G>A and m.11696G>A mutations which could not be phenotyped syndromicly were detected in one case each. SURF1 (n=2), MTATP6 (n=2) and PDSS2 (n=1) mutations were found in the patients with LS. NARS2, PNPT1, and RNASET2 mutations were found in the patients with Alpers syndrome, combined oxidative phosphorylation deficiency-13, cystic leukoencephalopathy without megalencephaly, respectively. Muscle weakness, developmental delay and skeletal deformity were the most common findings. The most common finding in brain magnetic resonance imaging was increased T2 signal in bilateral basal ganglia.

Conclusion: The most common genetically diagnosed mitochondrial disease was LS, the most common mutation was MFN2, and the most common clinical finding was muscle weakness.

Keywords: Mitochondrial diseases, Leigh disease, Charcot-Marie-Tooth disease, muscle weakness, genetics

ÖZ

Amaç: Mitokondriyal hastalıklar farklı organ sistemlerini tutabilmesine bağlı olarak nöromusküler tutulumlar sık gözlenmekte olup klinik pratikte aşamasında önemli yere sahiptir. Bu çalışmada nöromusküler tutulum gösteren mitokondriyal hastalık tanılı olguların klinik, radyolojik, elektrofizyolojik ve görüntüleme özelliklerinin incelenmesi amaçlandı.

Yöntem: Dokuz Eylül Üniversitesi Tıp Fakültesi, Çocuk Nörolojisi ve Çocuk Metabolizma ve Beslenme Bölümleri'nde takipli genetik tanılı mitokondriyal hastalığı olup genetik tanı almış 16 hastanın klinik, radyolojik ve genetik özellikleri retrospektif değerlendirildi.

Bulgular: Olgular 3-17 yaş aralığındaydı (ortalama: 8,8±4,2 yıl). Olguların %44'ü (n=7) erkekti. Klinik bulgular ortalama 30 aylıkken başlamıştı (2-132 ay). Olguların %81'inde (n=13) akraba evliliği vardı. Olguların 5 tanesi Leigh sendromu (LS), 4 tanesi Charcot-Marie-Tooth hastalığı (CMT) 2A, 2 tanesi CMT hastalığı-aksonal-tip 2K, 1 tanesi Alpers sendromu, 1 tanesi kombine oksidatif fosforilasyon eksikliği-13, 1 tanesi megalensefali eşlik etmeyen kistik lökoensefalopati tanısı almıştı ve birer olguda sendromik olarak fenotiplendirelemeyen mt.9804G>A ve m.11696G>A mutasyonu tespit edildi. LS alan iki olguda SURF1, iki olguda MTATP6, bir olguda PDSS2 mutasyonu saptandı. Alpers sendromu tanısı alan olguda NARS2, kombine oksidatif fosforilasyon eksikliği-13 tanısı alan

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olguda PNPT1, megalensefali eşlik etmeyen kistik lökoensefalopati tanısı alan olguda RNASET2 mutasyonu saptandı. Kas güçsüzlüğü, gelişimsel gerilik ve iskelet deformitesi en sık saptanan bulgulardı. Beyin manyetik rezonans görüntüleme incelemesinde en sık saptanan bulgu bilateral bazal gangliyonlarda T2 sinyal artışıydı.

Sonuç: Genetik tanılı mitokondriyal hastalıklarda en sık görüleni LS, en sık saptanan mutasyon MFN2, en sık görülen klinik bulgu ise kas güçsüzlüğüdür.

Anahtar kelimeler: Mitokondriyal hastalıklar, Leigh hastalığı, Charcot-Marie-Tooth hastalığı, kas güçsüzlüğü, genetik

INTRODUCTION

Mitochondrial diseases (MDs) are the most common neurometabolic disease group with an estimated incidence of 1/5,000 [1]. This incidence is conjectured to be higher by virtue of the challenges in diagnosis [2-4]. About 5% of the human genome is thought to be in the mitochondria [5]. Especially thanks to the frequent use of genetic techniques such as next-generation sequencing, more than 250 genes associated with MD have been described in the literature so far [6-13]. MDs are inherited in nuclear DNA (nDNA) or mitochondrial DNA (mtDNA) [14,15]. Inheritance of MD may be autosomal or X-linked for nDNA, whereas maternal inheritance is true for mtDNA. Sporadic cases due to *de novo* mutations have been also reported [16].

MDs have many diverse clinical manifestations as they can involve different organ systems and can occur at any age, and are classified in two groups as primary mitochondrial diseases (PMDs) and secondary mitochondrial dysfunctions (SMDs). PMDs are caused by mutations in the mtDNA and/or nDNA genes encoding electron transport chain proteins. Leigh syndrome (LS), Alpers-Huttenlocher syndrome, MEGDEL syndrome (3 methylglutaconic aciduria, deafness, encephalopathy, Leigh-like syndrome), Pearson syndrome, Sengers syndrome, congenital lactic acidosis, mitochondrial neurogastrointestinal encephalomyopathy syndrome, Kearns-Sayre syndrome, mitochondrial myopathy, encephalopathy, lactic acidosis, stroke-like attacks syndrome, myoclonic epilepsy with irregular red fibers, neurogenic muscle weakness, ataxia, retinitis pigmentosa are common PMDs. SMD basically encompasses all mitochondrial disorders that are not PMD. Although PMDs are genetically based diseases, SMD can be inherited or acquired. Many myopathies and muscular dystrophies also cause SMD over time as the disease progresses. Examples include spinal muscular atrophy, limb-girdle muscular dystrophy, Bethlem myopathy, Charcot-Marie-Tooth disease, (CMT) and inflammatory myopathies [17].

In this study, the demographic, clinical, radiological, electrophysiological and genetic features of the cases with mitochondrial disease that were followed up in the department of pediatric neurology in Dokuz Eylül University Faculty of Medicine were analyzed.

MATERIALS and METHODS

Archive records of all cases followed up in pediatric neurology and pediatric metabolism and nutrition departments in Dokuz Eylül University Faculty of Medicine between November 2012 and November 2020 were reviewed retrospectively, and 16 cases of genetically diagnosed MDs with neuromuscular involvement were included. The cases without neuromuscular involvement and/or the diagnosis of mitochondrial disease which was not proven by genetic tests were excluded. Demographic, clinical, radiological, electrophysiological and genetic findings of the cases were analyzed with the information obtained from patient files and system data.

Ethical Approval

The present study was conducted in accordance with the 1964 Declaration of Helsinki and approved by the Ethics Committee of Dokuz Eylül University Faculty of Medicine (approval number: 2021/14-59, date: 06.05.2021). Informed consent was obtained from patients and/or parents or legal guardians of the patients before their enrollment in the study.

Statistical Analysis

Statistical analysis was performed using the IBM SPSS Statistics for Windows version 22.0 (IBM Corp., Armonk, NY, USA). The normality of distribution of numerical variables was evaluated using the Kolmogorov-Smirnov test. The numerical variables were expressed as median [minimum (min)-maximum (max)] and categorical variables as numbers and percentages (%).

RESULTS

Demographic Features and Results of Genetic Evaluations

The mean age of 16 patients (7 males, 44%) included in the study was 8.8±4.2 years (minimum-maximum: 3-17 years). Clinical symptoms started at a mean age of 30 months (2-132 months). Consanguineous marriage was present in 81% (n=13) of the cases. The diagnoses of the cases were LS (n=5), CMT disease 2A (CMT2A)

(n=4), CMT disease axonal-type 2K (CMT2K) (n=1), Alpers syndrome (n=1), combined oxidative phosphorylation deficiency-13 (n=1), cystic leukoencephalopathy without megalencephaly (n=1). Furthermore, in two cases *mt.9804G>A* and *m.11696G>A* mutations that could not be syndromically phenotyped were detected. While nDNA mutation was detected in 12, and mutation on mtDNA was observed in the remaining 4 cases. SURF1 (n=2), *MTATP6* (n=2), *PDSS2* (n=1) mutations were detected in cases with LS. *MFN2* mutation was found in all four patients with CMT disease-2A, and *GDAP1* mutation in two patients with CMT disease-axonal-type 2K. *NARS2, PNPT1,* and *RNASET2* mutations were detected in the patients with Alpers syndrome, combined oxidative phosphorylation deficiency-13, and cystic leukoencephalopathy without megalencephaly (Table 1).

Clinical Findings

The most common clinical findings were muscle weakness (n=11, 68.7%), developmental delay (n=8, 50%), skeletal deformity (n=8, 50%), mental regression (n=6, 37.5%). ataxia (n=5, 31.2%), and spasticity (n=5, 31.2%). All five cases with LS, all two cases with CMT disease-

Table 1. Demographic characteristics, diagnoses, and mutations of the cases

	Syndrome	Age of onset (month)	Gender	Consanguineous marriage	Gene	Mutation site	Variant
Case 1	Leigh syndrome	6	Male	+	*SURF1*	nDNA	*c.484G>A*
Case 2	Leigh syndrome	18	Female	-	*SURF1*	nDNA	*c.845_846delCT*
Case 3	Charcot-Marie-Tooth disease-2A (CMT2A)	30	Male	+	*MFN2*	nDNA	*c.280C>T*
Case 4	Charcot-Marie-Tooth disease-2A (CMT2A)	12	Female	+	*MFN2*	nDNA	*c.296T>G*
Case 5	Charcot-Marie-Tooth disease-2A (CMT2A)	12	Female	+	*MFN2*	nDNA	*c.296T>G*
Case 6	Charcot-Marie-Tooth disease-2A (CMT2A)	56	Female	+	*MFN2*	nDNA	*c.404G>A*
Case 7	Charcot-Marie-Tooth disease, axonal, type 2K	18	Female	+	*GDAP1*	nDNA	*c.786delG*
Case 8	Charcot-Marie-Tooth disease, axonal, type 2K	36	Female	+	*GDAP1*	nDNA	*c.(695_1077)del*
Case 9	Leigh syndrome	12	Female	-	*MTATP6*	mtDNA	*m.8993T>G*
Case 10	*m.11696G>A* mutation (without a specific certain phenotype)	96	Male	+	*MTND4*	mtDNA	*m.11696G>A*
Case 11	Alpers syndrome	2	Male	+	*NARS2*	nDNA	*c.1096G>A*
Case 12	Leigh syndrome	132	Female	+	*PDSS2*	nDNA	*c.868G>A*
Case 13	Combined oxidative phosphorylation deficiency 13	4	Male	+	*PNPT1*	nDNA	*c.1576_1578dupGAT*
Case 14	*mt.9804G>A* mutation (without a specific certain phenotype)	42	Male	+	*mt.9804G>A*	mtDNA	*mt.980AG>A*
Case 15	Cystic leukoencephalopathy without megalencephaly	6	Female	+	*RNA SET2*	nDNA	*c.194A>G*
Case 16	Leigh syndrome	9	Male	-	*MTATP6*	mtDNA	*m.8993T>C*

nDNA: Nuclear deoxyribonucleic acid, mtDNA: Mitochondrial deoxyribonucleic acid

axonal-type 2K, one of the cases with CMTdisease-2A, the cases with Alpers syndrome, and those with *mt.9804G>A* and *m.11696G>A* mutations had muscle weakness. Four cases with LS and cases with Alpers syndrome, combined oxidative phosphorylation deficiency-13, *mt.9804G>A* mutation, cystic leukoencephalopathy without megalencephaly had developmental delay. Skeletal deformity was observed in all four patients diagnosed with CMT disease-2A, and in patients with *m.11696G>A* mutation and combined oxidative phosphorylation deficiency-13. Three of the cases with mental regression were among the patients with LS. Other mental regression cases had combined oxidative phosphorylation deficiency-13, *mt.9804G>A* mutation, and cystic leukoencephalopathy without megalencephaly. Ataxia was seen in two patients with CMT disease-axonal-type 2C, in two patients with LS and the patient with Alpers syndrome. Three patients diagnosed with LS had spasticity which was also present in patients with combined oxidative phosphorylation deficiency-13 and cystic leukoencephalopathy without megalencephaly. Hearing loss, cardiac involvements such as restrictive cardiomyopathy, left ventricular hypertrophy and/or dysfunction, renal involvement, epilepsy, recurrent respiratory failure, hypertrichosis and ocular involvements such as ptosis, nystagmus, strabismus, and optic atrophy were other clinical findings (Table 2).

Radiological Findings

While brain magnetic resonance imaging (MRI) results could not be obtained in four (25%) cases, 12 (75%) patients were examined by brain MRI which yielded normal signs in four (25%) of them. The most common abnormality was increased T2 signal intensity in bilateral basal ganglia. To assess other accompanying clinical findings, seven cases (43.7%) were evaluated with spinal MRI which was normal in five (31.2%) of them. Spinal MRI revealed abnormality in one of the cases with LS (increased T2 signal intensity in cervical spinal cord) and CMT disease-2A (S1-2 transitional vertebra anomaly). Magnetic resonance spectroscopy (MRS) was performed

Table 2. Symptoms and signs of the cases

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
Syndrome	**Leigh syndrome**	**Leigh syndrome**	**CMT2A**	**CMT2A**	**CMT2A**	**CMT2A**	**Charcot-Marie-Tooth disease, axonal, tip 2K**	**Charcot-Marie-Tooth disease, axonal, tip 2K**	**Leigh syndrome**
Muscle weakness	+	+	+	-	-	-	+	+	+
Seizure	-	-	-	-	-	-	-	-	+
Swallowing dysfunction	-	-	-	-	-	-	-	-	+
Mental regression	+	+	-	-	-	-	-	-	+
Developmental delay	+	+	-	-	-	-	-	-	+
Dystonia	-	-	-	-	-	-	-	-	-
Spasticity	+	+	-	-	-	-	-	-	+
Recurrent	-	+	-	-	-	-	-	-	-
Skeletal deformity	+	+	+	+	+	+	-	-	-
Ptosis	-	+	-	-	-	-	-	-	-
Nystagmus	NA	NA	NA	NA	NA	NA	NA	NA	NA
Strabismus	-	-	-	-	-	-	-	-	-
Hypertrichosis	-	-	-	-	-	-	-	-	-
Ataxia	+	-	-	-	-	-	+	+	-
Hearing loss	-	-	NA	NA	NA	NA	-	NA	-
Renal involvement	-	-	-	-	-	-	-	-	-

CMT2A: Charcot-Marie-Tooth disease-2A

Table 2. continued

	Case 10	Case 11	Case 12	Case 13	Case 14	Case 15	Case 16
Syndrome	**m.11696G>A mutation**	**Alpers syndrome**	**Leigh syndrome**	**Combined oxidative phosphorylation deficiency 13**	**mt.9804G>A mutation**	**Cystic leukoencephalopathy without megalencephaly**	**Leigh syndrome**
Muscle weakness	+	+	+	-	+	-	+
Seizure	-	-	-	-	-	+	-
Swallowing dysfunction	-	-	-	-	NA	-	-
Mental regression	-	-	-	+	+	+	-
Developmental delay	-	+	-	+	+	+	+
Dystonia	-	-	-	-	-	-	-
Spasticity	-	-	-	+	-	+	-
Recurrent	-	-	-	-	-	-	+
Skeletal deformity	+	-	-	+	NA	-	-
Ptosis	-	-	-	-	-	-	-
Nystagmus	NA	+	-	NA	-	-	-
Strabismus	-	NA	-	-	+	-	-
Hypertrichosis	-	NA	-	-	+	-	-
Ataxia	-	+	-	-	-	-	-
Hearing loss	NA	+	+	-	+	NA	-
Renal involvement	-	-	+ (CRF)	-	+ (CRF)	NA	-

CMT2A: Charcot-Marie-Tooth disease-2A

in eight cases (50%), and normal findings were detected in 3 (18.7%), lactate peaks in 4 (25%), and both lactate and lipid peaks in 1 (6.3%) patient. Three (18.7%) cases with lactate peaks had LS and one (6.3%) patient had Alpers syndrome. The case with LS had both lactate and lipid peaks (Table 3).

Electrophysiology

Electroencephalography (EEG) was performed in six (37.5%) cases in that the most common abnormality was generalized epileptic discharges. While EEG examination was normal in one case, focal epileptic discharge and encephalopathy were observed in one case each. However, most of these cases did not experience clinical seizures and only two of them were diagnosed with epilepsy. Ten patients (62.5%) were evaluated with electromyography which revealed sensorimotor polyneuropathy in eight cases and myopathic changes in one. One patient had normal electromyographic findings.

Other Diagnostic Approaches

Muscle biopsy was performed in five cases (31.2%) which yielded normal results in three patients, while complex I, II, III, IV deficiency was detected in one LS case. Two cases with normal biopsy findings had CMT disease-2A and one patient had LS. Mitochondrial staining could not be performed in one muscle biopsy specimen due to inappropriate sample collection. Elevated serum lactate (>2 mmol/L) levels were detected in eight patients including cases with LS (n=4), and elevated serum lactate levels were observed in cases with CMT disease-axonal-type 2C (n=1), combined oxidative phosphorylation deficiency (n=1), *m.11696G>A* (n=1) and *mt.9804G>A* mutations (n=1). A slight increase in creatine kinase (CK) values was observed in a case with LS (CK: 225 U/L) (n=1), and another one with *mt.9804G>A* mutation (CK: 219 U/L) (n=1) (Table 4).

Table 3. Magnetic resonance imaging results of the cases

	Syndrome	Brain MRI	Spinal MRI	MRS
Case 1	Leigh syndrome	Signal increase in bilateral basal ganglia	NA	Lactate and lipid peak
Case 2	Leigh syndrome	Signal increase in bilateral mesencephalon and bulbus	T2 hyperintensity in the cervical spinal cord	Lactate peak
Case 3	CMT2A	Normal	S1-2 transitional vertebral anomaly	NA
Case 4	CMT2A	NA	NA	NA
Case 5	CMT2A	NA	NA	NA
Case 6	CMT2A	Normal	Normal	NA
Case 7	Charcot-Marie-Tooth disease, axonal, type 2K	Normal	Normal	NA
Case 8	Charcot-Marie-Tooth disease, axonal, type 2K	NA	NA	NA
Case 9	Leigh syndrome	Bilateral signal increase in basal ganglia	Normal	Lactate peak
Case 10	*m.11696G>A* mutation	Normal	NA	NA
Case 11	Alpers syndrome	Leukodystrophy pattern in cerebral white matter, involvement in brainstem and bilateral middle cerebellar peduncles	NA	Lactate peak
Case 12	Leigh syndrome	Bilateral signal increase in cerebral and cerebellar white matter	Normal	Lactate peak
Case 13	Combined oxidative phosphorylation deficiency 13	Bilateral signal increase in cerebral white matter, thin corpus callosum, hypomyelination of posterior limb of capsula interna	Normal	Normal
Case 14	*mt.9804G>A* mutation	Thin corpus callosum, posterior cerebral periventricular gliotic changes	NA	Normal
Case 15	Cystic leukoencephalopathy without megalencephaly	Cerebellar atrophy, bilateral signal increase in the cerebral hemispheres	NA	Normal
Case 16	Leigh syndrome	NA	NA	NA

MRI: Magnetic resonance imaging, MRS: Magnetic Resonance Spectroscopy, NA: Not available, CMT2A: Charcot-Marie-Tooth disease-2A

DISCUSSION

Except for erythrocytes, every cell in the human body is dependent on mitochondria to function properly. Thence, mitochondrial dysfunctions give rise to multisystem involvement, especially in brain, heart and muscle tissues which all are in a bind for high energy levels [18]. A wide range of findings such as muscle weakness, developmental delay, mental regression, ataxia, spasticity, hearing loss, cardiological and renal involvements, seizures, recurrent respiratory failure, swallowing dysfunction, ptosis, nystagmus, strabismus were observed in this study.

Table 4. Results of the laboratory evaluation, electrophysiological study and muscle biopsy of the cases

	Syndrome	Lactate	EEG	EMG	ECHO	ECG	Muscle biopsy
Case 1	Leigh syndrome	Elevated	NA	Sensorimotor polyneuropathy	AF	Normal	NA
Case 2	Leigh syndrome	Elevated	NA	Sensorimotor polyneuropathy	MF, PFO	Normal	Inappropriate sampling
Case 3	CMT2A	NA	NA	Sensory loss in the upper extremities and axonal loss in the lower extremities	Normal	NA	NA
Case 4	CMT2A	NA	NA	Motor-predominant sensorimotor polyneuropathy in the lower extremities	NA	NA	Normal
Case 5	CMT2A	NA	NA	Motor-predominant sensorimotor polyneuropathy in the lower extremities	NA	NA	Normal
Case 6	CMT2A	NA	NA	Sensorimotor polyneuropathy	Normal	NA	NA
Case 7	Charcot-Marie-Tooth disease, axonal, type 2K	Elevated	NA	Axonal-predominant sensorimotor polyneuropathy	Normal	Normal	NA
Case 8	Charcot-Marie-Tooth disease, axonal, type 2K	NA	NA	Axonal-predominant sensorimotor polyneuropathy	NA	NA	NA
Case 9	Leigh syndrome	Elevated	Generalized	NA	Normal	Normal	Normal
Case 10	m.11696G>A mutation (without a specific certain phenotype)	Elevated	Generalized	Myopathic changes	NA	NA	NA
Case 11	Alpers syndrome	Normal	NA	NA	Normal	Normal	NA
Case 12	Leigh syndrome	Elevated	Encephalopathy	NA	HCMP, LVD (mild), MF, AS, AF	NA	NA
Case 13	Combined oxidative phosphorylation deficiency 13	Elevated	Normal	NA	Normal	Normal	NA
Case 14	*mt.9804G>A* mutation (without a specific certain phenotype)	Elevated	NA	Normal	LVH (mild), MF	Normal	NA
Case 15	Cystic leukoencephalopathy without megalencephaly	Normal	Focal	NA	MF	Normal	NA
Case 16	Leigh syndrome	Normal	Generalized	NA	RCMP, LVD (mild), MF, TF	NA	Complex 1, 2, 3, 4 deficiency

EEG: Electroencephalography, EMG: Electromyography, ECHO: Echocardiography, ECG: Electrocardiography, NA: Not available, AF: Aortic valve failure, MF: Mitral valve failure, PFO: Patent foramen ovale, HCMP: Hypertrophic cardiomyopathy, LVD: Left ventricular dysfunction, AS: Aortic valve stenosis, LVH: Left ventricular hypertrophy, RCMP: Restrictive cardiomyopathy, TY: Tricuspid valve failure, CMT2A: Charcot-Marie-Tooth disease-2A

Mitochondria need about 1500 proteins to function properly [19,20]. Of which, 13 are encoded by mtDNA and the rest by nDNA. Oxidative phosphorylation occurs by virtue of electron transport through the mitochondrial respiratory chain. There are four complexes [complex I (NADH: ubiquinone oxidoreductase), complex II (succinate dehydrogenase), complex III (Coenzyme Q-cytochrome c reductase), complex IV (cytochrome c oxidase)] and two mobile electron carriers [ubiquinone (coenzyme Q10) and cytochrome c] in the mitochondrial respiratory chain. The proton gradient formed by the mitochondrial respiratory chain induces ATP production via complex V (ATP synthase) [21]. While the coding of Complex II is entirely under the control of nDNA, both nDNA and mtDNA play a role in the coding of other structures involved in the respiratory chain [22]. A Poland cohort study have shown that pediatric MDs are caused by nDNA and mtDNA mutations at the rates of 91% and 9%, respectively [23]. In a study conducted in China, patients diagnosed with pediatric MDs were evaluated, and mtDNA and nDNA mutations were found to be responsible for 67.2%, and 32.8% of the cases, respectively [24]. Another study in China revealed these rates as 65% for mtDNA and 35% for nDNA mutations [25]. In our study, nDNA and mtDNA mutation rates were found to be 75% and 25%, respectively.

LS is the most common PMD in childhood [26]. In our study, similar to the literature, LS was the most common diagnosis with a rate of 31.2% in the PMD cases. Hu et al. [24] reported that LS was found to be the third most common diagnosis with a rate of 25.6% in 58 patients with pediatric MDs and the most common diagnoses were mitochondrial myopathy (33.3%) and MELAS (28.2%). Although the first signs and/or symptoms of LS become manifest usually between 3-12 months, in the literature onset times varying from birth to adult life have been reported [27,28]. The age of the onset of LS findings was between 6-132 months (mean 35.4 months) in our study. In LS, which presents a wide spectrum of clinical features such as global developmental delay or regression, hypotonia, dystonia, ataxia, ophthalmological abnormalities like nystagmus or optic atrophy [29], the most common symptoms in our study were muscle weakness (n=5, 100%), developmental delay (n=4, 80%), mental regression (n=3,60%). Ataxia (n=2,40%), cardiac involvement (n=2,40%), ptosis (n=1,20%), optic atrophy (n=1, 20%), swallowing dysfunction (n: 1, %) 20), hearing loss (n=1, 20%), renal involvement (n=1, 20%), respiratory failure (n=1, 20%) were other clinical features in LS. Ma et al. [30] reported that the most common findings in 75 patients with LS in China were motor retardation (55%), muscle weakness (29%), and epilepsy (25%). In the same study, ataxia was found in 11%, swallowing dysfunction in 7%, and ptosis in 4% of their patients. In a multicenter study of Sofou et al. [27], the most common clinical findings in LS cases were abnormal motor findings (99.2%), abnormal ocular findings (60.8%), and feeding difficulties (45.4%). In terms of abnormal motor findings, hypotonia with a rate of 74.6% was the most common feature, while ataxia, and muscle weakness were found at a incidence rates of 34.6%, and 26.2%, respectively. Among abnormal ocular findings, nystagmus was the most common finding (23.8%), as optic atrophy was observed in 14.6% and ptosis in 13.1% of the cases. Rates of the respiratory failure, hearing loss, cardiac, and renal involvement were 37.7%, 19.2%, 17.7, and 5.4%, respectively [27]. The low number of cases in our study and the diversity of underlying genetic factors in the cohorts can be shown as the reason for our diverse incidence rates compared to the literature. T2-weighted hyperintensities in the basal ganglia and/or brainstem are classic findings on brain imaging in LS [29]. This radiological finding was also obtained in 60% of our cases, and increased signal intensities in cerebral-cerebellar white matter were observed in one case. Similar to the clinical features, LS is a heterogeneous disease from a genetic perspective, as well. While more than 75 genes associated with LS have been identified 17 new genes have been reported in a recent study [29,31]. In our study, SURF1 (n=2, 12.5%), MTATP6 (n=2, 12.5%), *PDSS2* (n=1, 6.2%) mutations were found in cases diagnosed with LS. Li et al. [32] found SURF1 mutation in 12 of 178 cases with suspected mitochondrial disease in that one of them was later diagnosed with Leigh-like syndrome and the others with LS. In the genetic analysis of 64 cases clinically diagnosed with LS in South Korea, 3.1% of the cases had SURF1 and 7.8% of them MTATP6 mutations [31]. In the literature, MTATP6 mutation has been found in approximately 10% of LS cases [29]. López et al. [33] reported LS due to *PDSS2* mutation in a patient who presented with hypotonia and neonatal pneumonia, followed up with epilepsy, swallowing dysfunction and nephrotic syndrome, and died at the age of 8 months due to status epilepticus. The findings of our case with *PDSS* mutation started at a later age (132 months) compared to the literature, and muscle weakness, ataxia, hearing loss, nephrotic syndrome and chronic kidney failure were observed during the clinical course of the disease. Although in the case reported by López et al. [33], typically increased signal intensity in basal ganglia consistent with LS was

found, in our case increased signal intensity in bilateral cerebral and cerebellar white matter in brain MRI and a lactate peak in MRS were observed.

Several types of CMT with SMDs have been described in the literature including CMT2A and CMT2K, in which mutations in *MFN2* and *GDAP1* genes were causative factors [17]. While all four of our six cases with CMT disease-2A had *MFN2* mutation, *GDAP1* mutation was found in two cases with CMT disease-axonal-type 2K. In a multicenter study on the genetic etiology of CMT disease, after *PMP22* deletion/duplication was excluded in typical demyelinating CMT cases, the most common mutations revealed by next -generation sequencing were *GJB1* (5.5%), *SH3TC2* (3.6%), *MFN2* (3%). In the same study, *GDAP1* mutation was found with a rate of 1.8% [34].

CMT type 2A, the most common axonal hereditary polyneuropathy with *MFN2* mutations, has been typically associated with distal extremity muscle weakness, atrophy, and unlike other CMTs; optic atrophy [35]. In our study, muscle weakness was found in 25% of the cases with CMT2A. Although visual impairment has been reported in approximately 20% of these cases in the literature, in our study visual signs/symptoms were not observed in this particular disease [35]. According to the age of disease onset, CMT2A is divided into two groups as early (<10 years) and late- onset (>10 years) disease. Early- onset disease is associated with more severe clinical findings and earlier loss of ambulation. However, in some reported cases any correlation could not be found between the age of disease onset and its severity [35]. In support of the literature, in our study early-onset CMT2A cases aged between 12 and 56 months. However, due to the lack of long follow-up periods in our study, the relationship between the onset of the disease and its severity could not be demonstrated.

CONCLUSION

LS was the most common genetically diagnosed PMDs, while CMT2A was the most common SMDs. MDs, which can progress with multisystem involvements and have many various clinical presentations, should be considered in the differential diagnosis of the cases with neuromuscular involvement. Diagnosis of MDs remains challenging in many cases, and detailed evaluation of clinical findings, biochemical screening, histopathological studies, neuroimaging and molecular genetic testing play a substantial role in the diagnostic process.

Ethics

Ethics Committee Approval: The present study was conducted in accordance with the 1964 Declaration of Helsinki and approved by the Ethics Committee of Dokuz Eylül University Faculty of Medicine (approval number: 2021/14-59, date: 06.05.2021).

Informed Consent: Informed consent was obtained from patients and/or parents or legal guardians of the patients before their enrollment in the study.

Peer-review: Externally peer-reviewed.

Author Contributions

Surgical and Medical Practices: Ç.G., C.P., P.E., G.S.U., A.S.H.K., Z.A.G., P.T.K., N.A., U.Y., Concept: Ç.G., C.P., P.E., G.S.U., A.S.H.K., Z.A.G., P.T.K., N.A., U.Y. Design: Ç.G., C.P., P.E., G.S.U., A.S.H.K., Z.A.G., P.T.K., N.A., U.Y., Data Collection and/or Processing: Ç.G., C.P., P.E., G.S.U., A.S.H.K., Z.A.G., P.T.K., N.A., U.Y., Analysis and/or Interpretation: Ç.G., C.P., P.E., G.S.U., A.S.H.K., Z.A.G., P.T.K., N.A., U.Y., Literature Search: Ç.G., U.Y., Writing: Ç.G.

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Original Article

Comorbid Psychiatric Disorders and Related Sociodemographic Factors in Adolescents with Attention-Deficit Hyperactivity Disorder

Dikkat Eksikliği Hiperaktivite Bozukluğu Olan Ergenlerde Eşlik Eden Psikiyatrik Bozukluklar ve İlişkili Sosyodemografik Faktörler

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ABSTRACT

Objective: Attention-deficit hyperactivity disorder (ADHD) disorder is a neuropsychiatric disorder that begins in early stages of life and has a lifelong effect. Previous studies have found that 50-70% of children and adolescents with ADHD have comorbid psychiatric disorders. The aim of this study is to identify comorbid psychiatric disorders in adolescents with ADHD and to compare the sociodemographic characteristics of ADHD cases with and without psychiatric comorbidity.

Method: This study was conducted with 105 adolescents with ADHD. The Schedule for Affective Disorders and Schizophrenia for School-age Children-present and Lifetime-Turkish version was used to evaluate ADHD and comorbid psychiatric disorders.

Results: The study was completed with 73 male and 32 female adolescents. The mean age of the participants was 13.75±1.45 years. It was determined that 41 cases (39%) had at least one comorbid psychiatric disorder. The most common comorbid psychiatric disorders were conduct disorder (14.3%), specific learning disorder (8.6%), obsessive compulsive disorder (3.8%) and elimination disorders (3.8%). While the prevalence of comorbid psychiatric disorders was compared according to sociodemographic characteristics, it was found that the prevalence of comobidity was significantly higher in adolescents with ADHD living in families with low socioeconomic levels.

Conclusion: The findings of current study showed that adolescents with ADHD had a high rate of comorbid psychiatric disorders. We are opinion that presence of comorbid psychiatric disorder in ADHD will have negative effects on both ADHD and comorbid psychiatric problems. Therefore, all adolescents with ADHD should be evaluated for comorbid psychiatric disorders.

Keywords: Adolescents, attention deficit/hyperactivity disorder, comorbidity, psychiatric disorders

ÖZ

Amaç: Dikkat eksikliği/hiperaktivite bozukluğu (DEHB), yaşamın erken dönemlerinde başlayan ve etkisi yaşam boyu sürebilen nöropsikiyatrik bir bozukluktur. Önceki çalışmalarda, DEHB olan çocuk ve ergenlerin %50-70'inin komorbid psikiyatrik bozukluklara sahip olduğu bulunmuştur. Bu çalışmanın amacı, DEHB olan ergenlerde eşlik eden psikiyatrik bozuklukları belirlemek ve komorbid psikiyatrik bozukluğu olan ve olmayan DEHB olgularının sosyodemografik özelliklerini karşılaştırmaktır.

Yöntem: Bu çalışma DEHB tanısı alan 105 ergen ile yapılmıştır. DEHB ve eşlik eden psikiyatrik bozuklukları değerlendirmek için Okul Çağı Çocukları İçin Duygusal Bozukluklar ve Şizofreni Çizelgesi-Şu Anda ve Yaşam Boyu Türkçe versiyonu kullanılmıştır.

Bulgular: Çalışma, DEHB tanısı olan 73 erkek ve 32 kız ile tamamlandı. Katılımcıların yaş ortalaması 13,75±1,45 yıl idi. Kırk bir olguda (%39) en az bir ek psikiyatrik bozukluk olduğu belirlendi. En sık eşlik eden psikiyatrik bozukluklar, davranım bozukluğu (%14,3), özgül öğrenme bozukluğu (%8,6), obsesif kompulsif bozukluk (%3,8) ve eliminasyon bozuklukları (%3,8) idi. Komorbid psikiyatrik bozukluk sıklığı sosyodemografik özelliklere göre karşılaştırıldığında, sosyoekonomik düzeyi düşük ailelerde yaşayan DEHB'li ergenlerde komobidite sıklığının anlamlı derecede daha yüksek olduğu bulunmuştur.

Sonuç: Bu çalışma, DEHB olan ergenlerin yüksek oranda eşlik eden psikiyatrik bozukluklara sahip olduğunu göstermiştir. Hemen hemen her bozuklukta olduğu gibi DEHB'de de komorbid psikiyatrik bozukluk varlığının hem DEHB hem de komorbid psikiyatrik sorunlar üzerinde olumsuz etkileri olmaktadır. Bu nedenle, DEHB olan tüm ergenler komorbid psikiyatrik bozukluklar açısından değerlendirilmelidir.

Anahtar kelimeler: Ergen, dikkat eksikliği/hiperaktivite bozukluğu, psikiyatrik komorbidite

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INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by inattention and/or hyperactivity/impulsiveness [1]. It is one of the common psychiatric disorders of childhood and is becoming more prominent in children due to the increasing social and academic achievement demands of the families [2]. In population-based researches, the prevalence of ADHD is determined as approximately 5% in children and 2.5% in adults [2]. Studies show that the frequency is higher in boys than in girls, and this ratio varies between 2:1 and 9:1 depending on whether the sample consists of the general population or clinical population [3].

It is inevitable that a life-long psychiatric disorder will be accompanied by other psychiatric disorders. Previous studies have determined that only 13-32% of cases are diagnosed as non-comorbid ADHD, and many ADHD patients have comorbid psychiatric disorders [4]. The most common comorbid psychiatric disorders in children and adolescents with ADHD are disruptive behavioural disorders. It is stated that 30-40% of the children with ADHD have oppositional-defiant disorder, and 30-50% of them have conduct disorder (CD) [5]. The second most frequent comorbid psychiatric disorders are anxiety disorders and affective disorders. It is stated that approximately one third of ADHD patients have anxiety disorders [6]. In MTA study, it has been determined that 34% of cases with ADHD have anxiety disorders [7]. The prevalence of major depression in children with ADHD has been found as 6-30% [8]. In addition, ADHD may be comorbid with tic disorders, autism spectrum disorders, bipolar disorders, or other developmental disorders.

Comorbidity is common in psychiatric disorders [9]. However, the cause of the comorbidity is not fully known yet. There are various hypotheses regarding the development of comorbid psychiatric disorders in ADHD. It has been stated that emotion dysregulation in ADHD may be a predisposing factor to comorbidity with psychiatric disorders such as oppositional defiant disorder (ODD), anxiety, and depression [10]. Also, irritability may have a role in the development of comorbid mood and anxiety disorders, as well as reactive aggression [10]. Moreover, individual and familial sociodemographic characteristics have an effect on comorbidity. It has been found that the prevalence of psychopathology in the parents of children with ADHD and comorbid ODD/CD is higher than parents of children with pure ADHD [10]. It has been also stated that the families of those children have higher divorce rates and parent-child interactions are more negative [11,12]. Studies have also shown that there is a relationship between low socioeconomic status and comorbidity [13,14].

Comorbid psychiatric disorders affect the severity of impairment in mental health, quality of life, psychosocial adaptation, severity of symptoms and response to the treatment. Therefore, it is important to determine whether there are comorbid psychiatric disorders in patients diagnosed with ADHD or not. Previous studies investigating ADHD and comorbid psychiatric disorders have mostly been conducted in children and adolescents in a wide age range [4,13,15,16]. In studies, the prevalence of comorbid psychiatric disorder in adolescents with ADHD has been found as nearly 70-80% [17,18]. But, it can be said that studies on the adolescent age group are limited. Therefore, studies evaluating ADHD and psychiatric comorbidity in only adolescents are needed due to the characteristics of childhood periods. The aim of this study was to investigate the prevalence and distribution of comorbid psychiatric disorders in adolescents with ADHD and to evaluate their association with sociodemographic factors.

MATERIALS and METHODS

Participants and Psychiatric Evaluation

The participants consisted of adolescents who have applied to a child psychiatry clinic for the first time and were diagnosed with ADHD; adolescents who were followed up regularly for ADHD in this clinic; adolescents who were diagnosed with ADHD but refused to continue the treatment process, and adolescents who applied to our clinic while formerly being followed in another clinic. The records of the participants were reviewed retrospectively, and their clinical status at the application deadline was taken into account. Both adolescents who had never received ADHD treatment before and adolescents who had been followed up and treated with a diagnosis of ADHD were included in the study. It was conducted as a retrospective cross-sectional descriptive study.

Participants whose file information was complete and whose psychiatric examination was evaluated with the Schedule for Mood Disorders and Schizophrenia for School-Age Children-Now and Lifetime Version, Diagnostic and Statistical Manual of Mental Disorders (DSM-5) November 2016-Turkish Adaptation were included in the study. Adolescents with bipolar disorder,

autism spectrum disorder or mental retardation were excluded from the study. The study approved by the Fırat University Non-invasive Researches Ethic Committee (approval number: 2020/09-07, date: 12.06.2020) carried out its research in accordance with the principles of the Helsinki Declaration. Informed consent was not obtained from the participants because of retrospective design of the study.

Sociodemographic Data Form

Sociodemographic data form consists of eleven questions which was planned by the authors. The form included questions regarding gender, age, family structure, family income, and any psychiatric diseases of parents. Family income status was evaluated at three levels. The family income level that below the gross minimum wage was defined as low; between the gross minimum wage and twice the gross minimum wage was defined as medium, and over twice the gross minimum wage was defined as high.

Schedule for Affective Disorders and Schizophrenia for School-age Children-Present and Lifetime Version, DSM-5 November 2016-Turkish Adaptation (K-SADS-PL-DSM-5-T)

K-SADS-PL-DSM-5-T is a semi-structured interview schedule used to evaluate psychiatric disorders in children and adolescents based on DSM-5 diagnostic criteria. This interview schedule was firstly developed by Kaufman et al. [19] in 1997. It was updated again by Kaufman et al. [19], in 2016 according to DSM-5 diagnostic criteria. The validity and reliability of this semi-structured interview schedule was performed by Ünal et al. [20].

Statistical Analysis

Statistical analyses were carried out with SPSS version 22.0. Descriptive data related to the quantitative variables were given as the mean ± standard deviation, while data related to the qualitative variables were given as numbers and percentages. Pearson Fisher's, chi-square test was used for statistical analysis of qualitative variables. Values of $p<0.05$ were accepted as statistically significant.

RESULTS

This study was conducted with 105 adolescents (73 males, 32 females), 50 (47.7%) of whom were diagnosed with ADHD for the first time. It was determined that 25 adolescents (23.8%) with ADHD have received regular treatment for the last 6 months, and 30 adolescents (28.5%) with ADHD have not continued the treatment regularly. The mean age of the cases was 13.75±1.45 years. It was determined that, in terms of family structure, 89% (n=94) of participants live as nuclear family. The vast majority of cases (nearly 83%, n=87) report that they lived in urban areas while 17% (n=18) report that they lived in rural areas. In addition, 50 (47.6%) participants had a medium family income and 29 (27.6%) participants had a low family income. Moreover, it was found that 10 patients (9.5%) had additional physical diseases such as asthma, diabetes mellitus, and hypertension. The sociodemographic characteristics of participants were shown in Table 1.

Table 1. Sociodemographic characteristics of participants

		Mean ± SD	Minimum-maximum
Age		13.75±1.45	11-16
		n	**%**
Gender	Female	32	69.5
	Male	73	30.5
Living area	Rural areas	18	17.1
	Urban areas	87	82.9
Family structure	Nuclear	94	89.5
	Extended	11	10.5
Family income	Low	29	27.6
	Middle	50	47.6
	High	26	24.8
Physical illness	No	95	90.5
	Yes	10	9.5

SD: Standard deviation

According to the psychiatric evaluation conducted with K-SADS-PL-DSM-5-T, 64 cases (61%) met only ADHD diagnosis, and 41 cases (39%) met ADHD diagnosis and at least one comorbid psychiatric disorder. The results of comorbid psychiatric disorders were presented in Table 2. The most common comorbid psychiatric disorders of cases were CDs (n=17, 14.3%), and specific learning disorders (LD) (n=9, 8.6%), respectively. These disorders were followed by elimination disorders and obsessive-compulsive disorder (OCD).

The prevalence of comorbid psychiatric disorders in boys was higher than in girls, but this difference was not statistically significant (p=0.664). While determining the relationship between socioeconomic status and comorbid psychiatric disorders, statistical analysis was performed by combining middle and high income groups due to the low number of families with high income. It was determined that the prevalence of comorbidity was higher in adolescents with ADHD living in families with low socioeconomic level and the difference between the groups was statistically significant. However, no statistically significant difference was detected between other sociodemographic characteristics (family structure and physical illness) and the presence of comorbid psychiatric disorders (Table 3).

Table 2. Comorbid psychiatric disorder

Comorbid psychiatric disorder	n	%
No	64	61.0
Conduct disorder/oppositional defiant disorder	17	16.2
Learning disorder	9	8.6
Elimination disorders	4	3.8
Depressive disorder	2	1.9
Anxiety disorder	3	2.9
Obsessive compulsive disorder	4	3.8
Tic disorder	1	1.0
Stuttering	1	1.0

DISCUSSION

In this study, the prevalence and the distribution of comorbid psychiatric disorders in adolescents previously diagnosed with ADHD and diagnosed as ADHD for the first time were investigated by using a semi-structured psychiatric interview schedule. It was determined that approximately 40% of patients had comorbid psychiatric disorders and the most common comorbidities were CDs and specific learning disabilities. In addition, no association was found between the presence of comorbid psychiatric disorder and age, gender, familial sociodemographic characteristics and physical illness. In addition, no association was found between the presence of a comorbid psychiatric disorder and other sociodemographic characteristics except socioeconomic level.

In this study, 41 (39%) of 105 patients had comorbid psychiatric disorders. This rate was lower than the rates obtained from other many studies. In a population-based study, Mohammadi et al. [2] reached the result that the prevalence of comorbidity as 61% in children

Table 3. Presence of psychiatric comorbidities in cases with ADHD according to the sociodemographic characteristics

		Have psychiatric comorbidity	No psychiatric comorbidity		
		Mean ± SD	Mean ± SD	F	p
Age		13.97±1.48	13.62±1.43	0.058	0.232
		n (%)	n (%)	X^2	p
Gender	Female	11 (34.4)	21 (65.6)	0.422	0.664
	Male	30 (41.1)	43 (58.9)		
Living area	Rural areas	8 (44.4)	10 (55.6)	0.266	0.607
	Urban areas	33 (37.9)	54 (62.1)		
Family structure	Nuclear	36 (38.3)	58 (61.7)	0.212	0.747
	Extended	5 (45.5)	6 (54.5)		
Family income	Low	16 (55.2)	13 (44.8)	4.377	0.036
	High-middle	25 (32.9)	51 (67.1)		
Physical illness	No	37 (39.4)	57 (60.6)	0.002	1.000
	Yes	4 (40.0)	6 (60.0)		

ADHD: Attention-deficit hyperactivity, SD: Standard deviation

and adolescents with ADHD. In another study with 14,825 children and adolescents with ADHD, Jensen and Steinhausen [4] found that 48% of patients had pure ADHD, and 52% had at least one comorbid disorder. Hergüner and Hergüner [18] determined that 81% of the adolescents with ADHD had comorbid psychiatric disorders in their study with 133 children and adolescents consisting of clinical samples. Similarly, in another study, the frequency of comorbid psychiatric disorders in adolescents was found as 80% and in this study, there might be several reasons for the low rates of comorbid psychiatric disorders [17]. In our study, only a 6-month window was used to evaluate comorbid disorders. Considering developmental comorbidity in ADHD, comorbid psychiatric disorders might not have appeared within this short period of time. Another reason may be methodological differences between studies. Previous studies have been conducted with participants diagnosed as ADHD for the first time [17,18]. In this study, apart from newly diagnosed cases, patients who were followed up and treated with ADHD were also included. Previous studies have shown that ADHD treatment has also a therapeutic effect on comorbid psychiatric disorders [21-25]. However, inadequate recognition of comorbid disorders in patients could not be completely excluded. Sometimes the severity of comorbid psychiatric disorders is higher than the severity of ADHD and might dominate the clinical picture. Therefore, the underlying ADHD cannot be noticed.

Consistent with the literature findings, the most common comorbid psychiatric disorder in this study was CD/ODD which occur in 16.2% of the cases. In previous studies, it has been found that ODD and/or CD frequently accompanies to ADHD at rates ranging from 16% to 75% [15,16]. ADHD is considered as a risk factor for the development of ODD and CD [26]. In addition, some studies suggest that the psychosocial outcome of CD/ODD comorbidity is worse than other comorbid psychiatric disorders [26]. It has been found that ADHD patients with comorbid CD in childhood have a higher risk of substance use in adulthood [26]. In studies which have been conducted with the clinical sample of ADHD cases in our country, the frequency of comorbid ODD and CD is determined as 50% and 75%, respectively [15,18]. We think that this inconsistency was due to the methodological differences. Participants in this study consist of an adolescents group only. In addition, adolescents who were diagnosed with ADHD for the first time, as well as adolescents who received treatment for ADHD were included.

In previous studies, it has been suggested that there is a clear association between ADHD and LD [27]. And several theories have been suggested to explain this association. One of the mostly supported hypothesis is that both disorders have a common genetic etiology [28]. The results of population-based twin researches have reported that there is a strong genetic correlation between ADHD and LD [29]. Previous studies state that 8-76% of children and adolescents with ADHD have comorbid LD [27]. Most of this variability depends on the difference in methodological procedures. In our study, specific LD were determined as the second most frequently comorbid psychiatric disorders in adolescents with ADHD. In their studies evaluating comorbid psychiatric disorders in children and adolescents with ADHD, Jensen and Steinhausen [4] have found specific disorders of development (15.4%) as the second most common comorbid psychiatric disorder. Jensen et al. [12] have examined the disorders in the fields of motor, language, and scholastic skill development. In this study, only the disorder in the field of scholastic skill development was evaluated, and only adolescents were included. Therefore, we think that the frequency was lower.

However, while anxiety disorders and depression are among the common psychiatric disorders in children and adolescents with ADHD in previous studies, the prevalence rates of anxiety disorders and depression are quite low in this study. In their study conducted with 14825 children and adolescents, Jensen and Steinhausen [4] have found the frequency of anxiety disorder and depression as 2.9% and 1.9%, respectively, which is close to our study. The reason for the low prevalence might be that only a period of 6 months has been used to evaluate comorbid psychiatric disorders in our study. Depression and anxiety disorder have symptoms which could mimic the phenotype of ADHD, including inattention, distractibility, aggression and irritability. Underlying ADHD in patients with depression and anxiety disorders might not be detected in such a short time. Another reason could be that ADHD patients who still receive treatment were included in this study. It has been determined that ADHD pharmacotherapy treatment might have a protective effect for reducing the risk of later major depressive disorder [25]. Also, it has been found that ADHD pharmacotherapy reduces the anxiety symptoms [26].

In this study, it was found that the third most frequently comorbid psychiatric disorders were obsessive compulsive disorder and elimination disorders.

Although OCD and ADHD are very different disorders in terms of pathophysiology, phenomenology and treatment protocols, there have been studies showing that there might be a relationship between ADHD and OCD [30]. In some studies, it has been determined that the frequency of ADHD-OCD comorbidity varies between 0-60%. Also, it has been reported that among patients with OCD-ADHD comorbidity, the symptoms onset earlier, the symptoms are more severe, and the risk of persistence is higher [26]. However, the relationship between these two disorders has not been clearly established yet. Another psychiatric disorder that is associated with ADHD is the elimination disorders (enuresis and encopresis) determined as the third most comorbid disorder in this study. The risk of developing elimination disorders has been found to be higher in children with ADHD [31]. Elimination disorders has been detected in 1-28% of children and adolescents with ADHD [15,16]. On the other hand, ADHD has also been detected in 30-40% of children with enuretic [32]. Because of the key role of neurodevelopmental delay in the ethology of both disorders, these disorders might often accompany with each other [26].

In this study, it is found that age and gender do not affect the presence of comorbid psychiatric disorders. In previous studies, it has been found that the frequency of comorbid psychiatric diagnosis rise with the increase of age and there is a linear relationship between age and number of psychiatric disorders [18]. However, not only adolescents but also children have been included in these studies. The results of this study have suggested that age has no effect on presence of the comorbid psychiatric disorder during adolescence. When the effect of gender on the presence of comorbid disorders has been examined, no effect has been found in this study, similarly to previous studies [18]. The absence of a relationship between the sociodemographic characteristics of the adolescent and his/her family (except socioeconomic level) and the presence of comorbid psychiatric disorder has suggested that comorbid psychiatric disorders are directly related to ADHD, regardless of these factors [18].

In previous studies, it has been shown that there is a negative relationship between socioeconomic status and health problems. It has been found that individuals with low socioeconomic levels have more health problems. Larson et al. [13] have stated that children and adolescents diagnosed with ADHD with a low socioeconomic level have more comorbid psychiatric disorders. Similarly, in another study, it has been shown that comorbidity is more common in adolescents with ADHD with a low socio economic level [14]. In current study, comorbidity was found to be higher in adolescents with low socioeconomic level, in line with literature data.

Study Limitations

This study had some potential limitations. It was a cross-sectional study, and had a limited sample size. Among the participants, there were adolescents who were both diagnosed for the first time and previously treated for ADHD. Data was obtained by retrospective examination of patient records. Since the study was conducted retrospectively, complete information about the patients' past treatment processes could not be obtained, and the effect of the treatment processes on comorbid psychiatric disorders could not be clearly evaluated. Also, since there was no control group in our study, no comparison was made in terms of the prevalence and the distribution of psychiatric disorders. For these reasons, the findings of the study could not be adapted to the general population. In addition, another limitation was that the ADHD diagnosis subtypes could not be made. Despite these limitations, the fact that this study was carried out in a clinical sample of adolescents who were diagnosed for the first time as ADHD, and followed up with ADHD, and that psychiatric disorders were identified by a semi-structured interview schedule constituted the strengths of this study.

CONCLUSION

The prevalence of comorbid psychiatric disorders in adolescents with ADHD was determined as 39% in this study, and the prevalence of comorbidity was found to be higher in adolescents with ADHD living in families with low socioeconomic level. The most common comorbidities were found as CD/ODD, learning disorder, OCD and elimination disorders, respectively. Depressive disorders and anxiety disorders, tic disorders, and stuttering also accompanied with ADHD. Comorbidity of other psychiatric disorders in ADHD aggravates the clinical picture, worsens the course, makes treatment difficult and increases the cost of the treatment [18]. Therefore, it can be said that it is crucial to investigate comorbid psychiatric disorders in adolescents diagnosed as ADHD, especially in adolescents with ADHD living in families with low socioeconomic level.

Ethics

Ethics Committee Approval: The study approved by the Fırat University Non-invasive Researches Ethic Committee (approval number: 2020/09-07, date: 12.06.2020).

Informed Consent: Informed consent was not obtained from the participants because of retrospective design of the study.

Peer-review: Externally and internally peer-reviewed.

Author Contributions

Surgical and Medical Practices: S.K., Y.E.D., Concept: S.K., Y.E.D., Design: S.K., Y.E.D., Data Collection and/or Processing: S.K., Y.E.D., Analysis and/or Interpretation: S.K., Y.E.D., Literature Search: S.K., Y.E.D., Writing: S.K., Y.E.D.

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Original Article

Mast Cell Counts and Microvessel Density Expressions in Hodgkin's Lymphoma and Reactive Lymphadenopathy in Children

Çocuklarda Hodgkin Lenfoma ve Reaktif Lenfadenopatilerde Mast Hücre Sayısı ve Mikrovessel Dansite Ekspresyonları

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ABSTRACT

Objective: Mast cells (MCs) have been shown to make a significant contribution to both normal and tumor-associated neo-angiogenesis. The aim of this study is to analyse the relationship between microvessel density (MVD) and MCs in tissues of children with Hodgkin's lymphoma (HL) and reactive lymphadenopathy (RL).

Method: This retrospective study was conducted with 29 newly diagnosed HL patients and 30 patients with RL. MCs and microvascular density expressions were studied immunohistochemically in the tissues obtained from formalin-fixed and paraffin embedded blocks of archival specimens in our clinic.

Results: The mean MC count in HL was higher compared to the RL group ($p<0.001$). MVD expression in HL was lower than RL ($p<0.001$). In RL group, MC counts were correlated with MVD expression ($r=-0.055$, $p>0.05$). MC counts in nodular sclerosis subgroup were higher compared to mixed cellularity subgroup ($p<0.05$). In HL group, MC counts were positively correlated with age and nodular sclerosis histology, and negatively correlated with serum lactate dehydrogenase enzyme levels. Microvascular density expressions were positively correlated with advanced stages.

Conclusion: Our data suggest that MCs may have limited contribution to angiogenesis in childhood HL rather than RL group.

Keywords: Hodgkin lymphoma, mast cell, microvessel density

ÖZ

Amaç: Mast hücrelerinin (MH) hem normal hem de tümörle ilişkili neo-anjiyogenezde önemli bir katkı sağladığı gösterilmiştir. Bu çalışmanın amacı, Hodgkin lenfoma (HL) ve RL'li çocukların dokularındaki mikrovessel dansite (MVD) ve MH arasındaki ilişkiyi incelemektir.

Yöntem: Bu retrospektif çalışma, HL tanısı konmuş 29 hasta ve 30 RL'li hasta ile yapıldı. Kliniğimizde formolinle fikse ve parafine gömülü arşiv bloklarından elde edilen dokularda MH ve mikrovasküler dansite ekspresyonu immünohistokimyasal olarak çalışıldı.

Bulgular: HL'de ortalama MH sayısı RL grubuna göre daha yüksekti ($p<0,001$). HL'de MVD ekspresyonu RL'den daha düşüktü ($p<0,001$). RL grubunda, MH sayısı MVD ekspresyonu arasında korelasyon vardı, HL grubunda ise yoktu. Nodüler skleroz alt grubunda MH sayısı, miks sellüler alt grubuna göre daha yüksekti ($p<0,05$). HL grubunda, MH sayısı, yaş ve nodüler skleroz histolojisi ile pozitif korelasyon gösterdi ve serum laktat dehidrojenaz enzim seviyeleri ile negatif korelasyon gösterdi. Mikrovasküler dansite ile ileri evreler arasında pozitif korelasyon saptandı.

Sonuç: Verilerimiz, RL grubunun aksine, MH'nin çocukluk çağı HL'sinde anjiyogeneze sınırlı katkısının olabileceğini düşündürmektedir.

Anahtar kelimeler: Hodgkin lenfoma, mast hücre, mikrovasküler dansite

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INTRODUCTION

Angiogenesis is defined as a formation of new blood vessels and occurs in both physiological and pathologic conditions such as embryonic development, wound healing and cancer. The progression of solid tumors and hematologic malignities are associated with their degree of angiogenesis [1]. In several studies, mast cells (MCs) have been shown to make a significant contribution to both normal and tumor-associated neo-angiogenesis through secreting several factors including vascular endotelial growth factor, basic fibroblast growth factor, transforming growth factor-B, tumour necrosis factor-α, interleukin-8, histamine, tryptase, matrix metalloproteinase-9, and heparin [2-4]. First study regarding the association between MCs and induction of tumor angiogenesis was reported in MC deficient mice, which displayed slow angiogenesis, and recovery after local reconstitution of MC. In the last two decades, the association between MCs and angiogenesis has been displayed in several tumors, such as hemangioma, carcinomas, lymphomas and multiple myeloma, but the studies in pediatric Hodgkin's lymphoma (HL) and reactive lymphadenopathy (RL) are scarce in the literature [5-10]. The aim of this study is to analyse the relationship between microvessel density (MVD) and MC in HL and RL tissues of childhood.

MATERIALS and METHODS

Patients Characteristics

This retrospective study was conducted to analyse retationship between angiogenesis and MCs in tissues of HL and RL in children. A total of 29 newly diagnosed HL patients and 30 patients with RL who had undergone excisional lymph node biopsy as a control group were enrolled into the study. Ages of the patients with HL varied between 4 and 17 years, mean age was 10 years [standard deviation (SD) ±4.4 years] and 68% (n=20) of them were males. In the RL group, ages varied between 1 and 18 years, mean age was 7.8 years (SD ±4.7 years) and 68% (n=20) of them were females. Any statistically significant difference was not found between mean ages of the groups (p>0.05) (Table 1).

The tissues were obtained from formalin-fixed, paraffin-embedded blocks of the archival specimens of our clinics. Diagnosis of HL was performed by histopathological and immunophenotyping studies according to the World Health Organization classification of samples collected through excisional lymph node biopsies. Staging was carried out according to the Ann Arbor system for HL patients. Diagnostic work-up included physical examination, abdominal and cervical ultrasound, thoracic and abdominal computerized tomography scans, and bone marrow biopsies. The demographic and clinical data of the patients were retrospectively obtained from the files. Patients' age, gender, histopathologic subgroups, stages, B-symptoms, bulky involvement and laboratory parameters were recorded. This study was approved by the Research Ethics Committee of the Ankara Children Hematology and Oncology Training and Research Hospital (approval number: 2015-059). There was no conflict of interest for the present study.

Table 1. Demographic and clinical features of patients with Hodgkin's lymphoma and reactive lymphadenopathy

	HL	RL	p
Age (years)	4-17 y (median: 10 y)	1-18 y (median: 7.8 y)	p<0.05
Gender			
Male	20/29	10/30	-
Female	9/29	20/30	-
B-symptoms			
Positive	12/29	-	-
Negative	17/29	-	-
Histopathologic subtypes			
Nodular sclerosis	13/29	-	-
Mixed cellularity	15/29	-	-
Lymphocyte rich	1/29	-	-
Bulky disease positive	7/29	-	-
Stages			
1/2	8/29	-	-
3/4	21/29	-	-

HL: Hodgkin's lymphoma, RL: Reactive lymphadenopathy

The characteristics of the patients are given in Table 1 and 2.

Immunohistochemistry

MC and MVD expressions were studied immunohistochemically using sections prepared from formalin-fixed, paraffin-embedded blocks. All immunohistochemical stains were performed on the Ventana Benchmark automated staining system (Ventana Benchmark GX, Tucson, AZ, USA) using 4 µm-thick paraffin tissue sections. The primary antibodies used in this study were: CD34 (Mouse Monoclonal Antibody, Clone: QBEnd/10, Leica, Newcastle, United Kingdom) and MC Tryptase (AA1, 1:100, Thermo Scientific, USA). Diaminobenzidine was used as chromogen. We used appendices as positive controls. For negative controls, primary antibodies were omitted. A pathologist evaluated immunohistochemical staining of CD34 and MC Tryptase blinded. MCs were counted per high-power field (original magnification x 400; objective x 40, and eye piece x 10) and mean numbers per 10 high-power fields were calculated (Figure 1) [11].

When CD34 staining was used, MVD expressions were calculated according to the method described by Weidner et al. [10]. In brief, each section was observed under low-powered fields at ×100 magnification to find its high points of MVD (in three such hot spots in each case). After the most intense area of neovascularization in the tumor (hot spot) was identified, MVDs were evaluated on a 200× field (20× objective and 10× ocular; 0.785 mm^2) (Figure 2). MCs and MVDs were counted in the same area of malignant tumor tissue in HL and interfollicular areas in RL tissues. All counting was performed by one of the authors.

Table 2. Laboratory features of patients with Hodgkin's lymphoma

	Mean ± SD	Minimum-maximum
WBC/mm^3 (mean ± SD)	11 214±4419	(5000-21000)
Lymphocyte/mm^3 (mean ± SD)	2 400±947	(800-3800)
Hemoglobin/gr/dL (mean ± SD)	11±2.5	(5.2-14)
ESR/h (mean ± SD)	59±34	(16-125)
LDH/IU/dL (mean ± SD)	491±206	(178-1430)
Albumin (gr/dL)	4±0.8	(2.6-5)

WBC: White blood cell count, ESR: Erythrocyte sedimentation rate, LDH: Lactate dehydrogenase, SD: Standard deviation, IU: International unit

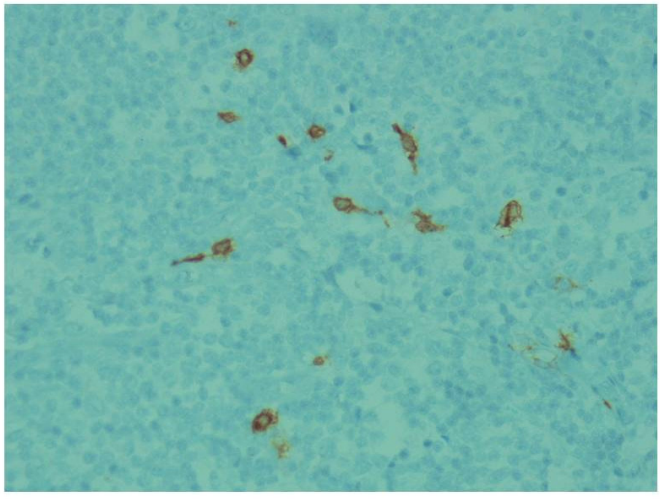

Figure 1. Distrubution of mast cells in patients with Hodgkin lymphoma visualized by immunohistochemical staining for mast cell tryptase (original magnification, ×400)

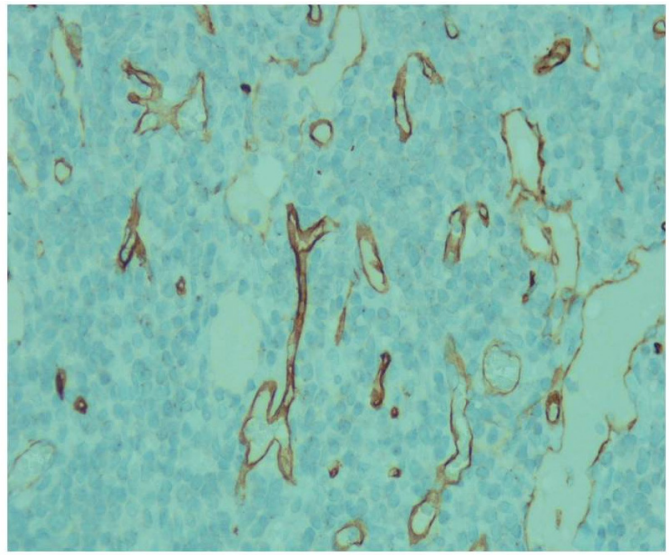

Figure 2. Expression of CD34 in tumour vasculature (original magnification, ×400)

Statistical Analysis

Statistical analyses were performed using the SPSS software version 17. The Kolmogorov-Simirnov test was used to determine if variables were normally distributed. To compare groups, Student's t-test and Mann-Whitney U tests were used, where appropriate and the Pearson corelation test was used to investigate the association between variables.

RESULTS

The MC and MVD values of HL and RL groups are summarized in Table 3. The MC counts and MVD expressions in the HL group ranged from 10 to 138 (mean ± SD: 70±31) and 21 to 38 (mean ± SD: 27±3.8), respectively. In the RL group, the MC values ranged from 10 to 125 (mean ± SD: 56±27) and MVD 20 to 49 (mean ± SD: 33±7.5), respectively. In comparison of MC between both groups Student's t-test revealed a significantly revealed significantly different ($p<0.001$) and higher MC values in HL. In comparison of mean MVD expressions between both groups Student's t-test revealed significantly different ($p<0.001$) and higher MVD expressions in RL as compared to HL. No correlation was found between levels of MC and MVD in HL ($r=-0.055$; $p>0.05$). On the other hand in RL, correlation analysis revealed a significant and positive correlation between MC values and MVD expressions ($r=0.405$; $p<0.05$).

Comparison between MC values and MVD expressions in terms of histopathologic subgroups (nodular sclerosis vs mixed cellularity), bulky involvement (positive vs negative), B-symptoms (positive vs negative), disease stages (early vs advanced) in HL are summarized in Table 4. MC values ranged from 10 to 138 (mean ± SD: 82±34.5) in nodular sclerosis and from 23 to 117 (mean ± SD: 61±26) in mixed cellularity subgroup. In comparison of MC values between two groups, statistical tests revealed significantly different ($p<0.05$) and higher MC counts in nodular sclerosis subgroup as compared to mixed cellularity subgroup (Figure 3). Similarly, mean MC counts were significantly different according to presence or absence of a bulky disease (mean ± SD: 89.5±24, range 70-138 vs mean ± SD: 63±31, range 10-117, respectively) ($p<0.05$). Although MC values of B symptom- positive patients were higher (75±31, range: 10-111) compared to B-symptom- negative patients (65±31, range: 24-138), the difference was not statistically significant ($p>0.05$). Also, MC values in advanced stages (stages 3 and 4) of HL (68±35, range: 10-138) were lower compared to early stages (stages 1 and 2) (75±19, range: 41-101), but the difference were not statistically significant ($p>0.05$). The mean MVD values were not statistically different between histopathologic subgroups contrary to MC counts (Figure 4). In addition, no difference was observed in MVD values with respect to bulky involvement or presence of B-symptoms. While mean MVD values were statistically significantly different, and higher in advanced stages ($p<0.05$) (Figure 5). According to Pearson correlation test, MC counts were positively correlated with patients' ages ($r=0.470$) ($p=0.01$), and histologic subgroups ($r=0.404$; $p=0.03$), while negatively correlated with serum lactate

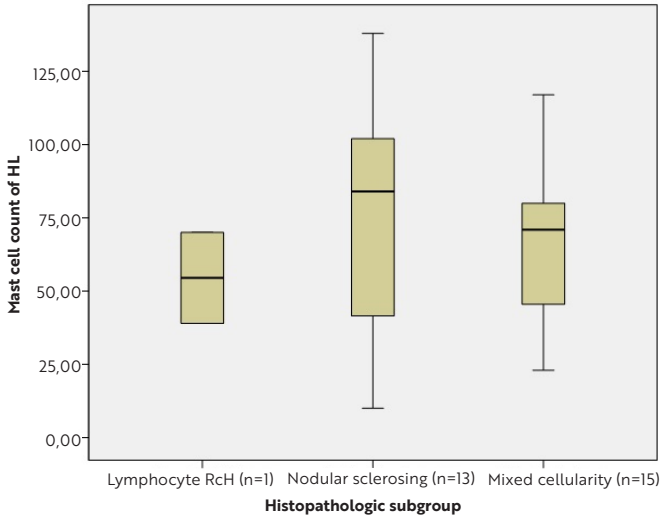

Figure 3. The comparison of mast cell count according to histopathologic subgroups

ML: Modgkin's lymphoma

Table 3. The comparison of mast cell count and microvessel density in Hodgkin lymphoma and reactive lymphadenopathy tissues

	Hodgkin lymphoma (n=29)	Reactive lymphadenopathy (n=30)	p
	Mean ± SD (min.-max.)	Mean ± SD (min.-max.)	
Mast cell count	70±31 (10-138)	27±3.8 (21-38)	p<0.001
MVD expression	27±3.8 (21-38)	33±7.5 (20-49)	p<0.001

MVD: Microvessel density, SD: Standard deviation, min.: Minimum, max.: Maximum

dehydrogenase enzyme levels (r=-0.404; p=0.04) at initial diagnosis. Any correlation was not found between MC and MVD, in terms of the presence of B-symptoms, and advanced stages of the disease (r=-0.055, p=0.778; r=0.134, p=0.497; r=-0.105, p=0.589, respectively). The MVD expression was only positively correlated with advanced stages (r=0.474; p=0.009), but not with age, histologic subgroups, presence of a bulky disease or B-symptoms (r=0.338, p=0.07; r=-0.079, p=0.685; r=-0.200, p=0.317; r=0.033, p=0.867, respectively).

DISCUSSION

Angiogenesis is a hallmark of tumor growth and progression in both solid tumors and hematological malignancies. Currently, antiangiogenic therapy is a promising tool for preventing tumorogenesis as well as initiating cancer treatment. MCs secrete proangiogenic and angiogenic factors and contribute to the formation of new blood vessels by increasing migration, proliferation of endothelial cells that facilitates growth of the tumor.

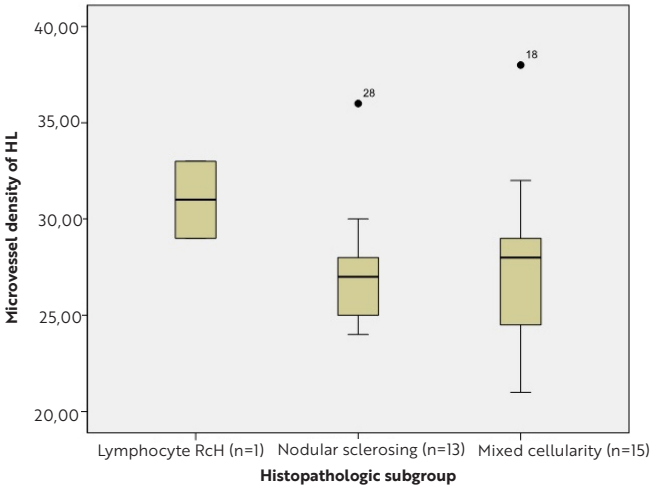

Figure 4. The comparison of microvessel density expression according to histopathologic subgroups

ML: Modgkin's lymphoma

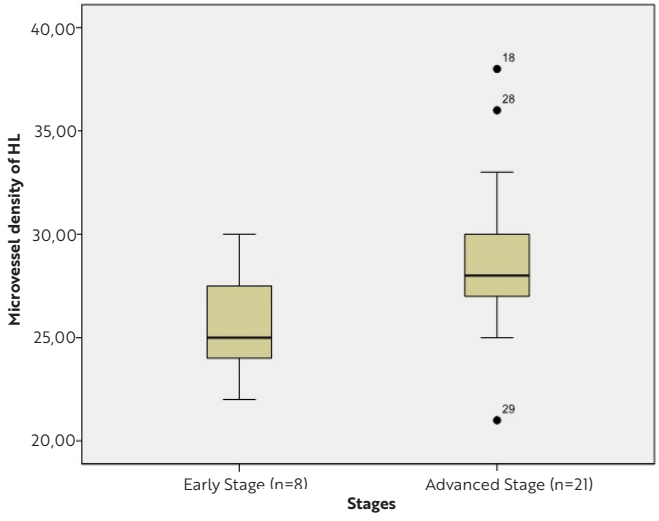

Figure 5. The comparison microvessel density according to stages

ML: Modgkin's lymphoma

Table 4. The Comparison of mast cell count with microvessel density between histopathologic subgroups, Bulky disease (positive vs negative), B-symptom (positive vs negative), stages (early vs advanced) in Hodgkin lymphoma

	Mast cell count Mean ± SD (min.-max.)	p	MVD expression Mean ± SD (min.-max.)	p
Histologic subtype				
Nodular sclerosis	82±34.5 (10-138)	p<0.05*	28±4.2 (24-38)	p>0.05
Mixed cellularity	61±26 (23-117)		26±3 (21-32)	
Bulky disease				
Positive	89.5±24 (70-138)	p<0.05*	25±2 (21-29)	p>0.05
Negative	63±31 (10-117)		28±3 (22-38)	
B-symptom				
Positive	75±31 (10-111)	p>0.05	28±3 (22-38)	p>0.05
Negative	65±31 (24-138		27±3 (21-36)	
Englund				
Early stage (1/2)	75±19 (41-101)	p>0.05	24±2 (22-29)	p<0.05*
Advanced stage (3/4)	68±35 (10-138)		28±3 (21-38)	

MVD: Microvessel density, SD: Standard deviation, min.: Minimum, max.: Maximum

Several studies have shown the effect of MC through their strong angiogenic potential in occurence and progression of solid and hematological tumors. Also, it was reported that angiogenesis and tumorogenesis were decreased in MC- deficient mice [12-14]. In the present study, we aimed to determine the relationship between MVD and MC in HL and RL tissues of children. It was noticed that MC in HL tissue was increased compared to RL. Also, MVD was found to be lower in the HL group than in the RL group. On the other hand, MVD in HL, which is an indicator of angiogenesis, was found to be high in patients in advanced stage rather than early-stage disease.

Previously, MC was found to be highly correlated with angiogenesis in chronic inflammatory diseases, and benign lymphadenopaties as well as tumors. Ribatti et al. [4] reported that angiogenesis and MC density together with tryptase activity increased simultaneously with pathological progression in B-cell non-HLs. In the present study a positive correlation was determined between MC and angiogenesis in the RL group. However; any correlation could not be found between MC and MVD in HL. We supposed that MC contributes to the formation of angiogenesis in RL, but angiogenesis is more complicated process in HL.

HL differs from other malignant lymphomas in that it displays distinct histopathological features. It is characterized by the presence of a few tumour cells, Hodgkin and Reed-Sternberg (HRS) cells, surrounded by various inflammatory cells including B and t-cells, eosinophils, basophils, macrophages, plasma cells and MCs. HRS cells interact with the cells in the surrounding microenvironment by production of both cytokines and chemokines and through direct cell contact. Several studies regarding the association between increased MC counts and nodular sclerosis histology in HL have been reported in the literature [10-14]. Andersen et al. [11] reported that a high number of tumor MCs were associated with nodular sclerosis subtype histology in adult HL. They have determined that degree of MC infiltration was not a prognostic factor in HL of nodular sclerosis subtype. In contrast, mixed cellularity HL with a high number of intratumoral MCs correlated significantly with poorer outcome both in terms of overall and event-free survival [11]. Molin et al. [15] reported that patients with increased MC infiltration had poor prognosis in HL with a proposed mechanism involving the stimulation of HRS by CD30L produced by MCs. In the present study, the number of MCs was found to be higher in the nodular sclerosis subgroup and bulky disease than in the mixed cellularity subgroup which made us think that MCs play an important role in the formation of the tumorogenesis and fibrosis which is distinctive feature of nodular sclerosis histology. Similarly, a significantly positive correlation was reported between the rate of fibrosis and the number of MCs in nodular sclerosis histology [16]. Therefore, according to our data the presence of higher MC counts in the nodular sclerosis subtype can be considered as evidence of its involvement in the histopathological structure and the formation of fibrotic bands. Keresztes et al. [17] retrospectively studied histological samples from 104 patients with HL, and correlated MC positivity with better overall survival. However inconsistent with previous studies, in their study this difference had only a borderline statistical significance. In the present study, because of the limited number of patients and high survival rates (93%), we could not statistically evaluate this correlation.

So far, studies regarding the contribution of MC to tumor angiogenesis are still contradictory and limited in number especially in pediatric HL. Korkolopoulou et al. [18] investigated angiogenesis in 286 HL patients using a morphometric approach. They reported that parameters of the vessels such as their calibers showed a gradual increase through Ann Arbor stages 1-4. Conversely, in their study MVD expressions declined in advanced stages of the disease. MVD expressions in HL were lower compared to the RL group, but higher in patients in the advanced stage rather than early stage of the disease. In addition, MVD expressions were correlated with advanced stage. On the other hand, although statistically insignificant, the number of MCs were lower in patients in the advanced stage of the disease despite higher MVD expressions. This result supports the fact that MCs are more active in the early stages and MC migration is reduced by various cytokines in the advanced stages Similarly, Glimelius et al. [8] studied the relationship between the extent of angiogenesis and MC, but any significant correlation could not be found between increased MVD expressions and higher MC counts. Also, they reported that increased MVD expressions are important for the prognosis of HL.

Englund et al. [19] studied MC infiltration in tissues of pediatric patients with HL. They determined increased MC counts in cases with advanced stages and in the presence of B-symptoms. In cases with high MC counts (≥62 per 10 HPF), hemoglobin and albumin levels were lower, but ESR was elevated. In cases with MC counts over median values (≥24 per 10 HPF), ESR and CRP were elevated. In the present study, MC counts were negatively correlated with LDH which is an indicator of advanced disease, and positively correlated with age and nodular

sclerosis subtype. There weren't any correlation with other prognostic factors such as increased white blood cell counts, albumin levels, ESR, and advanced stage of the disease.

Study Limitations

There are some limitations to the present analysis. Firstly, we could not analyse MC and MVD in patients with relapsed or primary refractory disease, because of the limited number of patients. Secondly, we could not determine whether increased MCs have an impact on poor prognosis of pediatric patients with HL.

CONCLUSION

The mean MC counts were higher especially in nodular sclerosis subtype of HL. On the other hand, MC in HL was not found to be correlated with MVD contrary to RL. Our data suggest that MC may have limited contribution to angiogenesis in childhood HL.

Ethics

Ethics Committee Approval: This study was approved by the Research Ethics Committee of the Ankara Children Hematology and Oncology Training and Research Hospital (approval number: 2015-059).

Informed Consent: Since our study had a retrospective design, informed consent was not obtained from the patients.

Peer-review: Internally peer-reviewed.

Author Contributions

Surgical and Medical Practices: D.Ö., E.K., S.E., A.Y.E., M.I., Concept: D.Ö., E.K., Design: D.Ö., S.E., Data Collection and/or Processing: D.Ö., E.K., Analysis and/or Interpretation: D.Ö., Literature Search: D.Ö., Writing: D.Ö.

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Original Article

Child and Adolescent Forensic Psychiatry Experiences During the COVID-19 Pandemic

COVID-19 Pandemisi Sürecinde Çocuk ve Ergen Ruh Sağlığı Adli Kurul Deneyimleri

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ABSTRACT

Objective: Coronavirus disease-2019 (COVID-19) changed the status-quo in psychiatric interview with the advent of telemental health practices, save for a select group of patients; forensic psychiatric interviews among them. The present study aimed to identify the predictors of completing forensic psychiatric evaluations mandated by the judicial authorities in the hospital setting during the COVID-19 outbreak.

Method: Twenty-six patients who had completed an initial forensic psychiatric assessment and were required to complete a child and adolescent forensic psychiatry board interview during the height of the COVID-19 pandemic were recruited. Their records were retrospectively examined, sociodemographic data, Beck Depression Inventory (BDI), the Screen For Child Anxiety Related Disorders (SCARED), and Wecshler Intelligence Scale for Children-revised scores were recorded and analyzed.

Results: Statistical analysis revealed an association between conduct disorder and concomitant substance use with missed appointments, and maternal employment and completed interviews. BDI and SCARED total scores showed no difference between the patients who missed or completed their mandatory forensic psychiatry board assessment. BDI individual items of loss of pleasure (item 4), suicidality (item 9), and loss of interest (item 12) were associated with missed appointments.

Conclusion: The results of this study support the established relationship between conduct problems and depressive symptoms, and this demographic group may be among the most affected by the limitation of access to mental health services during the COVID-19 pandemic, as they are already less likely to seek help overall.

Keywords: COVID-19 pandemic, child and adolescent psychiatry, forensic psychiatry, conduct disorder, depression

ÖZ

Amaç: Çalışmamızın amacı, adli makamlarca tamamlanması zorunlu tutulan adli kurul randevularına pandemi döneminde katılan ve katılmayan gençler arasındaki farkları saptamaktır.

Yöntem: Çalışmamıza, ilk adli psikiyatri muayenesi bir çocuk psikiyatristi tarafından tamamlamış olup pandeminin erken üç aylık döneminde Çocuk ve Ergen Ruh Sağlığı Adli Kurulu tarafından değerlendirmesi planlanmış 26 genç dahil edilmiştir. İlk adli psikiyatrik görüşme kayıtları geriye dönük incelenmiş ve sosyo-demografik verileri, psikiyatrik tanıları; Beck Depresyon Ölçeği (BDÖ), Çocukluk Çağı Kaygı Bozuklukları Özbildirim Ölçeği (KAYBÖ) puanları kaydedilmiştir.

Bulgular: İstatistiksel analiz sonucunda annenin çalışmasının pandemi döneminde adli kurul randevularına gelinmesini öngördüğü (p=0,009); anksiyete bozukluğu, zihinsel yetersizlik, dikkat eksikliği tanı kriterlerinin karşılanmasının randevuya gelme durumunu etkilemediği görülmüştür. Psikiyatrik tanılar arasında davranım bozukluğu tanısının ve madde kullanımının planlanan adli kurul randevusuna gelinmemesiyle ilişkili olduğu saptanmıştır (p=0,014, p=0,018). Gruplar arasında BDÖ ve KAYBÖ puanları açısından fark olmadığı, randevulara gelmeyen gençlerin toplam puandan bağımsız olarak BDÖ'nün 4. (anhedoni: p=0,015), 9. (suisidalite: p=0,009) ve 12. (ilgi kaybı: p=0,028) maddelerinde anlamlı yüksek puanlar aldıkları görülmüştür.

Sonuç: Çalışmamız, adli kurul randevularına gelinmemesinin davranım problemleri ve depresif belirtilerle ilişkili olduğunu göstermiştir. Eşik-altı depresif belirtileri olup davranım bozukluğu tanı kriterlerini karşılayan gençlerin psikiyatrik takip ve tedavi uyumları yaşıtlarına göre daha zayıf olup, bu grup COVID-19 salgını sırasında ruh sağlığı hizmetlerine erişimin kısıtlanmasından en çok etkilenen gruplar arasındadır.

Anahtar kelimeler: COVID-19, pandemi, çocuk ve ergen psikiyatrisi, adli psikiyatri, davranım bozukluğu, depresyon

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INTRODUCTION

Coronavirus disease-2019 (COVID-19) created a visible burden on mental health worldwide, for adults and children alike. Multiple studies have reported an increase in anxiety and depressive symptoms, especially in young people [1,2]. Exacerbation of existing mental health issues in young people also contributed significantly to the mental health burden wrought on by the COVID-19 pandemic as people with existing mental health problems were considered to be at-risk in addition to the elderly, young people, people with limited financial security [3-5].

A pandemic is a dynamic process, and dividing the allotted period into three specific phases may aid in painting a comprehensive picture of the pandemic process as each phase has unique demands from the healthcare system. The first phase, denoted as the preparation phase, is followed by the second punctum maximum phase, where peak numbers of confirmed cases and mortality rates are observed, and the third normalization phase is marked by a fall in cases and mortality rates [6]. Three distinctly defined phases of the COVID-19 pandemic required different interventions for the promotion of mental health. During the relatively short preparation phase, child and youth mental health services were mostly unaffected with the implementation of personal protective equipment by the mental health practitioners and the general public. However, the report of the index case was followed by a rapid increase in confirmed case numbers and marked the beginnings of the second phase of the COVID-19 pandemic. During the so-called punctum maximum (second) phase, halting mental health services instigated a shift towards telemental health globally with varying results [7-9]. The requisites and consequences of the last phase (the normalization phase) remain to be seen both globally and locally.

COVID-19 was declared a pandemic on March 11th by the World Health Organization, and country-wide precautions were instigated in Turkey in a stepwise manner. During this time, telemedicine approaches were instituted for the child and adolescent department in our institution on March 18th for three months except for inpatient and emergency mental health, and forensic psychiatric evaluations of youth. Child and adolescent forensic psychiatry is a subspecialty that could not benefit from telemental health interventions, as a face-to-face assessment is key in deciding the best course of action for sexual abuse victims, juvenile offenders, and evaluation of youth for marriage and custody.

Children and adolescents are referred to our institution by judicial authorities for a complete psychiatric evaluation. In our institution, a comprehensive forensic psychiatric assessment of a child or adolescent consists of two separate interviews. The first interview is conducted by a trained child and adolescent psychiatrist and the second interview by the child and adolescent forensic psychiatry board. The board consists of a multidisciplinary team of three forensic medicine specialists, one child and adolescent psychiatrist, and one neurologist. After referral of the patient to the forensic child and adolescent psychiatry board, a psychiatric report is prepared for judicial authorities.

The two-step process mentioned above was significantly affected during the COVID-19 pandemic due to patient no-shows. The missed board interview appointments, which are mandated by law, were of particular interest at that time. This study aims to detect, quantify and analyze the differences between the patients who braved a pandemic to complete their forensic psychiatric assessments and the patients who did not during the punctum maximum (second) phase of the COVID-19 outbreak.

MATERIALS and METHODS

Study Design

The established protocol for the forensic psychiatric assessment of children and adolescents referred to our department is as follows: The initial interviews are conducted by a trained child and adolescent psychiatrist, which were completed prior to the COVID-19 pandemic in the present study, where sociodemographic data and clinical assessments are recorded. A trained clinical psychologist with over 20 years of experience in child and adolescent forensic psychology administers the Wechsler Intelligence Scale for Children-Revised (WISC-R) version to assess intellectual disability and I.Q. scores for all referred patients. All eligible patients complete the Screen for Child Anxiety Related Disorders (SCARED) and Beck Depression Inventory (BDI) self-report questionnaires.

Patients who had a child and adolescent forensic psychiatry board interview appointment during the punctum maximum phase of the COVID-19 pandemic were selected. A total of 26 patients had completed their initial assessment and were referred to the child and

adolescent forensic psychiatry board interviews during the three-month pandemic period of March 18th-June 18th, 2020 were included in the study. Sixteen patients had completed their scheduled child and adolescent forensic psychiatry board interview in addition to the initial assessment, and a total of ten patients had missed their scheduled appointments during the punctum maximum phase of the pandemic and were rescheduled to a future date.

Records of the patients who completed their initial interviews, and then referred to be interviewed by the child and adolescent forensic psychiatry board during the COVID-19 pandemic were retrospectively reviewed. Relevant sociodemographic data, scores of self-report questionnaires, and psychometric tests were recorded. A missed interview with the board was rescheduled for no more than two accounts, and the legal guardians of the youth were notified of the new appointment. The presented study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and approved by the by the Ege University Faculty of Medicine Clinical Research Ethics Committee (approval number: 20-5.1T/66, date: 28.05.2020). Accordingly, informed consent was obtained from all participants.

Measures

Beck Depression Inventory

Developed and revised by Beck and Steer [10] BDI is a 21-item self-assessment scale that measures somatic, emotional, cognitive, and behavioral symptoms of depression. Items are scored between 0-3, and each item is designed to assess a core symptom of depression. Although higher scores in this self-report scale are correlated with the severity of depression, it is not used as a diagnostic tool. The BDI was found to be a highly reliable and valid measure for depressive symptoms in Turkish youth with a cut-off of 17 points for clinical mild depression [11].

The Screen for Child Anxiety Related Disorders

This self-report scale was developed by Birmaher et al.[12] in 1985 and consists of 27 questions at a reading level suitable for children and youth aged 7-17 years. This scale assesses the subcategories of panic/somatic symptoms, generalized anxiety, social anxiety, separation anxiety school avoidance on a 3-point Likert scale. The total score is highly correlated with the severity of anxiety symptoms in general, while the subscores can support diagnoses for various anxiety disorders. High reliability and validity were reported in its Turkish adaptation [13].

Wechsler Intelligence Scale for Children-Revised

Developed in 1949 and revised in 1974 by Wechsler [14], WISC-R is a widely used intelligence scale for children [15]. Standardized for Turkish children, this test was used in our study to diagnose intellectual disability, and individual verbal, performance and total I.Q. scores are also included in the statistical analysis [16].

Statistical Analysis

The differences between patients who did and did not complete their scheduled interviews during the punctum maximum phase of the pandemic were analyzed by statistical means. Statistical analyses were conducted with IBM SPSS Statistics v25.0. Fisher's exact test (two-tailed) was used to analyze the association between sociodemographic nominal variables and attendance, and Mann-Whitney U test was utilized to assess the levels of significance between the median patient, maternal, paternal ages. P-values <0.05 were considered statistically significant.

RESULTS

The median age of all patients was 16.50 years, with a minimum age of 8 and a maximum age of 23 years. Overall, 46.2% (n=12) of the patients were male and 53.8% (n=14) were female. Patients' reasons for referral and completion of the board interview during the punctum maximum phase, as well as sociodemographic data of the patients (n=26), are summarized in Table 1.

Statistically significant differences between groups were observed for maternal employment (p=0.009), meeting the diagnostic criteria for any psychiatric diagnosis (p=0.014), for conduct disorder (p=0.018), and substance abuse (p=0.018). Among six patients with substance abuse (n=6), four had used multiple substances (amphetamines, cannabinoids, sedative/hypnotics, other), one had used only a cannabinoid, and another one only sedative/hypnotic for at least six months. While the patients who had completed their child and adolescent forensic psychiatry evaluation were more likely to have an employed maternal figure, conduct disorder and substance abuse were higher in the group who had missed their appointments.

Table 1. Sociodemographic data of the patients referred to child and adolescent forensic psychiatry board assessment during the punctum maximum (second) phase of the COVID-19 pandemic

	Completed board assessment (n=16)	Missed board assessment (n=10)	Total number of patients (n=26)	p-value
Age, mean (±SD)	16.03 (±0.93)	16.35 (±0.58)	16.15 (±3.09)	0.653
Gender, n (%)				
Male	7 (43.8)	5 (50.0)	12 (46.2)	-
Female	9 (56.2)	5 (50.0)	14 (53.8)	-
Reason for admission, n (%)				
Sexual abuse victim	7 (43.8)	2 (20.0)	9 (34.6)	-
Physical abuse victim	1 (6.2)	-	1 (3.8)	-
Juvenile offender	7 (43.8)	6 (60.0)	13 (50.0)	-
Custody	-	2 (20.0)	2 (7.7)	-
Marriage	1 (6.2)	-	1 (3.8)	-
Education, n (%)				0.442
In school	10 (62.5)	4 (40.0)	14 (53.8)	-
Dropped out	6 (37.5)	6 (60.0)	12 (46.2)	-
Smoking, n (%)	9 (56.2)	6 (60.0)	15 (57.7)	1.0
Alcohol use, n (%)	3 (18.8)	2 (20.0)	5 (19.2)	1
Substance use, n (%)	1 (6.2)	5 (50.0)	6 (23.1)	0.018*
Psychiatric diagnoses, n (%)	6 (37.5)	9 (90.0)	15 (57.7)	0.014*
Conduct disorder	1 (6.2)	6 (60.0)	7 (26.9)	0.018*
Mental insufficiency	3 (18.8)	2 (20.0)	5 (19.2)	1
Anxiety disorder	1 (6.2)	1 (10.0)	2 (7.7)	1
ADHD	1 (6.2)	-	1 (3.8)	1
Maternal age, mean (± SD)	39.56 (±1.52)	41.28 (±2.54)	40.08(±6.19)	0.568
Maternal primary education, n (%)				1.0
Completed	7 (43.8)	3 (30.0)	10 (38.5)	-
Dropped out	7 (43.8)	3 (30.0)	10 (38.5)	-
Maternal employment, n (%)				0.009*
Employed	8 (50.0)	0	8 (30.8)	-
Unemployed	7 (43.8)	9 (90.0)	16 (61.5)	-
Maternal psychiatric history, n (%)	6 (37.5)	2 (20.0)	8 (30.8)	0.657
Paternal age mean (± SD)	44.28 (±1.73)	47.66 (±2.69)	45.3 (±6.55)	0.561
Paternal primary education, n (%)				1.0
Completed	5 (31.2)	2 (20.0)	7 (26.9)	-
Dropped out	9 (56.2)	4 (40.0)	13 (50.0)	-
Paternal employment, n (%)				1.0
Employed	15 (93.8)	9 (90.0)	24 (92.3)	-
Unemployed	-	-	-	-
Paternal psychiatric history, n (%)	2 (12.5)	1 (10.0)	3 (11.5)	1.0
Family type, n (%)				0.226
Married	6 (37.5)	6 (60.0)	12 (46.2)	-
Divorced	10 (62.5)	3 (30.0)	9 (34.6)	-
Family income, n (%)				
Below poverty threshold	5 (31.2)	5 (50.0)	10 (38.5)	-
Above poverty threshold	11 (68.8)	5 (50.0)	16 (61.5)	-
Family alcohol/substance use, n (%)	4 (25.0)	2 (20.0)	6 (23.1)	1
Family criminal history, n (%)	4 (25.0)	6 (60.0)	10 (38.5)	0.109

*p<0.05. COVID-19: Coronavirus disease-2019, SD: Standard deviation

SCARED was completed by 15 patients. Inadequate reading and writing skills were the primary cause of incomplete measures in 7, followed by multiple missing items in 2 and inappropriate age for the indicated test in 2 patients. Total scores and subscores were compared between the two groups with the Mann-Whitney U test, and the results for the analyses are summarized in Table 2.

BDI was completed by 15 patients. Inadequate reading and writing skills were the primary cause of incomplete measures in 6, followed by multiple missing items in 3, and inappropriate age for the indicated test in 2 patients. Differences in mean and individual item scores between the two groups were assessed with Mann-Whitney U test. The results are summarized in Table 2 and 3.

WISC-R was completed by 25 patients. One patient who was unable to take the test and was administered an age-appropriate developmental test, so this test was not applied for this patient. Differences in verbal, performance, and total I.Q. scores that were assessed with Mann-Whitney U test are summarized in Table 2.

No statistical significance in BDI scores, SCARED scores, and WISC-R IQ scores were detected between groups. However, when the cut-off point of 17 (indicating borderline clinical depression and above) was implemented, statistically significant differences were observed between groups (Table 3).

The answers to individual items in BDI between the patients who completed and missed the board assessment appointments differed significantly on items 4, 9 and 12. These findings further support the presence of an undiagnosed depressive episode independent of BDI total scores despite thorough forensic psychiatric evaluation in patients who had missed their mandatory child and adolescent forensic psychiatry interviews during the pandemic.

DISCUSSION

The present study aimed to present a cross-sectional snapshot of the seldom reported COVID-19's effects on a subspecialty of child and adolescent psychiatry and a population of youth. The multitude of sociodemographic parameters was found to be statistically insignificant in predicting the attendance to the board interviews during the punctum maximum phase of the pandemic, with the exception of maternal employment. Having a mother with an active economic role in the family was the singular statistically significant factor of attendance to the court-mandated psychiatric board interviews,

Table 2. Analysis of WISC-R, SCARED, BDI scores of the patients referred to child and adolescent forensic psychiatry board assessment during the punctum maximum (second) phase of the COVID-19 pandemic

	Board assessment completed (n=15)	**Board assessment missed (n=10)**	**Total number of patients (n=25)[a]**	**p-value**
WISC-R scores mean (± SD)				
WISC-R verbal IQ	76.86 (±4.88)	68.1 (±8.23)	73.36 (±21.96)	0.192
WISC-R performance IQ	81.46 (±5.84)	72.0 (±8.25)	77.68 (±24.01)	0.202
WISC-R total IQ	78.00 (±5.44)	68.3 (±8.57)	74.12 (±23.62)	0.222
	Completed board assessment (n=10)	**Missed board assessment (n=5)**	**Total number of patients (n=15)[b]**	**p-value**
SCARED scores mean (± SD)	24.66 (±5.52)	23.5 (±5.59)	24.2 (±14.98)	0.906
Panic/somatic	6.44 (±2.37)	7.0 (±2.43)	6.66 (±6.46)	0.678
Generalized anxiety	5.55 (±1.50)	5.50 (±1.80)	5.53 (±4.30)	0.953
Separation anxiety	5.11 (±0.75)	4.16 (±0.74)	4.73 (±2.08)	0.471
Social anxiety	6.11 (±1.28)	5.66 (±1.78)	5.93 (±3.91)	0.679
School avoidance	1.44 (±0.37)	1.16 (±0.74)	1.33 (±1.39)	0.461
BDI scores mean (± SD)	14.30 (±4.88)	27.0 (±1.37)	18.53 (±13.94)	0.220
BDI <17, n (%)	7 (77.8)	0	7 (46.7)	-
BDI ≥17, n (%)	3 (32.2)	5 (100.0)	8 (53.3)	0.026*

[a]One patient was unable to complete the WISC-R test and was administered an age-appropriate developmental test, is not included, [b]Nine patients were unable to complete the self-assessment inventories due to various reasons referred to in the text, *p<0.05, COVID-19: Coronavirus disease-2019. WISC-R: Wechsler Intelligence Scale for Children-Revised, SD: Standard deviation, SCARED: Screen For Child Anxiety Related Disorders, BDI: Beck Depression Inventory

Table 3. Analysis of beck depression inventory individual items' statistical significance between the two groups (completed vs missed board appointments)

BDI individual item scores	p-value
1. Sadness	0.471
2. Pessimism	0.093
3. Past failure	0.727
4. Loss of pleasure	0.015*
5. Guilty feelings	0.471
6. Punishment feelings	0.225
7. Self-dislike	0.891
8. Self-criticalness	0.394
9. Suicidal thoughts	0.009*
10. Crying	0.268
11. Agitation	0.065
12. Loss of interest	0.028*
13. Indecisiveness	0.648
14. Appearance	0.294
15. Concentration	0.099
16. Changes in sleep	0.158
17. Fatigue	0.209
18. Changes in appetite	0.147
19. Weight loss	0.834
20. Somatic/health	0.945
21. Loss of sexual interest	0.277

*P<0.05, BD: Beck depression inventary

independent of family type, maternal education levels, and household income.

Meeting the diagnostic criteria of a psychiatric disorder was also in line with our starting hypothesis in that resilient children would be more likely to attend the scheduled board interviews during the pandemic. Contrary to expectation, the diagnosis of conduct disorder was found to be a strong predictor for non-attendance while the other diagnoses (i.e. anxiety disorder) were not. No significant differences in the BDI and SCARED scores were observed between the two groups, including the five anxiety subscales defined in SCARED. When the scores were compared for individual items of the BDI, a statistically significant difference in individual items were observed between the groups in items 4 and 9. The presence of moderate depression was statistically significant in the non-attending group despite a thorough psychiatric examination has suggested otherwise. No diagnoses of major depressive disorder were made after the initial interview of the patient by the child and adolescent psychiatrist, which could be the result of youth downplaying their depressive symptoms during the forensic psychiatric interview.

The impact of the COVID-19 pandemic on the mental health of the general population as well as its potential effects on vulnerable groups such as the mentally ill have been reported thoroughly, as previously mentioned emphasizing a widespread but safe use of technology [17]. Successful implementation of telemental health practices for children diagnosed with ADHD and other disorders could be implemented rapidly and effectively [18,19]. Among these vulnerable groups, children with conduct disorder should not be disregarded.

Children diagnosed with conduct disorder are at risk for substance use disorder, depression, suicide, and overall premature death [20-22]. Major depressive disorder in the context of conduct disorder represents a different subtype of depression with no gender preponderance and different sociodemographic risk factors [23]. Cognitive and executive functions in children with conduct problems are less developed compared to their peers. Especially a deficit in language and meta-linguistic abilities could pose difficulty in communicating psychiatric complaints and decrease help-seeking behavior [24]. Addressing mental problems in juvenile offenders with conduct problems and depression is paramount for reintegrating them into the community. Continued utilization of mental health services was associated with lower levels of recidivism in previous studies [25,26].

The major limitation of this study was the number of patients scheduled for the board interview during the three-month period of the second phase of the pandemic. A more extended period would undoubtedly provide more cohesive data on resilience and risk factors among youth during a pandemic; however, the caveat of not being able to reach or adequately assess the patients would also remain. Though certainly not an accurate representation of the general population of forensic psychiatry experiences overall, our patients provide a practical means to create a basic framework to understand at-risk groups during this time and analyze the outcomes of these extraordinary circumstances.

The present study underlines a possible relationship between attendance to appointments, depression, and conduct problems supporting the established literature on youth diagnosed with conduct disorder accompanied by depression. Effective ways to assess depressive symptoms and establishing rapport with

juvenile offenders with conduct disorder may be outside the scope of forensic psychiatry. Still, the importance of early recognition of depressive symptoms by the forensic psychiatrist could prove to be the deciding factor in the youth's reintegration into society via effective referral to mental health services.

In the present study, we aimed to describe the common qualities and resilience factors of the children where the pandemic could not prevent from completing the forensic psychiatric board interview. Except for a statistically significant relationship between maternal employment and attendance to forensic psychiatry board interviews, we also observed the possible predictors of non-attendance instead.

Completion of the forensic psychiatry board interview is mandated by the courts of law in Turkey as the court cannot progress without an official psychiatric report. Non-attendance to the scheduled interviews, even during a pandemic is alarming. Even more disconcerting is the association between conduct disorder, loss of interest, loss of pleasure and suicidality.

CONCLUSION

We conclude that the pandemic could indeed bar certain disadvantaged children and youth from accessing mental health care. The potential implications of children and youth who are most likely to need mental health services during trying times are the ones who are least likely to be assessed in psychiatry clinics, even when the interview is mandatory. This study underlines the need for additional research on access of disadvantaged youths to mental health services during the COVID-19 pandemic.

Ethics

Ethics Committee Approval: The study was approved by the Ege University Faculty of Medicine Clinical Research Ethics Committee (approval number: 20-5.1T/66, date: 28.05.2020).

Informed Consent: Informed consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Author Contributions

Surgical and Medical Practices: B.Ş.P., İ.İ.K., S.E., A.K., S.K., B.Ö., T.B., Concept: B.Ş.P., İ.İ.K., S.E., A.K., S.K., B.Ö., T.B., Design: B.Ş.P., İ.İ.K., S.E., A.K., S.K., B.Ö., T.B., Data Collection and/or Processing: B.Ş.P., İ.İ.K., S.E., A.K., S.K., B.Ö., T.B., Analysis and/or Interpretation: B.Ş.P., İ.İ.K., S.E., A.K., S.K., B.Ö., T.B., Literature Search: B.Ş.P., İ.İ.K., S.E., A.K., S.K., B.Ö., T.B., Writing: B.Ş.P., İ.İ.K., S.E., A.K., S.K., B.Ö., T.B.

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Original Article

Evaluation of the Relationship Between Systemic Hypertension and Subfoveal Choroidal Thickness Using Optical Coherence Tomography in Pediatric Patients

Pediyatrik Hastalarda Optik Koherens Tomografi Kullanılarak Sistemik Hipertansiyon ile Subfoveal Koroid Kalınlığı Arasındaki İlişkinin Değerlendirilmesi

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ABSTRACT

Objective: Hypertension (HT) can cause vascular and microvascular changes. There is no barrier between systemic blood and ocular region. Changes in choroidal perfusion pressure due to HT may impair retinal function and oxygenation, and subfoveal choroidal thickness (SCT) may be affected by these changes. The aim of this study was to evaluate the effect of arterial HT on SCT in children.

Method: The study was performed on 102 cases (51 patients and 51 controls), prospectively. Optical coherence tomography was used for the measurement of SCT and mean values of 3 consecutive measurements were evaluated. All cases had blood pressure measurements during all day via ambulatory blood pressure monitoring. Also, both groups were evaluated for the target organ damage.

Results: There were 51 cases in patient group with the average age of 14.4±2.8 years, and the rest of 51 control cases were meanly 14.5±2.8 years in age (p=0.980). SCT was measured thinner in patients with target organ damage than the cases without target organ damage (p=0.027). SCT measurements of patients and control cases were not statistically significant different (p=0.569). Especially SCT was statistically significantly thinner in cases with increased left ventricular mass, left ventricular mass index and hypertensive nephropathy (p=0.02, p=0.00, p=0.039, respectively).

Conclusion: Choroidal thickness decreases in patients with HT who develop target organ damage. Therefore, close follow-up of hypertensive patients with appropriate life changes and medical treatments is important before target organ damage develops.

Keywords: Hypertension, subfoveal choroidal thickness, optical coherence tomography, target organ damage, ambulatory blood pressure monitoring

ÖZ

Amaç: Hipertansiyon vasküler ve mikrovasküler değişikliklere neden olabilir. Sistemik kan ile oküler bölge arasında bir bariyer olmayıp hipertansiyona bağlı koroid perfüzyon basıncındaki değişiklikler retina fonksiyonunu ve oksijenasyonu bozabilir ve subfoveal koroid kalınlığı bu değişikliklerden etkilenebilir. Bu çalışmanın amacı çocuklarda arteriyel hipertansiyonun subfoveal koroid kalınlığı üzerine etkisini değerlendirmektir.

Yöntem: Çalışma prospektif olarak 102 olgu (51 hasta ve 51 kontrol) üzerinde gerçekleştirildi. Subfoveal koroid kalınlığının ölçümü için optik koherens tomografi kullanıldı ve 3 ardışık ölçümün ortalama değerleri değerlendirildi. Tüm olgulara ambulatuvar kan basıncı takibi ile gün boyu kan basıncı ölçümleri yapıldı. Ayrıca, her iki grup da hedef organ hasarı açısından değerlendirildi.

Bulgular: Hasta grubunda yaş ortalaması 14,4±2,8 yıl olan 51 olgu bulunurken, 51 kontrol olgusunun geri kalanı ortalama 14,5±2,8 yaş idi (p=0,980). Subfoveal koroid kalınlığı hedef organ hasarı olan hastalarda hedef organ hasarı olmayanlara göre daha ince ölçüldü (p=0,027). Hasta ve kontrol olgularının subfoveal koroid kalınlığı ölçümleri istatistiksel olarak anlamlı farklılık göstermedi (p=0,569). Subfoveal koroid kalınlığı özellikle sol ventrikül kitlesi, sol ventrikül kitle indeksi artmış ve hipertansif nefropatinin olduğu olgularda istatistiksel olarak anlamlı derecede daha inceydi (sırasıyla; p=0,02, p=0,00, p=0,039).

Sonuç: Hedef organ hasarı gelişen hipertansiyonlu hastalarda koroid kalınlığı azalmaktadır. Bu nedenle, hedef organ hasarı gelişmeden önce hipertansif hastaların uygun yaşam değişiklikleri ve tıbbi tedavilerle yakın takibi önemlidir.

Anahtar kelimeler: Hipertansiyon, subfoveal koroid kalınlığı, optik koherens tomografi, hedef organ hasarı, ayakta kan basıncı takibi

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INTRODUCTION

Hypertension (HT) may cause many eye changes and variety of ocular disorders, such as retinopathy, choroidopathy, vascular pathologies [1-3]. Early diagnosis is important in the treatment and to determine the reversibility of target organ damage. Eye is a critical organ reflecting hypertensive microvascular effects and allows direct observation. Evaluation of these impacts provides predictive and prognostic value in the management of systemic complications secondary to HT, diabetes mellitus, cardiovascular, cerebrovascular and other systemic vascular diseases. HT can induce many eye diseases. It has been observed that ocular findings of especially severe HT may be more pronounced and these changes may be indicative of optic neuropathy, choroidopathy and retinopathy [2,3]. Although advanced routine ophthalmoscopic evaluation is not mandatory for managing HT, digital imaging and computer analysis, which are new methods, provide early recognition of microvascular changes that are very important for ocular disorders and cardiovascular risk factors. While subfoveal choroidal thickness (SCT) has been investigated in several studies in adults, SCT has not been evaluated in children [4]. Advances in imaging technology can show important changes such as thickening, thinning, and vascular insufficiency in the choroidal layer. Optical coherence tomography (OCT) is becoming a new and important tool for obtaining cross-sectional images from chorioretinal region. Additional priorities of OCT are its being a noninvasive method which provides high resolution images. With the aid of near infrared 840 nm diode laser light, OCT uses optically reflective properties of tissues to provide detailed information about inner retinal structures. In this study, we aimed to evaluate SCT via spectral domain OCT and determine the relationship between HT, and SCT in children.

MATERIALS and METHODS

The population of this prospective study consisted of 51 hypertensive (32 male, 19 female) children followed up in Pediatric Cardiology Clinic in Medical Faculty of Manisa Celal Bayar University, Turkey between 15 November 2016-17 April 2017. Fifty-one age-, and gender-matched healthy children (33 male, 18 female) were included in the study as a control group.

The participants had chronic hypertensive patients, receiving medical treatment with cardiology follow-up. The criteria established by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents were used for the diagnosis of HT (2004) [5]. All hypertensive cases underwent blood pressure measurements during all day via ambulatory blood pressure monitoring (ABPM), achieved using a portable device (Del Mar Reynolds Tracker NIBP 2 Model no: 90207, Hertford, England UK) that recorded data every 30 min from 24.00 to 8.00 a.m. and every 15 min from 08.00 a.m. to 24.00. The measurements were taken on normal working days, and patients were advised to keep on with their daily routines. Evaluation of ABPM was made according to the American Heart Association ABPM measurement guidelines [6].

The cases with a decrease in blood pressure measurements (systolic and diastolic) more than 10% at night (compared to day) was defined as "dippers". HT patients were first classified as those with primary or essential HT. Then, they were grouped according to their ambulatory blood pressures, as being dippers and non-dippers. All patients were asked about lifestyle assessment (avoidance of inactivity and obesity, salt and alcohol-free diet, sodium-potassium intake), drug use, family history and smoking. Physical examination and anthropometric measurements including body mass index (BMI) calculation were performed. In laboratory evaluation, in addition to routine tests, fasting glucose, glycated hemoglobin and lipids were studied. The following definitions were used.

- Underweight-BMI <5th percentile for age and sex,

- Normal weight-BMI between the 5th and <85th percentile for age and sex,

- Overweight-BMI between >85th and 95th percentile for age and sex,

- Obese-BMI ≥95th percentile for age and sex,

- Severely obese-BMI ≥120 percent of the 95th percentile values, or a BMI ≥35 kg/m^2 (whichever was lower) [7,8].

National Cholesterol Education Program's adult Treatment Panel III (NCEP_ATPIII) and International Diabetes Federation (IDF) criteria were used for diagnosis of cases with metabolic syndrome [9,10].

For ocular measurements, patients with a present or past history of macular abnormality, glaucoma, amblyopia, Type 1 diabetes mellitus, autoimmune thyroiditis, surgery or trauma, and incompatible to standard deviation (SD)-OCT examination were excluded from the study. Each participant underwent a complete ocular examination to determine the best-corrected visual acuity. SD-OCT

(Retinascan RS-3000; NIDEK, Gamagori, Japan) was used for measuring SCT of right eyes between 10.00 a.m. and 11.00 a.m., day time (Figure 1). SCT was evaluated according to Macula Line Raster scan protocol. SCT was measured as the perpendicular distance between hyperreflective border of retinal pigment epithelial-Bruch membrane (automatically detected by the SD-OCT device) and sclero-choroidal interface manually drawn by two experienced ophthalmologist who were blinded to the study protocol. All cases had 3 consecutive measurements, then highest signal strength was recorded.

Evaluation of Target Organ Damage: Target organ damage was defined as the involvement of kidney(s), eye(s), blood vessel(s), heart or one or more target organs. Diagnosis of target organ damage was established in all children as noted below.

Kidneys: For the evaluation of renal damage as a target organ damage caused by HT, microalbuminuria was measured. Microalbuminuria was defined as a urinary albumin excretion rate of 30-300 mg (20-200 µg/min) in 24-hour urine samples and 2-30 mg/mmoL creatinine (20-300 mg/g creatinine) in the first urine sample collected in the morning [11].

Blood vessels: Common carotid artery, carotid bulb and internal and external carotid artery diameters were measured by ultrasound in the target-diastolic phase from all patients, and normal measurements of carotid intima-media thickness (cIMT) in healthy children were used as reference [12].

Heart: In all patients transthoracic echocardiogram was performed by the same cardiologist, using the 3S-RS (3.5 MHz) probe via GE-Vingmed Vivid 7 system (GE-Vingmed Ultrasound AS, Horten, Norway). We used standard methodology for all echocardiographic data. All cases had 3 consecutive measurements, then the mean values of them were recorded. We calculated the left ventricular mass and mass index using the Devereux formula. Following the formula validated by Devereuz and Reichek was used to calculate left ventricle (LV) mass [13]. To prevent alterations according to age, sex and weight, LVmass was indexed for height$^{2.7}$ [14]. We used 95th percentile values for the definition of left ventricular hypertrophy as LVmass index left ventricular mass index ≥36.88 g/m$^{2.7}$ in girls and ≥39.36 g/m$^{2.7}$ in boys [15].

Eyes: Detection of the findings of hypertensive retinopathy on funduscopic examination was considered the presence of hypertensive retinopathy.

This study was approved by the Manisa Celal Bayar University Faculty of Medicine Clinical Research Ethics Committee (approval number: 20.478.486-385, date: 23.11.2016), and informed consent was taken from all participants.

Statistical Analysis

All data were analyzed with SPSS for Windows 15.0. Data were expressed as mean and SD. An independent t-test was performed in independent groups for normal distribution parameters. Mann-Whitney U test was performed in the independent groups with non-

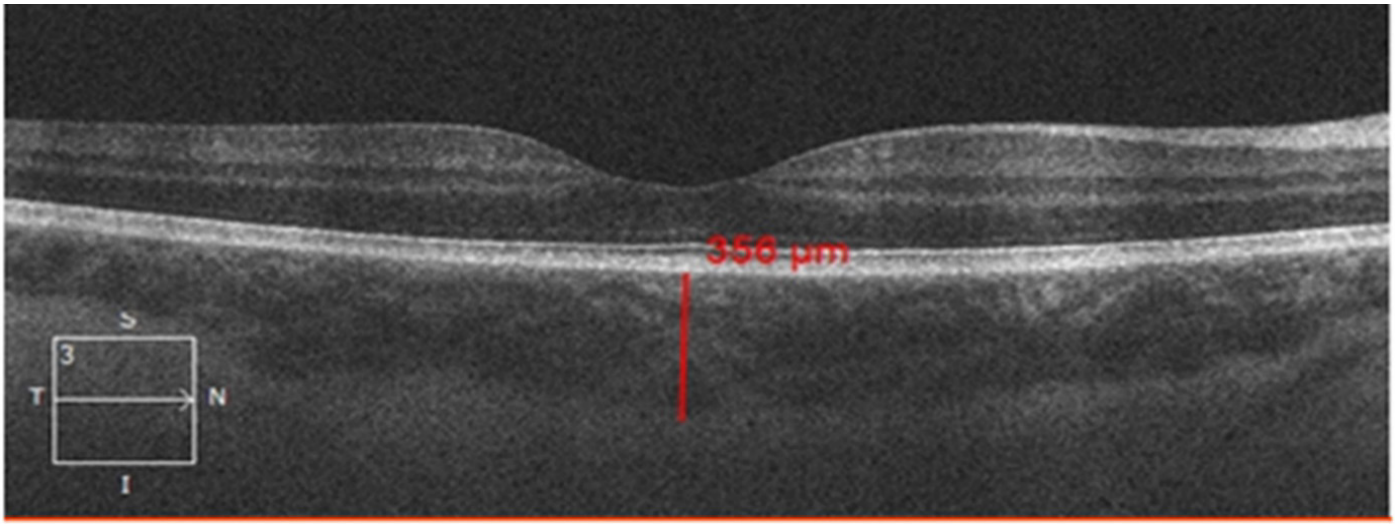

Figure 1. Measurement of subfoveal choroidal thickness with OCT

OCT: Optical coherence tomography

normal distribution. Pearson correlation was used for the comparison of two continuous variables. P<0.05 was accepted as the level of statistical significance.

RESULTS

Our study included 51 right eyes of 51 hypertensive children (32 male, 19 female) and 51 right eyes of age- and gender- matched healthy control children (33 male, 18 female). The mean ages of the patients were 14.4±2.8 years (4-19) and 14.5±2.8 years (5-19) in hypertensive and control groups; respectively, without any significant intergroup difference. When systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements were evaluated in the hypertensive and control groups, SBP and DBP measurements were found to be higher in the patient group with a statistically significant intergroup difference (p=0.000). The BMI values were higher in the hypertensive group than the control group without any statistically significant intergroup difference (p=0.051). The clinical characteristics of groups are documented in Table 1.

Primary and secondary HT patients were detected in 39 of 51 (76.5%) and 12 of 51 (23.5%) cases, respectively, without any statistically significant SCT difference (p=0.549). All HT patients were divided into groups of dippers (37 patients) and non-dippers (14 patients) in terms of mean blood pressure decreases overnight according to ambulatory measurements, and any statistically significant intergroup difference was not found in terms of SCT measurements (p=0.160) (Table 2).

We documented hypertensive cases according to the presence of cardiovascular or metabolic risk factors. There was no statistically significant difference in terms of SCT, whether cardiovascular or metabolic risk factors are present or not (Table 3).

All HT patients were divided into those with and without target organ damage. Among all 51 cases with HT, only 9 of them (17.6%) had target organ damage. These patients had hypertensive retinopathy (n=3; 5.8%), microalbuminuria (n=1; 1.9%) and increased

Table 1. Demographic characteristics and SCT of HT and control group

	Systemic HT group (n=51)	Control group (n=51)	p
Age (year)	14.4±2.8	14.4±2.8	0.917
Gender (male/female) (%)	32 (62.7)/19 (37.3)	33 (64.7)/18(35.3)	0.837
BMI (kg/m^2)	25.79±5.79	20.45±4.14	0.051
Systolic BP	126.27±15.87	114.70±13.57	0.001
Diastolic BP	83.33±12.51	73.72±11.12	0.001
Mean subfoveal CT (mμ)	400±71.37	404±67.73	0.569

SCT: Subfoveal choroidal thickness, BMI: Body mass index, BP: Blood pressure, HT: Hypertension, CT: Choroidal thickness

Table 2. Comparison of the effect of the distribution of patients in the HT group on SCT

	Mean SCT (mμ)	p
HT etiology		
Primer (n=39)	403±72.39	0.549
Seconder (n=12)	388±69.71	
Dipper group (n=14)	374±72.98	0.160
Non dipper group (n=37)	409±69.22	
Smoking (pack-year)		
Ever (n=2)	409±18.38	0.917
Never (n=49)	399±72.77	
Treatment of HT		
Yes (n=30)	396±68.49	0.730
No (n=21)	405±76.64	

SCT: Subfoveal choroidal thickness, HT: Hypertension

Table 3. Comparison of the HT group on SCT according to presence of cardiovascular and metabolic risk factors

	Mean SCT (mμ)	p
NCEP-ATPIII		
Yes (n=15)	391±70.21	0.515
No (n=36)	403±72.54	
IDF		
Yes (n=12)	422±65.90	0.210
No (n=39)	393±72.38	

NCEP-ATPIII: The National Cholesterol Education Program's adult Treatment Panel III, IDF: The International Diabetes Federation criteria for metabolic syndrome, SCT: Subfoveal choroidal thickness, HT: Hypertension

LVmass index (n=5; 9.6%). There was a close relationship between target organ damage and SCT (p=0.027). SCT was thinner in patients with target organ damage (increased LVmass, LVmass index, hypertensive retinopathy and nephropathy) than the cases without target organ damage (p=0.027) (Table 4).

We compared choroidal thickness (CT) results of patients receiving only non-pharmacological treatment (41.2%) or add-on drug management (58.8%), and no statistically significant difference was found between both groups (p=0.730). The duration of HT had not any statistically significance impact on CT (p=0.966).

DISCUSSION

The estimated prevalence of HT ranges between 2% and 5% and it is a common chronic disease in children [16]. Pediatric HT may be secondary to another disease process, or it may be essential. Parallel to the increment of obesity, prevalence of pediatric HT is increasing. Renal disease, endocrine disease and coarctation of aorta are commonly observed as the causes of secondary HT in children [17]. There are pores on choroidal vessels, thus there is no barrier between systemic blood and ocular region and these vascular differences of retina, choroid and optic nerve cause each region to respond differently to HT [18]. It has been noted that a reduction in choroidal blood flow triggers sympathetic activation and noradrenaline discharge, stimulating alpha-1 receptors that in turn trigger vasoconstriction [19,20]. Wang et al. [21] reported a close relationship between regulation of HT and vascular alterations, such as microvascular changes and focal arteriolar narrowing and concluded that vascular spasm led to focal contraction that could become permanent with fibrosis. SD-OCT has been successfully used in the early diagnosis of most ocular changes in primary and secondary HT caused by chronic cardiovascular diseases, diabetes, and neurodegenerative disorders [22]. Akay et al. [4] reported that choroidal thickness decreases in patients with systemic arterial HT because of arteriolar sclerosis and vascular contraction caused by high intravascular pressure in the choroid. However, target organ damage was not taken into consideration in their study.

Table 4. Comparison of choroidal thickness of HT group with and without target organ damage

	Mean SCT (mμ)	p
Target organ damage		
Yes (n=9)	354±67.63	0.027
No (n=42)	409±68.90	
Retinopathy		
Yes (n=3)	435±20.00	0.285
No (n=48)	397±72.92	
Nephropathy		
Yes (n=1)	244±0.0	0.039
No (n=50)	403±68.43	
Cardiopathy		
Yes (n=5)	327±8.5	0.02
No (n=46)	407±70.70	

HT: Hypertension, SCT: Choroidal thickness

Gök et al. [19] did not find any difference in SCT measurements in adult HT patients. Except for hypertensive patients with target organ damage, we found no difference between HT cases and controls in terms of SCT measurements. We reported that SCT decreased significantly in hypertensive patients with target organ damage. We thought that fibrosis resulting from decreased choroidal blood flow caused by vasoconstriction in patients with target organ damage due to prolonged or poorly controlled HT may play a role in SCT thinning. Chen et al. [23] and Hsu et al. [24] reported about SBP, CT, and myopic maculopathy and found an inverse correlation between SCT and SBP. Donati et al. [25] showed a significant reduction in SCT in hypertensive patients. Zhang et al. [26] found statistically significant difference between BMI and macular thickness in school-age children in contrast to our findings. Kong et al. [27] showed that HT had a negative relationship with macular thickness in most subfields except for the fovea especially in subjects with an elevated fasting glucose level. Yumusak et al. [28] also found a correlation between BMI and CT in obese women. In our study, we did not find any difference between BMI and SCT. We found that SCT decreased in hypertensive patients with target organ damage, especially in patients with increased left ventricular mass, left ventricular mass index and hypertensive nephropathy. However, SCT values were not different between patients with hypertensive retinopathy and-those with normal cIMT.

Whereas, SCT values were not also different between patients with hypertensive retinopathy. There are only a few studies on SCT in HT patients, but not in pediatric HT patients. The present study aims to evaluate SCT and reveals the relationship between SCT and arterial HT children. It was found that the duration of HT had no statistically significant effect on SCT. Even when pediatric patients are diagnosed at the first onset of HT, signs of target organ damage can be found.

Therefore, SCT scans can be meaningful. Since OCT is a reproducible, easily performed, noninvasive and reliable imaging technique, it can be used as a screening method for early detection of microvascular changes, especially ocular complications of HT.

Study Limitations

Our scarce number of cases with target organ damage is the limitation of the study.

CONCLUSION

This study has demonstrated the presence of a negative correlation between SCT and target organ damage, particularly with increased LVmass, LVmass index and hypertensive nephropathy. The aim of effective HT treatment is to provide normotensive values before target organ damage develops. While SCT in HT has been investigated in several studies in adults, SCT has not been evaluated in children. Considering that onset of HT in childhood may cause more destructive and irreversible damages in later life, it will be important to evaluate all effects of HT. The data suggest that irrespective of the duration of HT, SCT measurement has a predictive role in pediatric systemic arterial HT. Therefore, close follow-up of hypertensive patients with appropriate life changes and medical treatments is important before target organ damage develops. Larger, prospective studies are needed to support our study and specifically evaluate the relationship between HT and SCT using OCT.

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Ethics

Ethics Committee Approval: This study was approved by the Manisa Celal Bayar University Faculty of Medicine Clinical Research Ethics Committee (approval number: 20.478.486-385, date: 23.11.2016),

Informed Consent: Informed consent was taken from all participants.

Peer-review: Externally and internally peer-reviewed.

Author Contributions

Surgical and Medical Practices: F.A., Ş.C., Concept: F.A., S.Ş., E.Ç., H.M., Ş.C., Design: T F.A., S.Ş., E.Ç., H.M., Ş.C., Data Collection and/or Processing: F.A., S.Ş., E.Ç., H.M., Analysis and/or Interpretation: F.A., H.M., Literature Search: F.A., H.M., Writing: F.A.

Conflict of Interest: The authors have no conflict of interest to declare.

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Original Article

The Evaluation of Child Sexual Abuse: Child Advocacy Center Example

Çocuk Cinsel İstismarının Değerlendirilmesi: Çocuk İzlem Merkezi Örneği

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ABSTRACT

Objective: The purpose of the research was to evaluate the child sexual abuse cases admitted to the Child Advocacy Center (CAC) in terms of the child, family, and abuser, and to identify the associated factors.

Method: The data were collected retrospectively and descriptively from the cases in the CAC using the juridical reports, family interview reports Provincial Directorate of Family and Social Policies representative reports and the data collection form developed by the researchers.

Results: Within the scope of the research, 175 child victims of sexual abuse were evaluated According to this; the mean age of the abused children was in the study was 13.33±3.33, 81.7% were girls, and 42.9% were high school students. According to the results of the study, 34.3% of the children were diagnosed with mental illness. Among the mothers and fathers included in the study, 76% of the mothers and 33.7% of the fathers are not working and also 85.1% of the mothers and 79.5% of the fathers are primary school graduates. In addition, 60% of families have a low income level. It was determined that 57.7% of the children were exposed to abuse many times and irregularly, 40.6% were exposed to sexual touching, 35.4% were exposed to penetration, and 44% medical examination.

Conclusion: The study showed that family dynamics play a pivotal role in the sexual abuse of children, and low socio-economic/education level and being an adolescent girl is among the significant factors.

Keywords: Child, family, sexual abuse, child advocacy center

ÖZ

Amaç: Araştırmanın amacı Çocuk İzlem Merkezi'ne başvuran çocuk cinsel istismarı olgularını çocuk, aile ve istismarcı açısından değerlendirmek ve ilişkili faktörlerini belirlemektir.

Yöntem: Çocuk İzlem Merkezi'ne gelen olgular adli, aile ve Aile Sosyal Politikalar İl Müdürlüğü temsilcisinin görüşme raporları, araştırmacılar tarafından oluşturulan veri toplama formu ile retrospektif tanımlayıcı olarak toplandı.

Bulgular: Araştırma kapsamında, cinsel istismar mağduru 175 mağdur çocuk değerlendirilmiştir. Buna göre; çocukların yaş ortalaması 13,33±3,33, %81,7'si kız ve %42,9'u lisede öğrenim görmektedir. Çocukların %34,3'ü ruhsal hastalık tanısı almıştır. Annelerin %76'sı, babaların %33,7'si çalışmıyor. Annelerin %85,1'i babaların %79,5'i ilköğretim mezunudur. Ailelerin %60'ı düşük gelir düzeyine sahiptir. Çocukların %57,7'sinin birçok kez ve düzensiz şekilde istismara maruz kaldığı, %40,6'sının cinsel dokunma, %35,4'ünün penetrasyon olacak şeklinde maruz edildiği, %44'üne iç beden muayenesi yapıldığı belirlenmiştir.

Sonuç: Çocuğa yönelik uygulanan cinsel istismarda, aile dinamiklerinin önemli rol oynadığı, düşük sosyo-ekonomik ve eğitim düzeyinin, ergenlik döneminde ve kız çocuğu olmanın çocuk cinsel istismarında önemli faktörü olduğu belirlenmiştir.

Anahtar kelimeler: Çocuk, aile, cinsel istismar, çocuk izlem merkezi

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INTRODUCTION

Child sexual abuse is a serious violation of children's rights and a global danger including medical, legal, and psychosocial dimensions that every child is at risk of encountering worldwide. Child sexual abuse is the involvement of a child or a teenager in sexual activity that s/he is not developmentally prepared, cannot understand the outcomes, give informed consent, and resist due to legal and/or social taboos [1]. The term sexual abuse refers to a wide spectrum of violent behaviors (rape, physical harm, murder, etc.), and non-touching (verbal abuse, obscene telephone conversation, talking about sexuality openly, exhibitionism, voyeurism, exposure to auditory sexual activity) or touching (stroking, genital stimulation, oral stimulation, pornographic intercourse) acts [1,2].

Society is only as aware of the true extent of childhood sexual abuse and neglect as the tip of the iceberg. Reported sexual abuse cases constitute only a small part of all existing cases [3]. This is because children who are victims of sexual abuse tend to keep it as a secret because of feelings like guilt, fear and shame. Sexual abuse is a dreadful experience that makes disclosure difficult for the victim due to the community perspective they will face [2,4]. It is not something that the family and society can easily accept. Since child neglect and abuse usually occurs in secrecy, other people rarely witness them [3].

According to the statistics of the Child Advocacy Center (CAC) in the USA in 2017, 334,626 children were registered as victims of abuse. Of these children, 36% were boys, 64% were girls, 67% were sexually abused, 20% were physically abused, and 7.3% were neglected. The most abused age group was in the 7-12 age group, their rate was 38.6%, and 91.6% knew the abuser [5]. According to 2018 data in Turkey, 21,068 cases applied to 30 CAC in 27 provinces between January 2011 and May 2016 and 85% of these cases are girls and 15% are boys [6].

Sexual abuse is a crime according to the law, which is subject to a legal investigation. It has been reported that the obligation of children to testify repeatedly during the investigation process causes additional stress in children and families. Particular attention should be paid to avoid additional trauma to the sexually abused child [1,7,8]. For this reason, CAC was first established in the USA in 1988 to reduce the secondary emotional trauma caused by repeated forensic interviews. Since 2010, a growing number of CAC has also been established in various provinces in Turkey [9]. These centers are places in which various professionals are involved in the process as a multidisciplinary approach. The main identified aim of CACs is to prevent children from constantly having to testify in front of different authorities and to prevent them from being mentally worn out [8].

Experiencing sexual trauma in childhood is a shocking experience that deeply hurts the emotional world of the victims, radically changes their lives and has a lifelong impact Children are often exposed to some types of abuse or all types of abuse and neglect at the same time. Children who have been sexually abused often experience emotional abuse too [4,10,11]. Sexual abuse, which affects the psychological, social, and cognitive development of children, is a universal problem that can be encountered at all ages, at every socio economic level, in every region, and in all kinds of ethnic groups and cultures [11].

Exposure of children to sexual abuse is an issue that has psychological and social consequences, legal and moral dimensions, and sanctions for themselves, their families, the abuser who attempted this crime, and society. Child sexual abuse and neglect is a problem that profoundly damages the concept of a "healthy society", which requires a social struggle. The primary goal in this struggle is to prevent child abuse and neglect. The underlying cause of child neglect and abuse is the complex interaction between various risk factors. Even is the presence of conditions considered as risk factors does not conclusively prove the existence of neglect and abuse, it provides the first data for early diagnosis and treatment [3,9,11]. It is essential to identify the risk factors associated with abuse and neglect to struggle with the problem. Issues such as preventing and diagnosing child neglect and abuse, identifying risk groups, providing consultancy services are also important in terms of crisis management and provision of protective services [10,12].

Considering all these facts, this study was planned to make a general evaluation about the types of admission, reasons for admission, diagnoses, and associated risk factors for child sexual abuse cases at the CAC. As a result of the study, it is thought that the data obtained on the child, his family, and the abuser will contribute to the existing literature in taking protective and preventive measures against child sexual abuse.

MATERIALS and METHODS

Research Type

The study was conducted retrospectively and descriptively to evaluate the child sexual abuse cases admitted to the CAC in terms of the child, family, and the abuser, and to identify the associated factors.

Population-sample

No sample selection was performed in the study, and all cases who were admitted to the CAC between 11.02.2019 (the date the center was opened) and 20.08.2020 (the onset of collecting the data) included in the sample (n=175).

Data Collection Tools

The data were collected using a data collection form developed by the researchers including questions about the child, the abuser, and family dynamics like the age and gender of the child, economic status and education level of the family, type of abuse, the abuser, and the degree of relationship. The relevant information in the interview reports in the CAC was transferred to the data collection form.

Before starting the study, ethics committee approval was obtained from the Ethics Committee of the Gümüşhane University with the number 2020/06 and date 11.06.2020, as well as the institutional approval from the institution where the data of the study was collected.

Statistical Analysis

The evaluation of the data was made using the SPSS (Statistical Package for Social Sciences) 22.0 statistical package program. Descriptive statistical methods like numbers and percentage calculations and arithmetic mean were used in the analysis of the data.

RESULTS

Within the scope of the research, 175 children who were exposed to sexual abuse were evaluated. The study showed that the mean age of the victim children was 13.33±3.33, 81.7% were girls, and 42.9% were high school students. 34.3% had a mental illness, 57.7% of the parents lived together, 16.6% of the parents had a consanguineous marriage, 76% of the mothers and 33.7% of fathers were unemployed, and 13.7% of fathers had a criminal record. 16% of the victims had a family member with a disability, 85.1% of mothers and, 79.5% of fathers were primary school graduates, 48% did not have health insurance, and 60% had a low financial situation. In addition, 9.7% of the families of abused children had suicide case and 6.9% of those who committed suicide were sexually abused children (Table 1).

According to the children's statements, the mean age of the abusers was 26.22±17.86, and 97.7% were male.

Abusers was described as "lover/friend" by 33.7% of the victimized children, also 81.7% of the children were only abused by one person and 57.7% were irregularly abused many times. The study shows that; 40.6% of the children were exposed to sexual touch, 35.4% were exposed to abused including penetration. In addition to all this 45.1% of those exposed to penetration had vaginal penetration, 44% had a medical examination and 2.9% were pregnant (Table 2).

According to our results, 36.6% of the people who reported the abuse were teachers, 74.3% of the families had a "protective" attitude towards the victim child, 52.6% of the families, and 58.3 of the victims filed a complaint against the abuser (Table 3).

"Counselling" was the protective injunction given to 83.4% of abused children (Table 4).

DISCUSSION

In the study, the child sexual abuse cases admitted to the CAC were evaluated. It is believed that identifying risk groups for sexual abuse and associated factors with a retrospective and descriptive study will be a guide to struggling against sexual abuse.

Discussing the Findings Regarding the Victim

In the study, most of the sexually abused children were found to be girls, and in some societies, being a girl is considered as a risk factor for sexual abuse [13]. Similar studies also report that victims of abuse are mostly girls [14,15]. In our study, children were mostly exposed to sexual abuse during adolescence. Literature has citations that being a girl during adolescence can be considered a significant risk factor for sexual abuse, which is consistent with our finding [14-16].

In the study, it was determined that 10.3% of the cases had a diagnosis of physical disease, 34.3% of them had a diagnosis of mental illness, and children with a diagnosis of depression, mood disorder and mental retardation were predominantly mental disorders. Malnutrition, moodiness, sleep problems, excessive crying, hyperactivity, behavioral disorders, chronic diseases, mental and physical problems are often observed in abused children [13,17]. Various studies conducted with sexually abused children highlighted that a significant number of victims had diagnosed with a mental illness [18,19]. The literature on sexual abuse cases report that children's perceptions of good and bad touch are distorted, their beliefs that they are loved through sexuality are reinforced, the victims blame themselves and feel lonely and desperate as they think that this situation only happens to them, they are exposed to threats and exploitation of emotions by their closest relatives, and their basic sense of trust is damaged [20,21].

Table 1. Sociodemographic characteristics of children and their families (n=175)					
Characteristics	**n**	**%**	**Characteristics**	**n**	**%**
Age (mean ± SD)	13.33±3.33 (minimum: 5; maximum: 18)	-	**Presence of a mental illness**		
Gender			No	115	65.7
Female	143	81,7	Psychotic disorder	3	1.7
Male	32	18.3	Depression	16	9.1
Education level			Mood disorders	9	5.1
			Mental retardation	14	8.0
			ADHD	7	4.0
			Impulsive disorder	3	1.7
			Dyslexia	2	1.1
Preschool	7	4.0	Others	8	4.5
Primary school	20	11.4	**Presence of a physical illness**		
Secondary school	62	35.4	No	157	89.7
High school	75	**42.9**	Speech disorder	11	6.3
Special education	7	4.0	Diabetes	3	1.7
No education	4	2.3	Heart disease	1	0.6
			Blind	1	0.6
			Growth retardation	1	0.6
			Asthma	1	0.6
Consanguineous marriage			**Employment status of the mother**		
Yes	29	16.6	Yes	42	24
No	146	83.4	No	133	76
Parents' criminal status			**Employment status of the father**		
No	149	86.2	Yes	116	66.3
Mother	2	1.1	No	59	33.7
Father	2	13.7			
Having a sibling			**A family member with a disability**		
Yes	158	90.3	Yes	28	16.0
No	17	9.7	No	147	84.0
Biological or Stepparents			**The status of parents being alive**		
Biological	159	90.9	Both alive	157	89.7
Step	16	10.2	One of both parents deceased	18	10.3
Mother's education level			**Father's education level**		
Primary and secondary school	149	**85.1**	Primary and secondary school	139	**79.5**
High school	24	13.7	High school	31	17.7
University	2	1.1	University	5	2.9
Health insurance			**Socioeconomic situation**		
Yes	91	52	High	3	1.7
No	84	**48**	Middle	67	38.3
			Low	105	**60**
Suicide history			**Parents living together**		
No	158	90.3			
Mother	2	1.1	Yes	101	57.7
Father	3	1.7	No	74	42.3
Victim child	12	**6.9**			

Table 2. The characteristics of the abuse and the abusers according to the victims					
Characteristics	**n**	**%**	**Characteristics**	**n**	**%**
Age					
Gender of the abuser			**The number of abuses**		
Female	2	1.1	Once	61	34.9
Male	171	97.7	More than once	101	**57.7**
Female and male	2	1.1	Regularly	13	7.4
Degree of relationship with the abuser			**The number of abusers**		
Family (biological)	16	9.1	1	143	81.7
Family (step)	7	4.0	2-3	24	13.7
Close relative	24	13.7			
Neighbor	32	19.4			
Lover/friend	59	**33.7**	4+	8	4.6
Stranger	24	13.7	**Pregnancy**		
Teacher	9	5.1	Yes	5	**2.9**
More than one person	4	2.3	No	162	92.6
			Suspected	8	4.6
Types of abuse			**Penetration location (n=62)**		
Penetration	62	35.4	Vaginal	28	45.1
Verbal abuse	3	1.7	Anal	17	27.4
Exhibitionism	7	4.0	Anal and vaginal	17	27.4
Pornography	2	1.1			
Sexual touch	71	40.6			
Genital touch	2	1.1			
Medical examination					
Yes	77	44.0			
No	98	56.0			

Table 3. Attitudes of the families of child victims towards abuse					
Characteristics	**n**	**%**	**Characteristics**	**n**	**%**
The reporter of the abuse			**Family attitude to child victim***		
Victim	16	9.1	Protective	130	**74.3**
Family	50	28.6	Rejecting	12	6.8
Teacher	64	**36.6**	Accusatory	16	9.1
Physician	22	12.6	Not accepting	25	9.8
Relative/neighbor	22	12.6			
Police	1	0.6			
Family filing a complaint			**Victim filing a complaint**		
Yes	92	**52.6**	Yes	102	**58.3**
No	43	24.6	No	55	31.4
Indecisive	40	22.8	Indecisive	5	2.9
			No reasoning	13	7.4
*More than one option has been chosen					

Table 4. The protective injunctions given for the abuse		
Characteristics*	**n**	**%**
Providing care	37	21.1
Staying with the family	133	76.0
Health care	52	24.7
Counseling	146	83.4
Social investigation	31	17.7
Education	11	6.3
*More than one option has been chosen		

The families of the victims are questioned about whether their children have been diagnosed with a mental disorder or not when they are admitted to CACs, and health care injunctions are provided when necessary. After the health care measures, some cases are also diagnosed with mental disorders, so it is thought that the actual rates are higher than the findings obtained in our study.

Discussing the Findings Regarding the Family

Most of the parents in the study were alive and significant number of parents were separated or divorced. In similar studies in the literature, the parents of sexually abused children are generally separated, and the rate of parental loss is higher than the rest of the society [22,23]. It is believed that family dynamics play a critical role in child abuse and that not only the divorced or separated parents but also the absence of one or both may cause the parents to lose their authority over the child, and this situation will pave the way for the children to experience in appropriate situations for their developmental level.

The rate of consanguineous marriage in the study was found to be 16.6%. Metin [24] found the rate of consanguineous marriage in families of sexually abused children as 17.8%, and Bhatta and Haque [25] found that women who had consanguineous marriages were exposed to domestic violence more than the others. In addition to consanguineous marriage between parents, factors such as low income, education level and violence can lead to child neglect and then sexual abuse cases.

The families in the study mostly had a low-income level, and most of the mothers were unemployed. Being a family with a low-income level is a risk factor for the exposure of children to sexual abuse [14,23,26]; however, some studies suggest that that child sexual abuse is not related to socioeconomic status and can occur at any socioeconomic level [27,28]. In national studies, child abuse is generally reported to be more common in families with middle- or low-income levels [29,30]. Therefore, to obtain more objective and concrete data, further comprehensive studies with large samples including regional and cultural differences are recommended.

In this study, 13.7% of the fathers had a criminal record. In a study by Cetin and Altıner [23], the rate of a criminal record was reported to be 18% in the family members of sexually abused children. Having a criminal record of any of the family members can be considered a significant factor for the possibility of repetition of the crime and harming the family members.

Within the scope of protective and preventive interventions especially in primary health care services; it is thought that the evaluation of risk factors for crime in the family and the provision of supportive trainings such as anger control, problem solving skills and coping methods to risky family members will play a role in reducing the crime rate.

Most of the parents in the study were primary school graduates, which is parallel with the literature reporting that families with low education levels constitute a risk group for child sexual abuse [14,31]. The reason for this situation may be because families with low education levels have an inadequate level of awareness of abuse and neglect of their children due to financial problems.

It was determined that 9.7% of family members committed suicide and 6.9% of those who committed suicide were sexually abused children. In similar studies in the literature, a history of abuse was seen in adolescents who attempted suicide [32,33]. Adolescents aged 13-18 years can experience substance addiction, running away from home, suicide attempts, and social withdrawal [13]. It can be assumed that sexually abused children cannot cope with their negative emotions and consider suicide an escape.

In the study, it was determined that the majority of parents (74.3%) showed a protective approach against

sexual abuse. Child sexual abuse can negatively affect not only the victims, but also the families of the children and even the clinicians working with them [34]. Learning of the child's sexual abuse by the parents can generally create feelings of anger and disappointment in the parents, and it can also cause the parents to question whether the abuse is the result of their own neglect and their parenting style. Parents may develop mixed feelings such as anger towards their children or shame with the thought that they tarnish the family name, and they may hesitate to love and touch their children [35]. Difficulties in believing the case, indecision or denial in the parents after learning about the child's sexual abuse are common reactions that cause psychological distress and inconsistency [36]. Studies have found that parent' attitudes towards abuse are based on various factors, and these factors are related to how mothers learn about abuse, the size of the crime committed, the consequences of hiding the abuse, and the level of stress. In addition, the poor care history of children, sociodemographic characteristics, psychosocial support and coping methods also affect the reactions of mothers to the traumatic situation [37,38]. As it is known, health professionals working in CAC evaluate family dynamics, inform families, and offer suggestive approaches to reduce parents' fears and concerns. It is thought that the communication and interaction between health professionals and parents for the best interests of the child plays an important role in parents' protective approach towards their children.

Discussing the Findings of Abuse

The mean age of the abusers in the study was found to be 26.22±17.86, and most of them were male. Child victims often described the abuser as a lover/friend, and they reported exposure to sexual abuse many times. Güney [39] indicated that 37.6% of the sexually abused adolescents abuses were their family members (parents, stepparents, siblings, relatives), and 62.4% reported a stranger as their abuser. A similar study found that most children were exposed to sexual abuse more than once [40]. It is known that the age of the victim, the frequency of abuse, the occurrence of the act by force, the presence of penetration, and the familiarity of the abuser cause more destructive and permanent effects on the victim [41]. The degree of relationship with the abuser is among the most critical variables associated with post-traumatic psychopathology, and those who are sexually abused by familiar person blame themselves more and have more difficulty in building trust again. Therefore, it is thought that child victims will be in a risk group in terms of mental disorders at later ages. Exposure to sexual abuse within the family adversely affects family integrity, creates a family crisis, and may lead to the blaming and exclusion of the victim child [42]. Children tend to trust a person they know more easily, which makes them more vulnerable to these people, which is a risk factor.

Many children in this study were exposed to sexual abuse in the form of sexual touch or penetration. Most of those sexually abused were exposed to vaginal penetration, and medical examination was performed in most of the cases. In a study conducted by Imren Gökçe et al. [33] with sexually abused children and adolescents, it was found that 56.1% of the sexual abuse occurred by touching, caressing, and rubbing, 36.7% of girls were exposed to vaginal penetration, and 38.5% of boys were exposed to anal penetration, in another study 58.3% of the cases were exposed to penetration, and 41.7% were exposed to sexual touch [39]. The findings in this current study are consistent with the similar studies.

Discussion of Findings on the Interlocutory Injunction

Considering the best interests of the child, within the scope of Child Protection Law No 5395, the protective injunction is given [43]. The protective injunction, including counseling, was given for most child victims in the study, and health care injunction, institutional care, social investigation, and education are among the other protective injunction types.

All children taken into institutional care in the study had been exposed to serious abuse, and their family dynamics were not at the desired level 83.4% of the cases were offered counseling injuction on issues such as family and child communication, adolescence characteristics, and risk factors, and in line with the observations of the forensic interviewer, health care injunctions were applied in some cases when necessary. It was thought that families with lower level of education might have limited awareness of child sexual abuse and also low socioeconomic status might also have formed the basis for this situation. It was determined that 83.4% of the cases were offered counseling injuction on issues such as communication between the family and the child, adolescence characteristics and risk factors, and also health care injunctions were taken when deemed necessary in line with the observations of the forensic interviewer. CACs are centers where children who are victims of abuse and their families are evaluated holistically, risk factors are determined and necessary precautions are taken for the best interests of

the child and therefore they are regarded as effective organizations in this respect.

Study Limitations

The main identified limitation of the study is that the data in the study is limited to the information obtained from the interview reports of the cases admitted to the CAC. In a larger sample, multicenter and multidisciplinary studies can be planned.

CONCLUSION

The study revealed that being a girl and being in the adolescent age group are significant factors for exposure to sexual abuse and that low education and economic status of parents are among the other associated factors for child sexual abuse. The majority of sexually abused children experience repeated victimization. After all these considerations, within the scope of protective injuctions, it is recommended to provide children training programs covering subjects like distinguishing between good and bad touch patterns, asking for help, family commutation and possible risk factors of adolescence, reporting abuse, etc. in accordance with their development level. Besides, there is a need for counseling training on the establishment of strong family dynamics, communication with the child, possible risk factors, symptoms that can be seen in sexually abused children, the approach to the child and how to report abuse etc.

Ethics

Ethics Committee Approval: Before starting the study, ethics committee approval was obtained from the Ethics Committee of the Gümüşhane University with the number 2020/06 and date 11.06.2020, as well as the institutional approval from the institution where the data of the study was collected.

Informed Consent: Since our study had a retrospective design, informed consent was not obtained from the patients.

Peer-review: Externally and internally peer-reviewed.

Author Contributions

Surgical and Medical Practices: N.G.B., D.A., Concept: N.G.B., D.A., F.Ü.T., Design: N.G.B., D.A., F.Ü.T., S.U., Data Collection and/or Processing: N.G.B., D.A., F.Ü.T., Analysis and/or Interpretation: F.Ü.T., S.U., Literature Search: N.G.B., D.A., F.Ü.T., S.U., Writing: N.G.B., F.Ü.T., S.U.

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Original Article

Process Validation and Reporting in Hospital Hemovigilance Services

Hastane Hemovijilans Hizmetlerinde Süreç Validasyonu ve Raporlaması

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ABSTRACT

Objective: Hemovigilance covers the entire transfusion chain, from the collection of the blood product and its components to the monitoring of adverse reactions. The aim of our study was to perform a process validation for the hemovigilance system of our hospital and to evaluate patients who developed blood transfusion reactions.

Method: University of Health Sciences Turkey, Dr. Behçet Uz Child Health and Diseases Training and Research Hospital; among the patients who received blood transfusion between January 2019 and December 2019, 238 patients were identified by systematic sampling method. Blood components used in patients undergoing treatment in different clinics; Examining the physician and nurse observation notes and the data in the hospital information system, whether the transfusion process is appropriate; It was evaluated by hospital hemovigilance coordinator, hemovigilance nurse, pediatric hematologist and pediatric intensive care specialist.

Results: Of the 238 randomly selected patients, 122 (51.3%) were male and 116 (48.7%) were determined as female. The median age was 91 (14-180) months. In the evaluation of the transfusion process; Only 1 patient (0.4%) was observed to exceed the optimal transfusion time. No error was detected in other blood transfusion processes. It was observed that 8 (3.3%) of the patients who underwent transfusion had a transfusion reaction.

Conclusion: In our study, it was found that there is no significant problem in recognizing, applying and reporting transfusion reactions before and during transfusion applications. In our country, there is no previous study on hemovigilance process validation. Prospective process validations are required.

Keywords: Hemovigilance, blood transfusion, process validation, transfusion reactions

ÖZ

Amaç: Hemovijilans, kan ürünü ve bileşenlerinin toplanmasından istenmeyen reaksiyonların izlenmesine kadar tüm transfüzyon zincirini kapsar. Çalışmamızın amacı, hastanemizin hemovijilans sistemine yönelik bir süreç validasyonu yapmak ve kan transfüzyon reaksiyonu gelişen hastaları değerlendirmekti.

Yöntem: Sağlık Bilimleri Üniversitesi, Dr. Behçet Uz Çocuk Sağlığı ve Hastalıkları Eğitim ve Araştırma Hastanesi'nde; Ocak 2019-Aralık 2019 tarihleri arasında kan transfüzyonu yapılmış hastalardan sistematik örnekleme yöntemi ile 238 hasta belirlendi. Farklı kliniklerde tedavisi süren hastalara kullanılan kan bileşenlerini; hekim ve hemşire gözlem notları ve hastane bilgi yönetim sistemindeki veriler incelenerek transfüzyon sürecinin uygun olup olmadığını; hastane hemovijilans koordinatörü, hemovijilans hemşiresi, çocuk hematoloji uzmanı ve çocuk yoğun bakım hekimi tarafından değerlendirildi.

Bulgular: Randomize seçilen 238 hastanın 122'si (%51,3) erkek, 116'sı (%48,7) kız olarak belirlendi. Hastaların yaş ortanca değeri 91 (14-180) ay idi. Transfüzyon sürecinin değerlendirilmesinde; sadece 1 hastada (%0,4) optimal transfüzyon süresinin aştığı görüldü. Diğer yapılan kan transfüzyon süreçlerinde hata saptanmamıştır. Transfüzyon uygulanan hastaların 8'inde (%3,3) bir transfüzyon reaksiyonu kaydı bulunduğu gözlendi.

Sonuç: Çalışmamızda, kan transfüzyonu öncesinde ve transfüzyon uygulamalarında, transfüzyon reaksiyonlarının tanınması, uygulanması ve bildiriminde önemli bir sorun olmadığı saptanmıştır. Ülkemizde daha önce hemovijilans süreç validasyonuna yönelik bir çalışma bulunmamaktadır. Prospektif olarak yapılacak süreç validasyonlarına ihtiyaç vardır.

Anahtar kelimeler: Hemovijilans, kan transfüzyonu, süreç validasyon, transfüzyon reaksiyonu

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INTRODUCTION

Hemovigilance which is defined as a set of surveillance procedures from blood collection to the follow-up of the recipients covers the entire transfusion chain and carries out the collection of data about unexpected or undesirable situations to prevent their recurrences. The term hemovigilance is derived from the Greek word "Haema" (blood) and the Latin word "Vigilance" (on alert). The ultimate goal of hemovigilance is to increase the safety of the blood donors and transfusion recipients by preventing the recurrence of adverse reactions and events [1]. Hemovigilance has varying methodologies due to differences in health infrastructure and regulatory requirements in every country [2-4]. The first attempt for the implementation of this system was established in Japan in 1993 [5]. Following the establishment of a hemovigilance system France in 1994; today it is applied almost all over Europe and is increasingly spreading in countries outside of Europe [6].

When we look at the historical background regarding hemovigilance in our country; following the establishment of transfusion committees in hospitals and the determination of their working principles and duties in 2004, surveillance reports of blood donation and transfusion were made mandatory and standard forms regarding hemovigilance notifications were created between 2007and 2009. With the publication of the first national guide in 2016; a permanent hemovigilance system was implemented in European standards. The guide was last updated in 2020.

Although it is important to carry out with a workflow in accordance with the national guidelines and standards, checking and validating the system is necessary to ensure the transfusion safety.

From this point of view, a process validation study has been planned to go through our hemovigilance system in order to detect malfunctions in the system.

MATERIALS and METHODS

To perform a process validation study for the hemovigilance system in University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital in Turkey, 238 patients were selected randomly by a systematic sampling technique at a 95% confidence interval from the patients who received a total of 6986 blood component transfusions between January 2019 and December 2019. For these patients an evaluation form was prepared to determine the patient demographic variables (age, sex, etc), blood transfusion variables (blood component, transfusion time, component volume, etc), follow-up variables (adverse events and effects).

The criteria evaluated for process validation were determined according to the 2020 hemovigilance guide. 180-240 minutes for ERT and 30-60 minutes for fresh frozen plasma and apheresis platelet concentrate were sought as the appropriate transfusion time [15]. Transfusion reactions are divided into two groups as early and late type. Those that developed in the first 24 hours were defined as acute type, and those that occurred from 24 hours to 28 days were defined as late type. They were also grouped among themselves as hemolytic and non-hemolytic. All transfusion reactions (febrile non-hemolytic transfusion reaction (FNHTR), mild allergic transfusion reaction) occurring in patients were recorded.

By examining the pre and post-transfusion patient records remarkable data on vital signs, laboratory findings, discordance between physician orders and notes and nursing observation notes were also registered at enrollment.

Nonconformities in the process were evaluated by the team consists of a hemovigilance coordinator, a hemovigilance nurse, a pediatric hematologist and a pediatric intensivist.

A written informed consent was taken from all parents of the participants.

The ethics committee approval for the study was obtained from the local ethics committee of the University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital (approval number: 83, date: 04.06.2020).

Statistical Anaysis

Statistical analysis was done using SPSS 22.0 software. All numerical and categorical data were evaluated using descriptive statistical methods. Mann-Whitney U test was used for numerical data that did not show normal distribution, and the chi-square test was used for the analysis of categorical data, and results with p -values below 0.05 were considered statistically significant.

RESULTS

122 (51.3%) of the blood transfusion patients were male and 116 (48.7%) were female. The median age of the patients was 91 (14-180) months. Although the median

age of the males was higher than females, no statistically significant difference was found between the two groups in terms of median age (p=0.433). The most frequent blood component used in transfusion was RBC with 66% (n=157) and it was followed by fresh frozen plasma with 15.5% (n=35). One hundred thirty-eighth (58%) of patients were transfused in pediatric hematology clinic, whereas 80 (33.6%) were in the pediatric intensive care unit, 17 (17.1%) were in a general pediatric clinic and 3 (1.3%) were in pediatric infection clinic. Looking from the viewpoint of transfusion indications, it was observed that thalassemia (34.5%) and malignancy (20.6%) were prominent in the cases (Table 1). Evaluating the procedures involved in blood transfusion the only finding for evidence of unconformity was prolonged time interval for blood transfusion in a patient (0.4%). The reason for the prolongation up to 5 hours was determined as the stand still of transfusion due to fever (38.5 °C) in the patient which was not considered as an adverse reaction associated with transfusion and attributed to the underlying disease.

Additionally, examination of physician orders and notes and nursing observation notes revealed no essential clinical finding to suggest pretransfusion infection while the laboratory measurements of white blood cell count, C-reactive protein and procalcitonin were normal and no growth detected on blood cultures of the patient. With these findings, the case commented as a FNHTR.

In total, transfusion-associated adverse reactions were detected in 8 cases (3.3%) in which 6 of them were mild allergic reactions and 2 were FNHTRs (Table 2).

Seven of these cases (2.9%) were patients followed in a pediatric hematology clinic and one case (0.4%) was a patient treated in the pediatric intensive care unit. It was also observed that all adverse reactions had been followed in concordance with the national hemovigilance guidelines, no conformity or error on pre- and post-transfusion processes were detected.

DISCUSSION

The main purpose of the hemovigilance system in inpatient treatment facilities is to detect transfusion-related adverse effects and events, including near-miss events, and to take measures to prevent their

Table 1. Blood components used in patients and transfusion indications

Indication	Erythrocyte suspension	Fresh frozen plasma	Apheresis platelet concentrate	Cryoprecipitate	Total
Thalassemia	81 (98.8%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	82 (34.5%)
Malignancy	25 (49.0%)	5 (9.8%)	19 (38.7%)	2 (4.0%)	51 (20.6%)
Cardiac disease	16 (44.4%)	16 (44.4%)	4 (11.1%)	0 (0.0%)	36 (16.0%)
Sepsis	6 (46.2%)	4 (30.8%)	2 (15.3%)	1 (7.6%)	13 (55%)
Acute abdomen	2 (20.0%)	5 (50.0%)	3 (27.3%)	1 (9.0%)	11 (4.6%)
Metabolic disease	7 (63.6%)	1 (9.1%)	3 (27.3%)	0 (0.0%)	11 (4.6%)
Hemophilia A	0 (0.0%)	0 (0.0%)	1 (11.1%)	8 (88.9%)	9 (3.8%)
Renal disease	7 (87.5%)	0 (0.0%)	0 (0.0%)	1 (12.5%)	8 (3.4%)
ROP operation	5 (71.4%)	2 (28.6%)	0 (0.0%)	0 (0.0%)	7 (2.9%)
Burn	3 (60.0%)	2 (40.0%)	0 (0.0%)	0 (0.0%)	5 (2.1%)
ABO blood group incompatibility	3 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.3%)
G6PD enzyme deficiency	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
Hereditary spherocytosis	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)

G6PD: Glucose 6 phosphate dehydrogenase, ROP: Retinopathy of premature

Table 2. Transfusion reactions and blood products administered to patients

Blood products	Febrile non-hemolytic transfusion reaction	Mild allergic transfusion reaction (ATR)	No transfusion reaction
Erythrocyte suspension	6 (2.5%)	0 (0.0%)	151 (63.4%)
Fresh frozen plasma	0 (0.0%)	0 (0.0%)	35 (14.7%)
Apheresis platelet concentrate	0 (0.0%)	2 (0.8%)	31 (13.0%)
Cryoprecipitate	0 (0.0%)	0 (0.0%)	13 (5.4%)

recurrence by performing root-cause analyzes. In this respect, the haemovigilance system, as an important part of the hospital quality management system, is the most important constituent for a safe transfusion by promoting traceability, error event reporting and audits to identify errors, adverse events and reactions associated with blood transfusion. In this point of view, a process validation study for the hemovigilance system of children's hospital was planned to with a retrospective, cross-sectional research method. It was also aimed to determine the demographic and clinical characteristics of patients who underwent blood transfusion and patients with transfusion reactions. One hundred and twenty-two (51.3%) of 238 patients who were randomly selected and included in our study with a systematic sample were male and 116 (48.7%) were female, and the median age of the patients was determined as 91 (14-180) months. Similarly, in a study conducted in Canada, it was found more frequently in males (52%) [2].

In pediatric studies, the median age characteristics vary according to hospital profiles, ranging from 1 month to 8 years [7,8]. In large-scale multi-center cohort studies from different countries, it has been reported that the most commonly transfused blood component is erythrocyte concentrate [2,9,10]. In the United States of America (U.S.A.), National Healthcare Safety Network records showed that blood components used in between 2010 and 2013 were erythrocyte concentrates in 57.1 percent, apheresis thrombocyte concentrates in 18.3 percent, fresh frozen plasmas in 18.7 percent and cryoprecipitates in 5.9 percent [3]. Similarly, in our study, the most commonly used blood component (66%) was determined as erythrocyte concentrate. Given that the majority of patients included in our study had underlying hematological diseases and malignancies it was an expected result. Similiarly, in the 11-year cohort analysis conducted in Canada, 50.7% of the patients who received blood transfusion were determined as hematology patients [2]. Even though it is life-saving in patients, blood transfusions can cause adverse effects ranging from simple reactions to fatal complications [11-13]. In a multicenter study in the U.S.A. transfusion-associated adverse reactions were reported in 5136 (0.23%) of 2,144,723 blood transfusions that were performed in 77 centers. The most common reactions had been observed in the study were allergic reactions (46.8%) and FNHTRs (36.1%) and it was stated that platelet transfusions had associated with adverse reactions more frequently [7]. In another study from Iran, allergic transfusion reactions and FNHTRs were reported in 42.5% and 37.1% of patients, respectively [14].

In our study, transfusion reactions were observed in 8 (3.3%) of the patients whereas 6 were mild allergic reactions and 2 were FNHTRs the most frequent blood component used in patients with transfusion reactions was found to be apheresis thrombocyte concentrate.

Process validation, within the scope of transfusion-related health applications; includes well-defined practices for blood donation and blood component preparation stages [15]. Although the hemovigilance system is a quality assurance system on its own in terms of transfusion services with its monitoring and control steps, validation of this process is also necessary and essential for transfusion safety.

In our study that there is no significant problem observed in the recognition, application and reporting of transfusion reactions before and during transfusion practices in our hospital, the hemovigilance system operates as defined, and work flow charts are applied to monitor and prevent adverse effects and events that may occur.

However, since the study was conducted retrospectively; It should be foreseen that patient findings and nurse observation and physician observation files cannot be evaluated simultaneously, and some problems (absence of physician's stamp and signature, incomplete datasets, time mismatch in records, etc) may have been corrected after the checks of the hemovigilance nurse. Hemovigilance requires regular training and continuous monitoring as well as a good electronic recording system. Although validation studies are carried out for various methods and processes at different levels in blood transfusion services, there is almost no study about process validation for hemovigilance entirely in hospitals [16,17].

Study Limitations

The most important limitation of the study is its retrospective design. Since the data in our study were analyzed retrospectively, transfusion-related errors may have been corrected by the interventions of the hemovigilance team.

CONCLUSION

For the validation of the hemovigilance process, it is necessary to determine the deficiencies through annual analyzes. Our hospital was validated to be safe in terms of the hemovigilance system. However, since some of

the deficiencies of the transfusion process are corrected with the work of the hemovigilance team in the process, the problems seen in the first place may not be detected retrospectively. Evaluating the process prospectively may be an important step to strengthen transfusion safety.

Ethics

Ethics Committee Approval: The ethics committee approval for the study was obtained from the Local Ethics Committee of the University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital (approval number: 83, date: 04.06.2020).

Informed Consent: A written informed consent was taken from all parents of the participants.

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Author Contributions

Concept: E.S., Y.O., H.A., Design: F.Y.A., Y.O., H.A., Data Collection and/or Processing: E.S., Analysis and/or Interpretation: F.Y.A., H.A., Literature Search: E.S., F.Y.A., Writing: E.S., Y.O., H.A.

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Original Article

Evaluation of the Pediatric Neurology Consultations Requested from the Pediatric Emergency Service: A Single-Center Experience

Çocuk Acil Servisinden İstenen Çocuk Nörolojisi Konsültasyonlarının Değerlendirilmesi: Tek Merkez Deneyimi

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ABSTRACT

Objective: Pediatric neurology opinion is one of the most frequently requested consultations in emergency service practice. Symptoms and/or signs such as headache, altered consciousness, seizures, and focal neurological deficits are the most common consultation reasons. We aimed to retrospectively evaluate patients who were consulted with the pediatric neurology department in the pediatric emergency service.

Method: This is a descriptive cross-sectional study in which the consultation notes of patients who presented to the pediatric emergency service and required a consultation with the pediatric neurology department between June 2016 and November 2019 were analyzed retrospectively.

Results: The number of the consulted patients was 1,265. Sixteen patients left the hospital after their parents signed treatment and examination rejection form, 1,249 consultations were included. The most common reasons for consultation were seizure, routine follow-up of patients that receive home mechanical ventilator support, and headache. The rate of emergency neurological pathologies detected in brain computed tomography and magnetic resonance imaging was 1.7%. The most common electroencephalographic abnormality was focal epileptic discharges. Consultation rate requiring emergent intervention was 14.8% and status epilepticus, central nervous system infections, intracranial masses were the most common causes.

Conclusion: The most common reason for consultation was seizure. The rate of consultations requiring acute intervention was low. We think that the emergency service admissions of patients that need examination and treatment in the outpatient clinic may harm the routine functioning of the emergency service. Community education for the use of the emergency room only when necessary is essential.

Keywords: Consultation, emergency service, neurology, epilepsy pediatrics,

ÖZ

Amaç: Pediatrik nöroloji görüşü acil servis pratiğinde en sık istenen konsültasyonlardan biridir. Baş ağrısı, bilinç değişikliği, nöbetler ve fokal nörolojik defisitler gibi semptom ve/veya bulgular en yaygın konsültasyon nedenleridir. Bu çalışmada çocuk acil servisinde çocuk nörolojisi bölümüne konsülte edilen hastaları retrospektif olarak değerlendirmeyi amaçladık.

Yöntem: Haziran 2016-Kasım 2019 tarihleri arasında çocuk acil servisine başvuran ve çocuk nörolojisi kliniğine konsülte edilmesi gereken hastaların konsültasyon notlarının retrospektif olarak incelendiği tanımlayıcı kesitsel bir çalışmadır.

Bulgular: Konsültasyon yapılan hasta sayısı 1265'ti. On altı hasta, ebeveynleri tedavi ve muayene red formunu imzaladıktan sonra hastaneden ayrıldı, 1249 konsültasyon dahil edildi. En sık konsültasyon nedenleri nöbet, evde mekanik ventilatör desteği alan hastaların rutin takibi ve baş ağrısı idi. Beyin bilgisayarlı tomografisi ve manyetik rezonans görüntülemede tespit edilen acil nörolojik patoloji oranı %1,7'ydi. En yaygın elektroensefalografik anormallik fokal epileptik deşarjlardı. Acil müdahale gerektiren konsültasyon oranı %14,8 olup status epileptikus, merkezi sinir sistemi enfeksiyonları, kafa içi kitleler en sık nedenlerdi.

Sonuç: En sık konsültasyon nedeni nöbetti. Akut müdahale gerektiren konsültasyonların oranı düşüktü. Poliklinikte muayene ve tedavi gerektiren hastaların acil servise başvurularının acil servisin rutin işleyişine zarar verebileceğini düşünüyoruz. Acil servisin sadece gerektiğinde kullanımına yönelik toplum eğitimi esastır.

Anahtar kelimeler: Konsültasyon, acil servis, nöroloji, epilepsi pediatri

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INTRODUCTION

Emergency service is the department providing continuous healthcare with a multidisciplinary approach for health problems occurring in case of sudden illness, accident, or injury [1]. Approximately 20-30% of the emergency patients are in the pediatric age group [2,3]. Pediatric patients with acute neurological emergencies often present to the emergency room with various combinations of symptoms/signs such as headache, physical signs of trauma, nausea, vomiting, altered consciousness, coma, or focal neurological deficits [4]. In Europe, neurological symptoms represent up to 15% of emergency visits [5-9] . For the pediatric age group, this rate was found to be 2.5% in France [10]. In Turkey, 0.7% of the pediatric patients presenting to the emergency department received a neurological diagnosis, and 4% of them were consulted with pediatric neurology department [11]. In this study, we aimed to evaluate the demographic, clinical, radiological and electrophysiological characteristics of the patients admitted to the pediatric emergency service of a tertiary hospital and required consultation from the pediatric neurology department.

MATERIALS and METHODS

This was a single-center retrospective cross-sectional study conducted in the pediatric neurology department of Dokuz Eylül University Faculty of Medicine in Turkey. The patients that applied to the pediatric emergency service, and required a consultation from the pediatric neurology department between June 2016 and November 2019 were included in the study. Patients who left the hospital after their parents rejected examination and treatment, and signed the rejection form were excluded. Age, gender, duration of consultation, date of consultation, complaints at the time of admission, pre-diagnoses, neuroimaging and electrophysiological studies, comorbidites, and secondary referral departments were evaluated within the consultation notes in the hospital operating system. Epilepsy and migraine were diagnosed according to the International League Against Epilepsy classification and International Headache Society criteria, respectively [12,13]. Conditions such as status epilepticus, intracranial mass presenting with neurological findings, central nervous system infections, drug intoxications, demyelinating diseases associated with an attack, status migrainosus, status dystonicus that would result in mortality and/or morbidity were defined as neurological emergencies. This study was approved by Dokuz Eylül University Faculty of Medicine Ethics Committee (approval number: 2021/10-11, date: 29.03.2021).

Statistical Analysis

Statistical analysis was performed using the IBM SPSS Statistics for Windows version 22.0 (IBM Corp., Armonk, NY, USA). The normality of distribution of numerical variables was evaluated using the Kolmogorov-Smirnov test. The numerical variables were expressed as median, minimum, maximum and categorical variables as numbers and percentages (%).

RESULTS

Demographic Features

Total number of 1265 pediatric neurology consultations were requested for the patients presenting to the pediatric emergency service of our hospital between June 2016 and November 2019. After exclusion of 16 patients whose parents refused treatment, 1,249 consultations belonging to 648 (52%) male, and 601 (48%) female patients were analyzed. The age of the patients ranged from 12 days to 17 years (median 5 months). Our study population consisted of 162 (13%) newborns (0-28 days old), 240 (19.2%) infants (28 days-2 years old), 612 (49%) children (2-12 years old), and 235 (18.8%) adolescents (12-17 years old). While 1,087 (87%) consultations were requested between 8:30 AM and 5:00 PM, the rest was requested between 5:00 PM and 08:30 AM. In case of seasonal distribution, 383 (30.7%) consultations were evaluated in autumn, 323 (25.9%) in summer, 274 (21.9%) in spring, and 269 (21.5%) in winter.

Indications for Applications

The evaluation of complaints at the time of admission indicated that the most common indications were seizures (n=854, 56.4%), follow-up (patients with home-type mechanical ventilator support that could not be examined in the outpatient clinic, patients presenting for tracheostomy tube replacement and other routine examinations) (n=121, 8%), and headache (n=71, 4.7%). Fever accompanying other findings were present in 97 (7.7%) cases (Figure 1).

Prediagnoses

Prediagnoses could be made in all of 1249 consultations. More than one prediagnosis was considered in 35 patients. The most common prediagnoses made by the physicians in the emergency department were epilepsy (n=889, 69%), febrile convulsion (n=86, 6.7%), and central nervous system infection (n=61, 4.7%) (Figure 2).

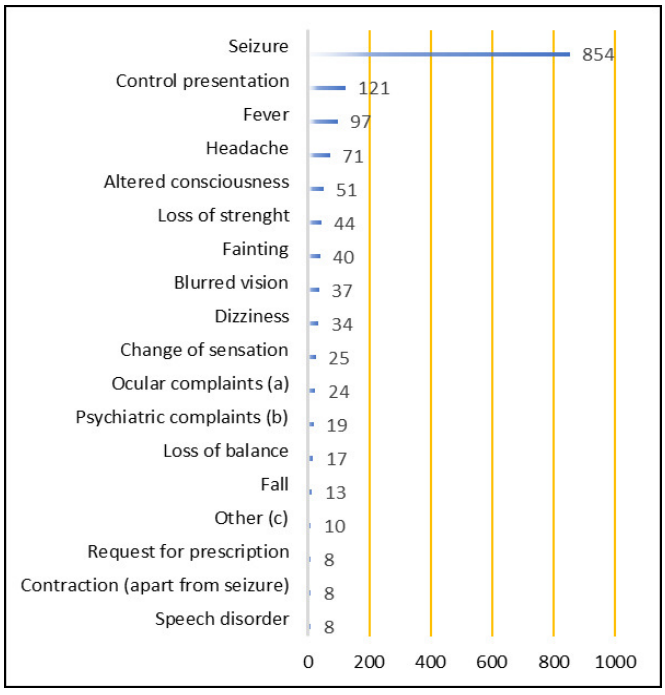

Figure 1. Distribution of the complaints. **(a)** Diplopia: 20, ptosis: 4; **(b)** behavioral disorder: 14, hallucination: 5; **(c)** facial asymmetry: 4, urinary incontinence: 2, hiccups: 2, sore throat: 1, request for evaluation after cardiac arrest: 1

After evaluation of the patients, the most common prediagnoses of the pediatric neurology department were epilepsy (n=254, 19.9%), non-neurological diseases (n=114, 8.9%), and non-epileptic paroxysmal events (n=73, 5.7%). Previous diagnosis of the epilepsy was also valid in 610 cases (49%). Among the patients presenting with seizures, 457 (36.5%) had a previous diagnosis of epilepsy. A total of 231 (18.5%) patients presented with their first afebrile seizure, including 41 (3.3%) patients with symptomatic seizures, and 190 (15.2%) cases with unprovoked seizures (Figure 3).

In our study, discrepancies between the prediagnoses made by emergency physicians and pediatric neurologists were easily noticed. Only 533 (41.2%) of 1,294 prediagnoses made by emergency physicians were the same as those of pediatric neurologists. The most significant diagnostic differences was in the most common prediagnosis of epilepsy (69% vs 19.9%). Only 28.5% of the patients consulted with a prediagnosis of epilepsy were actually diagnosed with this particular condition. While the majority of the remaining patients had no neurological diagnosis (n=70, 5.6%), the most common diagnoses were nonepileptic paroxysmal event (n=54, 4.3%), simple febrile convulsion (n=25, 2%), and complicated febrile convulsion (n=25, 2%-n=16, 1.3%). In addition, the patients presenting for routine follow-up (n=121, 8%) were also consulted with the prediagnosis of epilepsy. Febrile convulsion was another condition differing strikingly among the prediagnoses made by the physicians. Only 51.1% (n=44) of the patients with the prediagnoses of febrile seizures actually received this diagnosis. Diagnosis of neurological disease was not observed in 2.6% (n=32) of the patients consulted with a prediagnosis of febrile convulsion, while the most common diagnoses were simple febrile convulsion (n=34, 2.7%) and complex febrile convulsion and fever triggered seizure in ten cases each (0.8%).

Neurological Emergencies

In our study, diseases of the patients that would result in mortality and morbidity in the absence of emergency treatment or intervention were defined as neurological emergencies. Only 185 (14.8%) patients prediagnosed in the pediatric neurology department, had experienced neurological emergencies. Status epilepticus (n=96, 7.7%), central nervous system infection with neurological findings (n=26, 2%), and intracranial mass with neurological findings (n=12, 0.9%) were the most common neurological emergencies (Table 1).

Table 1. Neurological emergencies

Diagnosis	n	%
Status epilepticus	96	7.7
Central nervous system infection with neurological signs/symptoms	26	2
Intracranial masses with neurological signs/symptoms	12	0.9
Stroke/transient ischemic attack	11	0.9
Central nervous system demyelinating diseases	8	0.6
Febrile status	6	0.5
Drug intoxications with neurological signs/symptoms	5	0.4
Status migrainosus	5	0.4
Guillain-Barré syndrome	4	0.3
Pseudotumor cerebri syndrome	3	0.2
Transverse myelitis	2	0.2
Increased intracranial pressure syndrome due to other causes	2	0.2
Myelitis	2	0.2
Sinus venous thrombosis	1	0.1
Posterior reversible encephalopathy syndrome	1	0.1
Status dystonicus	1	0.1
Total	185	14.8

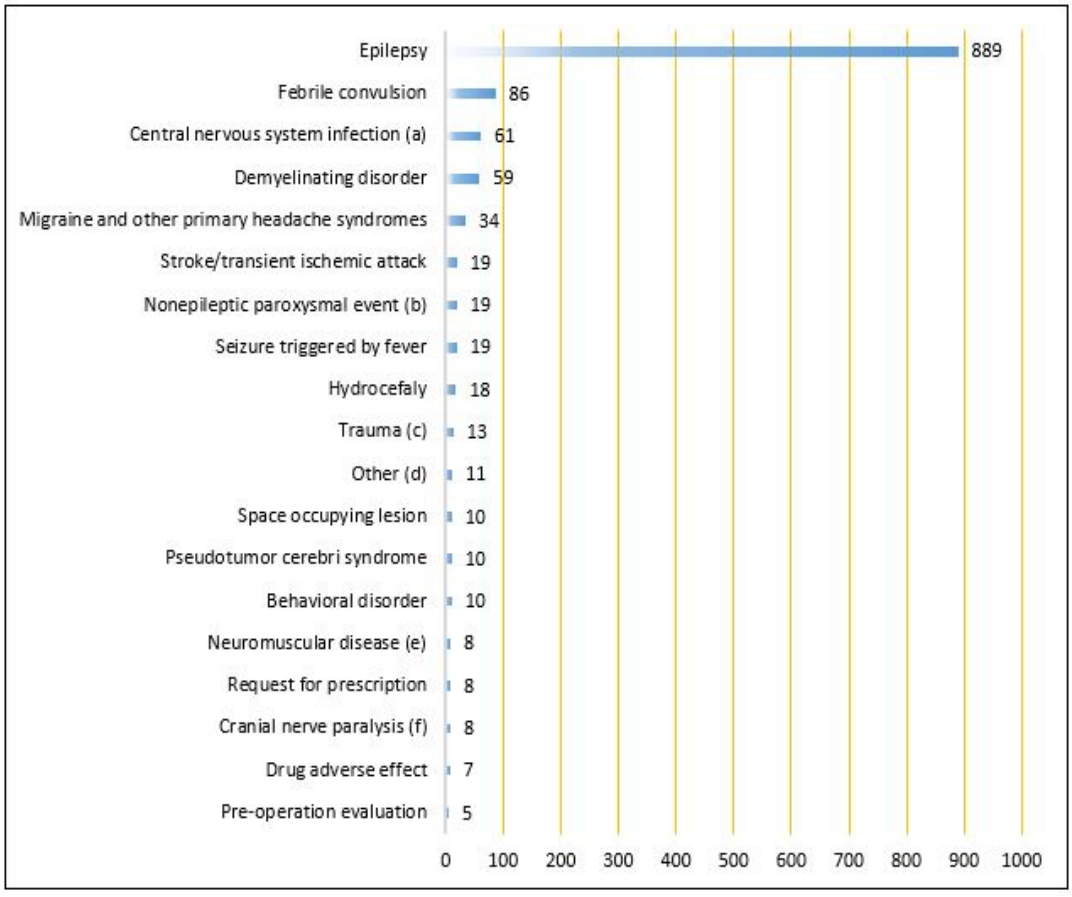

Figure 2. Prediagnoses of the physicians working in the pediatric emergency service

(a) Encephalitis: 44, cerebellitis: 10, meningitis: 7; **(b)** syncope: 14, movement disorder: 4, benign sleep myoclonus: 1; **(c)** head trauma: 12, other traumatic events: 1; **(d)** entrapment neuropathy: 4, leukodystrophy: 3, nistagmus: 1, strabismus: 1, intracranial hemorrhage: 1, intervertebral disc herniation: 1; **(e)** vMyasthenia gravis: 3, Spinal muscular atrophy: 2, Duchenne muscular dystrophy: 2, Charcot Marie Tooth disease: 1; **(f)** 7th cranial nerve paralysis: 4, 6th cranial nerve paralysis: 4

Neuroimaging

Brain computed tomography (CT) imaging was performed in 446 (35.7%) patients, and 372 (29.8%) of them were not pathologic. While nonspecific findings were observed in 53 (4.2%) patients, 21 (1.7%) patients required emergent intervention/treatment. Brain magnetic resonance imaging (MRI) was performed in 444 (35.5%) patients, including those with normal (n=336; 26.9%), and nonspecific findings (n=87; 6.9%). Only in 1.7% (n=21) of the patients a condition requiring emergent intervention or treatment was detected (Table 2).

Among the patients with a brain CT scan, 225 (18% of all consultations) were also evaluated with brain MRI. The results of the brain CT were normal in 198 (15.8%) of these patients. In 169 (13.5%) of the patients with normal brain CT results, brain MRI results were also within normal limits. Although 19 patients (1.5%) with normal brain CT imaging results had nonspecific MRI findings, 10 patients (0.8%) had a MRI finding requiring emergent intervention/treatment.

Electrophysiological Studies

Electroencephalographic (EEG) study was performed in 696 (55.7%), and yielded normal results in 330 (26.4%) patients. Focal and generalized epileptic discharges were seen in 194 (15.5%) and 111 (8.9%) patients, respectively, and background rhythm abnormalities were observed in 61 (4.9%) cases. Seventeen patients who underwent electromyographic examinations had acute sensorimotor axonal polyneuropathy (n=3), acute motor axonal polyneuropathy (n=2), demyelinating polyneuropathy (n=1), mixed-type polyneuropathy (n=1), and entrapment neuropathy (n=1).

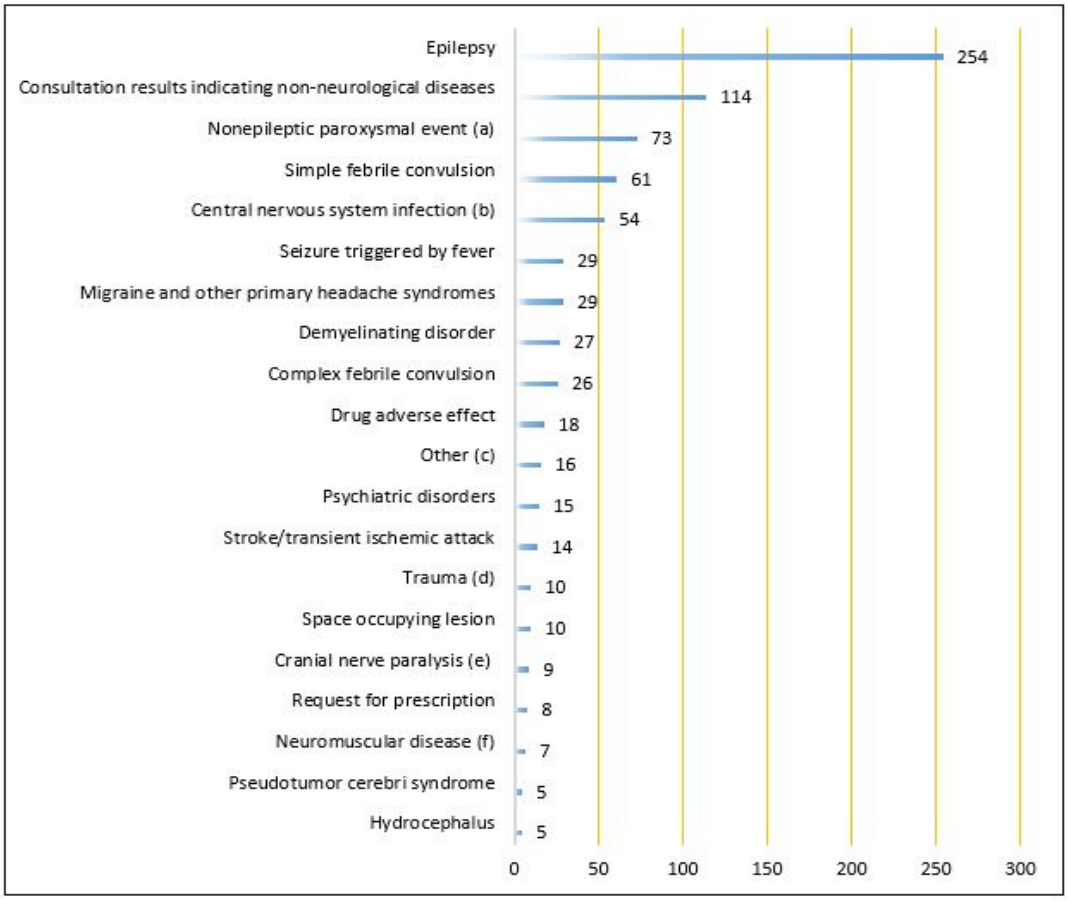

Figure 3. Prediagnoses of the pediatric neurology department

(a) Syncope: 47, breath-holding spells: 14, movement disorder: 7, benign sleep myoclonus: 3, apnea: 2; **(b)** encephalitis: 37, cerebellitis: 10, menengitis: 6, subdural empyema: 1; **(c)** entrapment neuropathy: 4, thrombosis: 2, vitamin B12 deficiency: 2, optic disc drusen: 1, intervertebral disc herniation: 1, leukodystrophy: 1, intracranial hemorrhage: 1, substance abuse: 1, metabolic myopathy: 1, strabismus: 1, autonomic dysfunction: 1; **(d)** head trauma: 9, other trauma: 1; **(e)** isolated 6th cranial nerve paralysis: 4, 7th cranial nerve paralysis: 4, isolated 3rd cranial nerve paralysis: 1; **(f)** duchenne muscular dystrophy: 2, other types of muscular dystrophy: 2, myasthenia gravis: 1, spinal muscular atrophy: 1, charcot marie tooth disease: 1

Table 2. Results of neuroimaging requiring emergent intervention or treatment

	Brain computed tomography (n)	Brain magnetic resonance imaging (n)
Space occupying lesions	9	3
Central nervous system infection	-	7
Demyelinating attack	-	6
Fracture	5	-
Stroke	3	3
Herniation	2	-
Sinus venous thrombosis	1	1
Intracranial hemorrhage	1	-
Myelitis	-	1
Total	21	21

Hospitalizations and Secondary Consultations

A total of 750 (60%) patients were hospitalized including those hospitalized in the pediatric health and diseases service (n=504; 40.3%), in the pediatric intensive care unit (n=16; 1.3%), and cases followed up in the pediatric emergency service (n=230; 18.4%). The most common conditions in patients hospitalized in the intensive care unit were status epilepticus (n=8) and central nervous system infection (n=3).

Most frequently consultations were requested with the recommendation of the pediatric neurology department from pediatric cardiology (n=170; 13.6%), pediatric metabolic diseases and nutrition (n=82, 6.5%), and pediatric infectious diseases (n=62, 4.9%) (Table 3).

DISCUSSION

To the best of researcher's knowledge, pediatric neurology consultations requested by pediatric emergency departments in Turkey have not been specifically investigated so far. A single-center study conducted in France evaluated pediatric neurological conditions in patients presenting to the emergency service within a six-month period and neurological conditions were reported with a rate of 2.5%. They also reported that 1.5% of all their cases (approximately 38/month) requested a pediatric neurology consultation [10]. In a single-center study in Turkey in which all presentations to pediatric emergency service and all consultations were investigated in a one-year period, the rate of pediatric neurology consultations was reported as 1.4% (approximately 29/month) [11]. The pediatric neurology consultation rate in our study (30.4/month) was similar to the literature.

In our study, the most common indications for admission were seizure (56.4%), follow-up (8%), headache (4.7%), and change in consciousness (3.3%). García-Peñas and Muñoz-Orduña (5) aimed to determine the incidence of pediatric neurological emergencies and reported that acute paroxysmal events (48%), headache (41%), and gait disturbance (5%) were the most common indications for consultation. Albertini et al. (10) reported that the most common indications for consultation were seizure (approximately 40%) and headache (approximately 4%).

In our study, the number of patients with epileptic seizures (n=889) was greater than the number of patients (n=854) presenting with the complaint of seizure. When the prediagnoses of the emergency service physicians made for patients presenting with seizures, fainting, and altered consciousness were evaluated, the rates of prediagnoses of epileptic seizure, febrile convulsion, and fever-induced seizure were 69%, 6.7%, and 1.5%, respectively. However, the rates of prediagnoses made in the pediatric neurology department for these complaints were quite different i.e. epileptic seizure (19.9%), simple febrile seizure (4.7%), fever-induced seizure (2.2%), and complex febrile convulsion (2%).

In this study, the prediagnoses made by emergency physicians were accurate in only 41.2% of the cases. This discrepancy was most common for the prediagnosis of epilepsy. Indeed, only 28.5% of the patients considered to have epileptic seizures by pediatric emergency physicians were regarded as having epileptic seizures by the pediatric neurology department. Most of the patients with this particular prediagnosis resulted in a non-neurological disease, and among the neurological conditions, most frequently non-epileptic paroxysmal

Table 3. Consultations recommended by the pediatric neurology department

	n	%		n	%
Pediatric cardiology	170	13.6	Pediatric genetic diseases	18	1.4
Pediatric metabolic diseases and nutrition	82	6.5	Otolaryngology	15	1.2
Pediatric infectious diseases	62	4.9	Pediatric immunology and allergy diseases	7	0.6
Brain, spinal cord and neural system surgery	51	4.1	Orthopedics and traumatology	5	0.4
Child and adolescent mental health and diseases	49	4	Pediatric endocrinology	5	0.4
Ophthalmology	34	2.7	Pediatric nephrology	4	0.3
Pediatric oncology	22	1.7	Dermatology	2	0.2
Pediatric hematology	21	1.7	Pediatric rheumatology	2	0.2
Physical medicine and rehabilitation	20	1.6	Anesthesia and reanimation	2	0.2
Pediatric gastroenterology, hepatology and nutrition	18	1.4	Medical pharmacology	1	0.1

events such as syncope, breath-holding spells, benign sleep myoclonus, febrile seizures, fever-induced seizures, and other symptomatic seizures were detected. Even by excluding patients on home-ventilator support who were consulted for routine follow-up, this considerable divergence may be caused by the lack of recognition of nonepileptic paroxysmal events, the lack of knowledge of the exact literature equivalent of the term epilepsy, or the inability to fully determine the etiologies that might classify the seizures of patients as "symptomatic", as in febrile seizures.

Albertini et al. [10] reported that 30% of the patients presenting to the emergency department were diagnosed with epilepsy. While patients with simple febrile seizures were not consulted, 42.8% of the patients with seizures were consulted in whom 86.6% had epileptic seizures. The reason of the lower rate of the epilepsy compared to the literature may be due to the consultations of the febrile seizures in our study. Another striking prediagnosis discrepancy was in febrile convulsions reported with a rate of 51.1%. Despite high frequency of the febrile convulsions in general pediatric practice, the discrepancy in the prediagnosis of this situation may be due to a lack of recognition of "febrile reactions" that can be observed with fever but not related to seizures, or a lack of familiarity with the concept of fever-triggered seizure.

In our study, 4.7% of the patients presented with headache, and 56.3% of them had at least one accompanying complaint. The most common accompanying findings were dizziness (0.9%), sensory changes (0.6%), and loss of strength (0.6%). In the literature, the incidence of headache varies according to age as 3-8%, 19.5, and 37-51.5% in children at 3, 5, and 7 years of age, respectively. Based on this frequency, appropriate management is essential in the emergency department [14-16]. The vast majority of headaches presenting to the pediatric emergency department have been reported to be primary, and benign headaches [17]. The most frequent causes of nontraumatic headache encountered in the pediatric emergency department include primary headaches (21.8-66.3%), potentially harmless secondary headaches (35.4-63.2%), and less frequently, potentially life-threatening secondary headaches (2-15.3%) [18]. Primary headache was observed in 40.8% of our patients, while secondary causes were seen in 59.2% of them. A small percentage (25.3%) of patients required urgent treatment/intervention due to headache which constituted 1.4% of all presentations. The most common neurological emergencies in which headache is the reason for presentation were status migrainosus (0.4% among all patients, and 7% among patients with headache), central nervous system infection (0.2% of all patients, and 3.5% of patients with headache), and demyelinating disease (0.1% of all applications, and 1.7% of the patients with headache).

Assessment and diagnosis of the headaches in pediatric patients can be difficult for physicians, therefore neuroimaging is often required as a part of the evaluation process [19]. CT is almost always the first neuroimaging method preferred in the emergency room in patients with suspected secondary headache due to its rapid turnover and easy accessibility. Although brain MRI provides superior quality images, the disadvantages of this particular technique are its higher procedural cost and requirement for sedation or anesthesia in young children [19,20]. Studies of the use of neuroimaging in the emergency department have shown that only 1.2% of neurologically normal patients have pathological findings that lead to a significant change in disease management [21]. Neuroimaging techniques should be spared for children with a suspicious clinical history, abnormal neurological examination findings or other symptoms of intracranial space-occupying lesions [22]. Changes in mood or personality over days or weeks, headache with severe vomiting, especially early in the morning, worsening of pain with cough or Valsalva maneuver, altered consciousness, papilledema, focal neurologic deficit or meningismus, seizures or fever, high-risk population (patients with sickle cell anemia, malignancy, recent head trauma, ventricular-peritoneal shunt, others), pain waking the child or occurring at the time of waking, change of the character of the headache in patients with primary headache, poor general condition, increased head circumference, cranial nerve palsies, abnormal ocular movements, squints, pathologic pupillary responses, visual field defects, ataxia, gait abnormalities, impaired coordination, sudden onset of headache (first or worst ever), increase in severity or characteristics of the headache, occipital headache (relative red flag), age <5 years (relative red flag) are the red flags that are the basis of existing guidelines and recommendations regarding the use of neuroimaging [18]. Tsze et al. [22] found at least one red flag in 87.9% of patients in their study, including headache present upon/soon after waking (39.7%), headache waking from sleep (34.8%), or headaches increasing in severity, frequency, and duration (46.3, 40 and 33.1%, respectively). They also reported the prevalence (1%) of emergent intracranial abnormalities. Abnormal neurological examination findings, severe vomiting especially early in the morning,

extreme pain and positional symptoms were found to be the required indications for emergency neuroimaging. Considering these results, unnecessary neuroimaging was thought to be commonly performed because of the high prevalence of nonspecific red flag findings [22]. In our study, although neuroimaging techniques were performed frequently in patients with headache, conditions requiring emergency intervention/treatment were rare, similar to the literature. Among patients consulted for headache, 59.1% of them were evaluated with brain CT, and 19.1% of these patients had pathologic findings. The most common abnormalities were space-occupying lesions (0.1%), white matter changes (0.1%), and arachnoid cyst (0.1%). In patients presenting with headache and underwent brain CT, an abnormality requiring emergent treatment/intervention (sinus venous thrombosis and space-occupying lesion) was seen in only 0.1% of them. The sensitivity and specificity of neurologic examination in detecting brain CT pathology in cases evaluated in the pediatric emergency department were reported at the rates of 87% and 94%, respectively [23]. To support this result, in our study abnormal neurological examination findings existed in all patients with emergency abnormality detected by brain CT. More than half (64.7%) of the patients consulted for headache were evaluated with brain MRI, and 28.3% of them had abnormal results with the most common pathologies being space-occupying lesions (2%), subdural effusion (1%), and demyelinating disease (1%). In only 0.6% of these patients, an abnormality requiring emergent treatment/intervention (demyelinating disease, subdural effusion, sinus vein thrombosis, space-occupying lesion, central nervous system infection) was detected.

In our study, EEGs were normal in approximately half of the patients. The most common abnormal findings were focal epileptic discharges. EEG study was most frequently requested for patients with suspicion of epileptic seizures. The vast majority of these patients had a previous diagnosis of epilepsy and presented with seizure recurrence, and EEG was performed for a treatment revision. EEGs were performed for other indications such as clarification of the first afebrile seizure or altered consciousness, and for differential diagnosis process in non-epileptic paroxysmal events. Various studies have reported that the use of EEG in the pediatric emergency department may be beneficial [24-28]. A study of 32 pediatric emergent electroencephalograms obtained for different indications such as altered mental status, paroxysmal movement (including seizure clusters) and prolonged febrile or afebrile seizures demonstrated that the EEG results influenced the treatment decision in 94% of the patients [25]. In another study with 70 pediatric emergent EEGs obtained for the suspicion of ongoing seizures or status epilepticus, 44% of total EEGs were normal and 59.1% of the patients were discharged from the emergency department mainly based on the EEG results thus preventing hospital admissions [27]. To determine the feasibility and clinical utility of point-of-care electroencephalograms (pocEEGs) for children admitted to the pediatric emergency departments with acute nontraumatic central nervous system disorders, 36 patients with acute seizures or altered mental status were analyzed and the treatment had been modified due to pocEEG results in 10 children in whom six presented with non-convulsive status epilepticus [28].

In this study, a significant increase in emergency department crowding (EDC) was observed due to the patients that did not have neurological disease (8.9%), who were admitted for routine follow-ups (8%), or for prescriptions (0.6%). In the literature, EDC was stated to be able to lead to many negative consequences such as delay in the treatment of life-threatening conditions, increased mortality and low patient satisfaction [29-33]. In our study, 14.8% of the patients presented with a neurological condition required emergency treatment/intervention, with a rate higher than 1.6% reported by Albertini et al. [10] Their low rate was explained by the fact that many cases in their center were taken directly to the intensive care unit without visiting the emergency department. Despite the higher rate of neurological emergencies in our study, many patients did not need urgent evaluation, possibly due to the difficulty of emergency service physicians encountered in distinguishing neurological conditions. Education of physicians working with large patient populations such as emergency services on neurological emergencies will contribute to improving this rate. Another reason may be the defensive medicine approach, which has become recently widespread among the physicians in whom more extensive questionnaire studies on this topic are needed.

CONCLUSION

The most common indications for consultation in the pediatric emergency service were seizures, routine follow-ups of patients receiving home-ventilator support, and headache. A small percentage (14.8%) of consultations required acute interventions. The most common conditions requiring acute intervention were status epilepticus, central nervous system infection,

and intracranial mass. In only 1.7% of the patients, both brain CT and MRI demonstrated emergency neurological abnormalities suggesting the overuse of the neuroimaging techniques. Preventing inappropriate use of emergency services will contribute to the delivery of a more qualified service within a shorter time for emergency patients, and reduce unnecessary health expenses, as well as workload of emergency service workers and consultant physicians.

Ethics

Ethics Committee Approval: This study was approved by Dokuz Eylül University Faculty of Medicine Ethics Committee (approval no: 2021/10-11, date: 29.03.2021).

Informed Consent: Since our study had a retrospective design, informed consent was not obtained from the patients.

Peer-review: Externally and internally peer-reviewed.

Author Contributions

Surgical and Medical Practices: Ç.G., C.P., G.S.U., D.S., Ö.K., D.E., S.H.K., U.Y., Concept: Ç.G., C.P., G.S.U., D.S., Ö.K., D.E., S.H.K., U.Y., Data Collection and/or Processing: Ç.G., C.P., G.S.U., D.S., Ö.K., D.E., S.H.K., U.Y., Analysis and/or Interpretation: Ç.G., C.P., G.S.U., D.S., Ö.K., D.E., S.H.K., U.Y., Literature Search: Ç.G., C.P., U.Y., Writing: Ç.G.

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Case Report

Long-Term Effects of Nusinersen Combined Physiotherapy in Spinal Muscular Atrophy Type 1: A Case Study

Nusinersen ile Kombine Fizyoterapinin Spinal Musküler Atrofi Tip 1'de Uzun Dönem Etkisi: Olgu Çalışması

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ABSTRACT

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder that is characterized by generalized muscle weakness. Any study does not exist showing the results of Nusinersen and physiotherapy in SMA type 1. Our case was diagnosed with SMA type 1 at the age of 3 months. At 8 months of age, Nusinersen treatment and physiotherapy were started. The motor skills were evaluated with CHOP-Intend and Hammersmith Infant Neurological Examinations-2 (HINE-2) before physiotherapy and Nusinersen treatments, and also applied before each dose of Nusinersen during 22 months. An increase of 14 and 13 points in CHOP-Intend and HINE-2 were shown from baseline to the last visit, respectively. This report revealed the improvement of motor functions of a child with SMA type 1 by the combination of physiotherapy and Nusinersen. Our study may encourage physiotherapists and physicians to long-term use of a combination of these two therapies for the aim of motor improvement in this neuromuscular disease.

Keywords: Physiotherapy, nusinersen, spinal muscular atrophy

ÖZ

Spinal musküler atrofi (SMA), genel kas zayıflığı ile karakterize otozomal resesif nöromüsküler bir hastalıktır. SMA tip 1'de Nusinersen ve fizyoterapinin sonuçlarını gösteren herhangi bir çalışma bulunmamaktadır. Olgumuza 3 aylıkken SMA tip 1 tanısı konuldu. Sekiz aylıkken, Nusinersen tedavisi ve fizyoterapi başladı. Motor becerileri, fizyoterapi ve Nusinersen tedavilerinden önce ve 22 ay boyunca da her Nusinersen dozundan önce CHOP-Intend ve Hammersmith Infant Neurological Examinations-2 (HINE-2) ile değerlendirildi. CHOP-Intend ve HINE-2'de ilk değerlendirmeden son değerlendirmeye sırasıyla 14 ve 13 puan artış gösterildi. Bu sonuç, SMA tip 1'li bir çocuğun motor fonksiyonlarının fizyoterapi ve Nusinersen kombinasyonu ile geliştiğini ortaya koydu. Çalışmamız, fizyoterapist ve hekimleri bu nöromusküler hastalıkta motor iyileştirme amacıyla bu iki tedavi kombinasyonunun uzun süreli kullanımına teşvik edebilir.

Anahtar kelimeler: Fizyoterapi, nusinersen, spinal musküler atrofi

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INTRODUCTION

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder characterized by the degeneration and loss of lower motor neurons, which leads to muscle atrophy and generalized muscle weakness. The incidence of this disease is estimated to be one in 11,000 live births [1]. The disease is divided into phenotypes (types 0-4) according to the age of onset of clinical symptoms and the best motor achievement. Approximately 60% of SMA patients are born with SMA type 1 which is the most severe form following type 0. The clinical signs occur before six months of age and the lifespan is limited to two years without respiratory support. The most frequently seen clinical symptoms are severe hypotonia and weakness without head control [2,3]. Weakness is usually symmetrical and the legs are weaker than the arms. Infants with SMA type 1 are unable to sit without support and have a typical respiratory pattern called "paradoxical breathing" as a result of wasting in intercostal muscles [3,4]. SMA was an incurable disease until a few years ago, but in recent years studies on the treatment of SMA have accelerated.

The survival motor neuron (SMN) gene encodes SMN mRNA and produces the SMN protein. People have two

SMN gene forms: the survival motor neuron 1 (*SMN1*) and survival of motor neuron 2 (*SMN2*). SMA occurs as a result of a mutation or homozygous deletion in *SMN1* gene. *SMN1* is responsible for producing full length of SMN protein while SMN2 acts like the compensatory gene encoding SMN protein of which the translated protein is truncated and non-full length genome that is rapidly degraded as a result of abnormal splicing [5]. The phenotype of the disease is determined according to the SMN copy number in which the disease appears milder in patients with a high number of *SMN2* gene copies [6]. Therefore, modifying *SMN2* splicing as in nusinersen treatment could be an important treatment strategy to increase the levels of SMN protein [7].

Nusinersen is an antisense oligonucleotide drug that has been developed for SMA patients. It is designed to increase production of functional SMN protein through modifying pre-mRNA splicing of *SMN2*. The phase I and II studies of nusinersen showed that drug is safe, tolerable, and could improve motor functions especially in early period of the disease [7,8].

Musculoskeletal and functional deficits, respiratory dysfunction, feeding and swallowing problems caused by weakness are dramatically common in SMA type 1. Thus, improving functional mobility/ability by positioning, contracture management, respiratory, strengthening, and range of motion exercises is the main focus of physiotherapy for these patients [9]. It has been known that different types of aerobic training may improve the motor and pulmonary functions and quality of life of SMA type 2 and 3 patients [10-13]. Although results of combined treatment with nusinersen and physiotherapy in SMA type 1 patients have not been demonstrated in the literature so far, nusinersen treatment, alone, has been proven to be effective on motor functions of patients with SMA type 1 [7,8,14]. Therefore, in this study we aimed to determine long-term effects of combined treatment with nusinersen and physiotherapy on motor function in a patient with SMA type 1.

CASE REPORT

Our case was a female patient who was born with normal spontaneous vaginal delivery with a normal birth weight of 3,300 gr at 40th gestational week. Fifteen days after her birth, her parents noticed decreased leg movements. Thus, the pediatrician referred the parents to a pediatric neurologist at the age of 3 months with symptoms of "floppy baby syndrome." Then the case was referred for genetic consultation by pediatric neurologist. DNA analysis revealed the deletion in exon 7 in *SMN1* gene and exon 8 (*SMN1* DelE7, *SMN2* DelE8) with 2 copy numbers of *SMN2* gene indicating SMA type 1 diagnosis. There was a consanguinity between the parents, but no family history of SMA disease was detected. Her mother had 5 pregnancies including 3 deliveries and 2 abortions. Our case was the third child of the parents and the only one with SMA diagnosis. The main symptoms of the patient before treatment were hypotonia, decreased deep tendon reflexes, decreased movements of the upper and lower extremities, and inability to sit without support. At 8 months of age, nusinersen treatment and physiotherapy were started. The researchers' expectation from treatment was to reduce the patient's clinical symptoms and improve her functional status which also matched with the parents' expectations. Written and verbal consents were obtained from the family.

This study had two primary efficacy end points. The primary endpoint was the motor-milestone response, which was defined according to the results on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP Intend). CHOP Intend is a validated functional test that developed to evaluate motor skills of infants with SMA. The test consists of 16 item scale scored between 0-4 points. The total score ranges from 0 to 64 points and higher scores indicate better motor function. CHOP Intend analyses to examine strength during spontaneous, reflexive, or target-specific movement, while also examining the behavioral state of infants [15].

Secondary outcome measure of the study was The Hammersmith Infant Neurological Examination (HINE). HINE is a validated scale which contains 37 items under three sections. Section 2 is related to the motor developmental milestones which we used in current study. The total score of Section 2 of HINE (HINE-2) ranges from 0 to 26 and assesses eight motor milestone achievement as voluntary grasp, kicking, head control, rolling, sitting, crawling, standing, and walking. Higher scores indicate better motor function [16]. The motor skills of the case were evaluated by CHOP Intend and HINE-2 before physiotherapy and Nusinersen treatments, and also applied before each dose of Nusinersen.

Range of motion, muscle tone, head control, and deep tendon reflexes of case were also assessed before treatment and before each Nusinersen dose. In addition, the history of pulmonary infection of the case and side effects of drug which was seen by the parents were asked.

Interventions

Nusinersen treatment has been started when the case was at 8 months of age within Expanded Access Programme. Nusinersen were delivered intrathecal injection by a pediatric neurologist on treatment days 1, 15, 29, 64, 183, 302, 421, 540, and 659. First four doses of Nusinersen were considered as loading doses [14].

Physiotherapy training started at the same time with first dose of Nusinersen. Physiotherapy session was performed by a physiotherapist, who has a 3-year experience in neuromuscular diseases, for one hour a day, 2 days a week during 22 months.

The physiotherapy session included following activity/exercises which were performed within a play activity suitable for the age of the case with encouragement of the therapist:

- Active limb movements followed initial active-assistive/passive normal range of motion exercises as the functional skills of the case improved.

- Assisted kicking to strengthen the leg muscles,

- Reaching to the objects to strengthen the arms in prone and supported sitting positions.

- Rolling from supine to prone and weight bearing in supine/prone/sitting positions.

- The case was also encouraged to transfer weight on forearms in prone.

- Activities to facilitate head control in supine/prone/sitting positions and weight bearing in supported sitting positions to strengthen neck and upper trunk extensor muscles on an exercise ball.

- Standing activity with a trunk-hip-knee-ankle-foot-orthosis (THKAFO) after gaining of full head control and independent sitting.

- Functional reaching and weight bearing exercises while standing with THKAFO.

Same activities/exercises were also taught to parents and were administered on remaining days of the week during 22 months. Parents were informed about appropriate positioning and carrying posture of the case. Postural drainage techniques were also taught to parents and was asked to practice at home each day.

The sustainability of the home program was achieved by regular interviews with the parents via calling or online face-to-face interview.

The case had a head circumference of 40 cm and body mass index (BMI) of 15.6kg/cm^2 before treatment. After 22 months, head circumference and BMI developed to 48 cm and 15.5 kg/cm^2, respectively. In physical examination, a contracture or scoliosis was not observed during treatment. The case had head control when held upright, but poor head control during traction in supine position before treatment. The case achieved head control in supine position at the age of 12 months with treatments. Sitting without support and head control from full head flexion to extension in sitting position were also accomplished during the treatment with Nusinersen and physiotherapy. In addition, she was able to roll from supine to prone and from prone to supine, and able to stand with the assistance of THKAFO after the treatment.

According to CHOP Intend score, motor function showed an increase of 11 points from baseline to the end of loading dose (a total of 4 doses Nusinersen treatment), and increase of 14 points from baseline to the last visit. In the secondary outcome measure, HINE, an increase of 2 points was observed from baseline to the end of loading dose, and an increase of 13 points from baseline to the last visit. Scores of Chop Intend and HINE according to baseline, after loading doses and last visit were shown in Figure 1.

After 8th dose of Nusinersen, a swallowing examination with videofluoroscopy was performed after a lung infection at 35 months, and the assessment revealed that the case had aspiration in liquid and viscous foods, and had no coughing response. Then the case has been started to be fed with nasogastric tube after aspiration was detected. Although she had five lung infection histories during the treatment course of 22 months, she did not need invasive or noninvasive respiratory support.

DISCUSSION

In this case report, long term effect of Nusinersen combined physiotherapy on motor functions were examined in a patient with SMA type 1. The treatment prevented the development of contracture and scoliosis, while the case gained ability to roll, full head control, sitting without support, and full range of active movement in upper extremity. She was also able to stand with an orthotic device. Despite all these improvements, swallowing and respiratory problems were detected after the 22 months treatment.

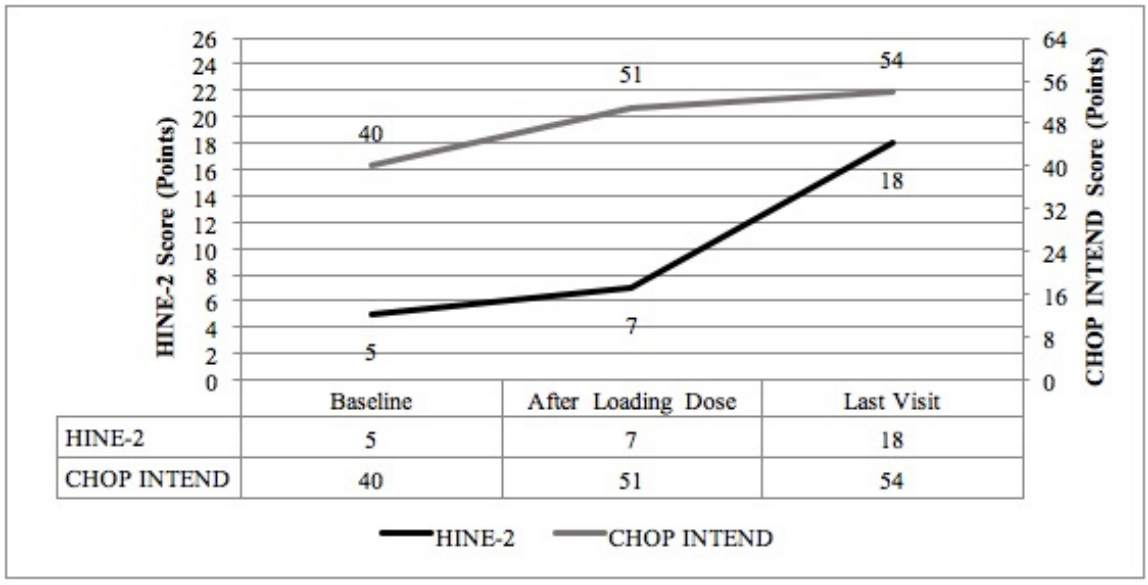

Figure 1. CHOP Intend and HINE-2 scores among the treatment process

CHOP INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, HINE-2: Hammersmith Infant Neurological Examinations-2

A 40-point CHOP Intention score was reported to be rare in SMA type 1 patients with 2 SMN copies [17,18]. Our case had a CHOP Intend score of 40 points even before starting Nusinersen and exercise therapy and at 8 months of age, and the patient was able to maintain head control for a short time in sitting position. For this reason, our patient may be one of the rare cases with SMA type 1 diagnosis. Although Nusinersen is known to be effective even in later-onset SMA patients, we observed that regular physical therapy sessions besides Nusinersen increased patients' motor functions and protected respiratory functions [19].

Although there are studies on the efficacy of Nusinersen and exercise treatment in literature, separately, within our knowledge, there is no study investigated the long-term effect of Nusinersen combined physiotherapy in patients with SMA. In a study which examined the efficacy of Nusinersen treatment, the mean increase in CHOP Intend score was 9 points, and the mean increase in HINE score was 1.4 after loading dose. In current study, the increase in CHOP Intend and HINE scores after loading dose was found to be higher than the study of Pechmann et al. [20]. Although the authors stated that physiotherapy was performed to the majority of their patients, the therapy procedure or techniques used were not clearly explained as well as the intensity, and the type of exercise given [15]. The higher motor improvement in our case may be due to the function-targeted therapy approach with functional activity and exercises, the frequency of the sessions, regular follow-ups besides long-term Nusinersen treatment, and the initial motor ability of the case.

In the study of Nusinersen phase 2 which included subjects with 3 SMN copies, patients were reported to receive a total of 2-9 doses with 6 mg or 12 mg Nusinersen. While the mean increase in CHOP Intend score was 11.5, the mean increase in CHOP Intend score who received 12 mg was declared to be 15.2 in this study [8]. Taking into account that our case had 2 SMN copies and received 12 mg dose, the higher increase in the mentioned study might origin from the genetic feature of the patients (3 SMN copies). Considering the mean decrease of 1.27 points in CHOP Intend scores of patients with SMA per year in the natural history of the disease, the Nusinersen combined physiotherapy achieved 14 points increase which gave rise to the significant efficacy of this combined therapy on motor improvement [18].

According to the secondary outcome measure of this study, HINE, a noteworthy increase up to 2.5 times was observed from the end of loading dose to the last visit. Improvement of two or more levels on at least one category were observed in most of the participants in Phase 2 study, while there was an improvement of two

or more levels in 4 motor milestone categories in our case [8]. It has been known that SMA type 1 patients can never achieve unsupported sitting in the natural history of the disease. Therefore, the development in our case as sitting without support and standing by holding the bars with THKAFO are promising for the efficacy of the combination of physiotherapy and Nusinersen treatments on better motor function in patients with SMA type 1.

In studies related to the effectiveness of exercise in SMA type 2 and type 3 patients, an increase in the motor functions of the patients was reported [10,11,21]. However in a study which the effect of cycling exercise was investigated in patients with SMA type 2, it was reported that SMN gene expression did not increase, but the motor performances of the patients increased [9,13]. Although the importance of physiotherapy is emphasized in care standards in patients with SMA, there is no study showing its effectiveness in SMA type 1 [4].

In current study, the physiotherapy sessions were planned to support patient to achieve motor skills considering the motor developmental milestones of an infant. Thus, according to the results, it can be stated that the activities/exercises which were applied keeping in mind the functional competence of a patient with SMA may contribute to the positive effects of Nusinersen treatment, and accelerate motor function development of patients. Besides, the importance of secretion clearance techniques such as postural drainage which are known to be crucial for the rehabilitation programmes of SMA patients, revealed one more time to maintain respiratory function, and prevent invasive or noninvasive respiratory support.

However, in this case, despite the improvements in motor development and respiration without an invasive/noninvasive ventilation, pulmonary infections and feeding with nasogastric tube are quite remarkable problems still. Despite all the advances in the treatment of SMA patients including Nusinersen treatment and physiotherapy, and in care standards, aspiration is still a matter that should be focused on seriously, indicating the importance of detection the early symptoms of swallowing problems.

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Author Contributions

Surgical and Medical Practices: G.A.Y., Concept: G.A.Y., N.B., A.A.K., Ö.Y., Design: G.A.Y., A.A.K., Ö.Y., Data Collection and/or Processing: G.A.Y., F.U., Analysis and/or Interpretation: G.A.Y., N.B., İ.A.G., Ö.Y., Literature Search: G.A.Y., Writing: G.A.Y., İ.A.G., Ö.Y.

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Case Report

An Uncommon Cause of a Breast Mass in a Child: Periductal Stromal Hyperplasia

Çocukta Nadir Meme Kitlesi Nedeni: Periduktal Stromal Hiperplazi

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ABSTRACT

Periductal stromal hyperplasia (PDSH) is a biphasic breast tumor characterized by spindle stromal cell proliferation. Fewer than 15 adult cases have been reported in the literature. A 14-year-old girl presented with swelling in axillary tail of the right breast persisting for 3 months. Ultrasonography was compatible with accessory breast tissue in both axillary regions. Macroscopic examination revealed 3x2x1 cm, non-encapsulated nodular lipomatous mass. Cut surface showed thin fibrotic bands through the adipose tissue. The major histopathological feature was spindle cell stromal cell proliferation concentrated around the ducts. There is no local recurrence during postoperative fourteen months. PDSH is a rare lesion frequently observed in older women. It has no specific clinical and radiological features. Definitive diagnosis can be made by histopathological examination of excision materials. The PDSHs do not show phyllodes tumor features. The spindle cells concentrating around ductal areas don't show marked atypia, demonstrate fewer mitosis and low proliferation index. Present case report is important in terms of unexpected age group and localization. PDSH should be kept in mind as a differential diagnosis of accesory breast tissue in children with axillary lump.

Keywords: Breast, periductal stromal hyperplasia, periductal stromal tumor, childhood

ÖZ

Periduktal stromal hiperplazi (PDSH) iğsi stromal hücre proliferasyonu ile karakterize bifazik meme tümörleridir. Literatürde 15'ten az erişkin olgu bildirilmiştir. On dört yaşında kız olgu, 3 aydır sağ aksiller bölgede ele gelen şişlik nedeniyle başvurmuştur. Ultrasonografide her iki aksiller bölgede aksesuar meme dokusu ile uyumlu görünüm izlenmiştir. Sağ aksiller eksizyon materyalinin makroskopik incelemesinde 3x2x1 cm boyutlarda, kapsülsüz nodüler lipomatö görünümde kitle izlenmiştir. Kesit yüzünün yağ dokudan zengin ve ince fibrotik bantlar içerdiği dikkati çekmiştir. Histopatolojik değerlendirmede duktusların çevresinde yoğunlaşan iğsi hücreli stromal hücre proliferasyonu izlenmiştir. Olgumuzun postoperatif 14. ayında lokal nüks izlenmemiştir. PDSH sıklıkla ileri yaş kadınlarda gözlenen nadir lezyonlardır. Spesifik klinik ve radyolojik özellikleri yoktur. Genellikle eksizyon materyallerinde kesin tanı histopatolojik olarak verilebilmektedir. PDSH'ler filloid özellikler göstermezler. Periduktal alanlarda yoğunlaşan, düşük mitoz ve proliferasyon indeksi gösteren, belirgin atipi bulunmayan iğsi hücreli stromal proliferasyon izlenmektedir. Olgumuz beklenmeyen yaş grubu ve lokalizasyon açısından oldukça önemlidir. Aksiller kitle ile başvuran çocuklarda aksesuar meme dokusunun ayırıcı tanısı olarak PDSH akılda tutulmalıdır.

Anahtar kelimeler: Meme, periduktal stromal hiperplazi, periduktal stromal tümör, çocukluk çağı

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INTRODUCTION

Periductal stromal hyperplasia (PDSH) is a biphasic tumor of the breast showing spinal cell stromal cell proliferation without phyllodes tumor features as leaf-like patern [1]. PDSH is an extremely rare fibroepithelial lesion of the breast with recurrence potential [1-3]. Less than 15 cases have been reported in the literature without any pediatric case. Here we present a case of PDSH detected in a 14-year-old girl by considering literature data.

CASE REPORT

A 14-year-old girl presented with swelling in the axillary tail of the right breast persisting for 3 months. Slight swelling was palpated in the left axillary region. Ultrasonographic examination revealed 25x10 mm sized mass consistent with accessory breast tissue. Excised

nodular mass weighed 5 grams with dimensions of 3x2x1 cm. It was non-encapsulated. Its cross-sectional surface showed adipose tissue with thin fibrotic bands. Histopathological examination demonstrated breast ducts with open lumens and spindle stromal cell proliferation especially concentrated around the ducts (Figure 1). There was no significant cytological atypia in stromal cells, 2 mitoses were observed in 10 high power fields. Stromal proliferation extended into the surrounding adipose tissue and surgical excision margins were positive (Figure 2). In focal areas gynecomastoid type ductal epithelial proliferation was observed (Figure 3). Stromal cells were diffusely positive with CD34 (Figure 4), and negative with estrogen (ER) receptor, and progesteron (PR) receptor by immunohistochemistry. Its Ki67 proliferation index was 3%. Breast lobule, acini, leaf-like formation did not exist through the lesion. According to morphological findings, our diagnosis was PDSH. Reexcision and medical therapy was not performed. There is no local recurrence during postoperative fourteen months. Informed consent was obtained from patient who participated in this case.

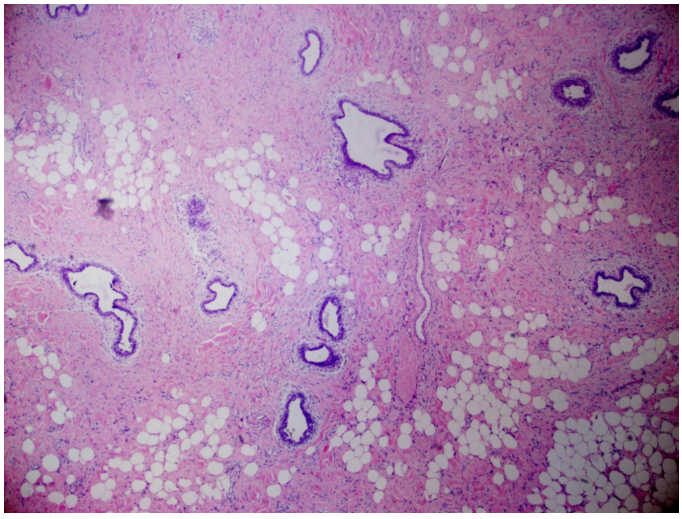

Figure 1. Spindle stromal cell proliferation especially concentrated periductal areas (H&E, x100)

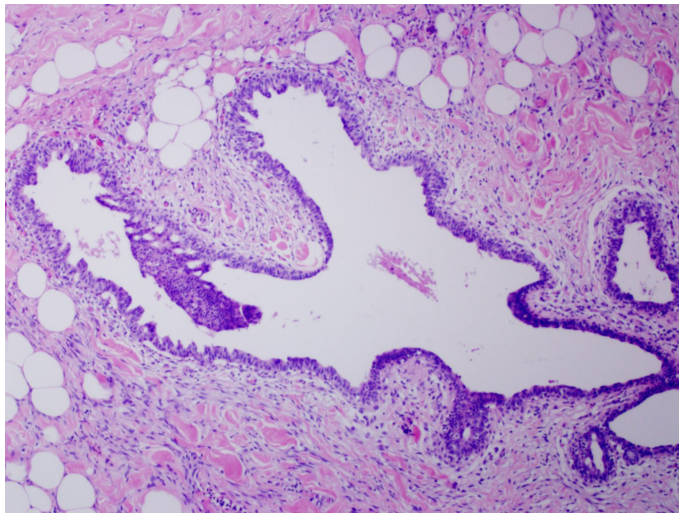

Figure 3. Gynecomastoid type ductal epithelial hyperplasia accompanying PDSH (H&E, x200)

PDSH: Periductal stromal hyperplasia

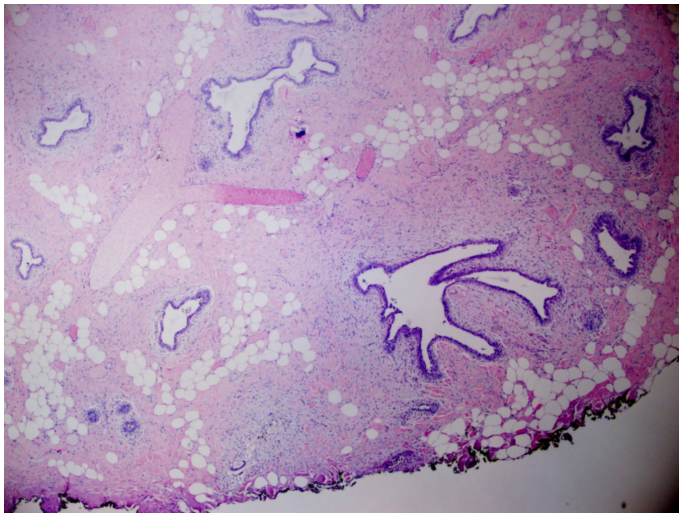

Figure 2. Surgical excision margins were positive (H&E, x100)

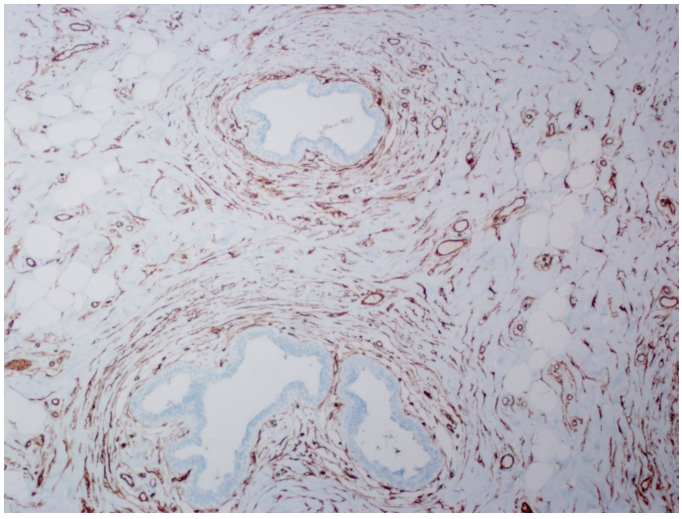

Figure 4. CD34 positivity in stromal cells (DAB, x200)

DISCUSSION

Biphasic tumors are frequent lesions of the breast. Tumors consisting epithelial and stromal proliferation can be either benign or malignant [1]. Among these tumors, fibroadenoma and phyllodes tumors are well-defined entities. PDSHs are rare breast lesions without specific clinical and radiological findings [1]. They show intermediate behaviour. Whether this tumor belongs to the phyllodes tumor spectrum or a separate entity is controversial [1]. Periductal stromal tumors (PDST), initially thought to be a variant of phyllodes tumors, are now recognized as a separate entity typically found in perimenopausal and postmenopausal women[1,4]. According to the criteria of the Armed Forces Institute of Pathology, PDST are divided into two groups as PDSH and periductal stromal sarcoma (PDSS) [1]. PDST have been described as rarely seen lesions behavioring like a low- grade sarcoma. There is no specific macroscopic specific finding of PDST [5,6]. Histologically, diagnostic criteria of PDSH are as follows: a) nodular mild stromal hyperplasia that enlarges by forming cuffs around normal or altered ducts b) lack of atypia or minimal atypia c) maximum 0-2 stromal mitoses per 10 HPF [1,6];

PDSS are defined as follows [6]: a) open tubules without phyllodes morphology and stromal spindle cell proliferation and atypia with variable cellularity around the ducts, b) one or more than one multiple nodules separated by adipose tissue, c) stromal mitotic activity (3/10 HPF) 4) stromal infiltration in surrounding breast tissue [1,6].

Immunohistochemically stromal cells stain diffusely positive with CD34, vimentin and negative with ER, PR [4].

In the literature 11 cases that met PDSH criteria have been shown [1]. The largest PDST case serial was reported by Burga and Tavassoli [6]. In this report, 20 of the cases were classified as PDSS and 7 of them as PDSH [6]. PDSH cases aged between 24-58 years. Histopathologically nodules of bland spindle cells surrounding the duct and tubules were examined. In some of them stromal edema and rare mitoses were observed (1-2/10 HPF). Atypia was not detected in spindle cell proliferation. They observed atypical features in two of the seven cases.

Burga and Tavassoli [6] defined PDSS and PDSH as PDST in peri- and postmenopausal women.

Askan et al. [3] presented a 50-year-old woman diagnosed as fibroadenoma based on tru-cut biopsy results, and excisional biopsy was performed during one year follow-up due to disease progression. Histopathological examination showed PDSH consisting of spindle cells with minimal atypia.

In the study of Coyne [2], a 52-year-old woman presented with a breast mass. This multinodular lesion had indistinct contours. In microscopic examination, they observed multinodular, mildly hypercellular, spindle cell proliferation surrounding individual or clustered ducts with one mitosis. They also observed a localized florid pseudoangiomatous stromal hyperplasia (PASH) directly adjacent to the periductal stromal tumor [2]. They emphasized that if PASH is a prominent feature in adjacent breast tissue, sampling with tru-cut biopsy may lead to erroneous diagnosis [2]. Fard and Zhang [1] presented a 57-year-old female patient with a history of stage IIB triple- negative right breast cancer treated with segmental mastectomy, adjuvant chemotherapy and radiotherapy. Ultrosonographic examination revealed a newly identified breast lesion [1]. Microscopic examination of the lesion revealed nodular periductal spindle cell proliferation that did not show phyllodes tumor features [1]. PDSTs are of mesenchymal origin [4]. Non-phyllodes sarcomas of the breast are included in the differential diagnosis of PDSH. These non-phyllodes sarcomatous breast tumors are very rare [7]. PDSSs generally don't form a mass lesion with regular smooth contours. It does not push or disrupt epithelium, like fibroadenoma and phyllodes tumor [8].

PDSTs, including PDSH, should be removed with wide excision, providing intact surgical margins [1,4]. Axillary lymph node dissection, chemotherapy or radiotherapy has no effect on the course of the disease. Their prognosis is better than the other stromal tumors of the breast [4]. Surgical border negativity is very important in recurrence and progression in PDSS [5,7].

PDSH is a rare lesion frequently observed in older women. It has no specific clinical and radiological features. Definitive diagnosis can be made by histopathological examination of excision materials. The PDSHs do not show phyllodes tumor features. The spindle cells concentrating around ductal areas don't show marked atypia, demonstrate fewer mitosis and low proliferation index. Present case report is important in terms of unexpected age group and localization. PDSH should be kept in mind as a differential diagnosis of accesory breast tissue in children with axillary lump.

Informed Consent: Informed consent was obtained from patient who participated in this case.

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Author Contributions

Surgical and Medical Practices: S.E., E.E.P., Concept: S.E., E.E.P., Design: S.E., E.E.P., Data Collection and/or Processing: S.E., E.E.P., Analysis and/or Interpretation: S.E., E.E.P., Literature Search: S.E., E.E.P., Writing: S.E., E.E.P.

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Case Report

Rare Causes of Stridor: Not All Stridors are Croups

Stridorun Nadir Nedenleri; Tüm Stridorlar Krup Değildir

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ABSTRACT

Stridor is a considerable finding, which arises from congenital or acquired causes, that might have a good prognosis or might be a life-threatening cause, and hence requires rapid assessment and intervention. Stridor is mostly considered as croup in pediatric emergency units. A multidisciplinary approach might be required for an accurate diagnosis. The patient's age, time and severity of initial symptoms, response to treatment, and coexistent findings assist in differential diagnosis. Detecting the underlying cause may be difficult and time consuming. In this study, we intended to present cases that we assessed regarding the etiological reasons presented with chronic stridor and to present remarkable characteristics of them in diagnosis and differential diagnosis, by considering the literature. Patients diagnosed with subglottic stenosis, subglottic hemangioma, laryngomalacia and laryngeal web were presented with distinctive history and clinical findings. Patients with intermittent respiratory problems coexisting with stridor can be diagnosed typically through an adequate medical history, a well-enough physical examination, and radiological methods. Flexible endoscopy provides a safe and complete examination of the children's airway.

Keywords: Stridor, dyspnea, infant, hemangioma, subglottic stenosis

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ÖZ

Stridor, doğuştan veya edinsel nedenlerden kaynaklanan, iyi bir prognoza sahip veya yaşamı tehdit edebilen, bu nedenle hızlı değerlendirme ve müdahale gerektiren önemli bir klinik bulgudur. Stridor, pediatrik acil servislerinde çoğunlukla krup, larenjit veya astım olarak değerlendirilir. Doğru bir teşhis için multidisipliner bir yaklaşım gerekebilir. Hastanın yaşı, başlangıç semptomlarının zamanı ve şiddeti, tedaviye yanıtı ve birlikte bulunan bulgular ayırıcı tanıya yardımcı olur. Altta yatan nedeni tespit etmek zor ve zaman alıcı olabilir. Bu çalışmada, kronik stridor ile ortaya çıkan etiyolojik nedenler açısından değerlendirdiğimiz olguları literatür eşliğinde sunmayı ve tanı ve ayırıcı tanıda dikkat çekici özelliklerini sunmayı amaçladık. Subglottik darlık, subglottik hemanjiyom, laringomalazi ve laringeal web tanısı alan hastalar, ayırt edici öykü ve klinik bulgular ile sunuldu. Stridor ile birlikte görülen aralıklı solunum problemleri olan hastalar tipik olarak ayrıntılı tıbbi öykü, dikkatli fizik muayene ve radyolojik yöntemlerle teşhis edilebilir. Fleksible endoskopi, çocukların hava yolunun güvenli ve eksiksiz bir şekilde incelenmesini sağlar.

Anahtar kelimeler: Stridor, solunum sıkıntısı, süt çocukluğu, hemanjiom, subglottik stenoz

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INTRODUCTION

Stridor may be the clinical manifestation of many problems related to the upper airway. The age of the patients, accompanying examination findings, the persistence of clinical findings and treatment responses should be the main markers for differential diagnosis.

Stridor is divided into two groups as acute and chronic based on its onset and duration. Stridor with an acute onset manifests within minutes, hours, or days (subacute) and usually progresses rapidly. Foreign body aspiration, anaphylaxis, bacterial tracheitis, epiglottitis, laryngotracheitis (croup), retropharyngeal abscess, peritonsillar abscess and airway burns may cause acute stridor.

Chronic stridor is typically caused by a congenital or acquired structural abnormality that leads to obstruction of the upper airway from inside or outside. Congenital causes include vocal cord paralysis, laryngomalacia, tracheomalacia, bronchogenic cyst, vascular ring, laryngeal malformations, infantile hemangiomas, and

subglottic stenosis. Stridor may develop due to acquired vocal cord dysfunction, respiratory papillomatosis, vocal cord paralysis, subglottic stenosis, laryngeal spasm due to hypocalcemia, and tumor compression [1-3].

In this study, we presented patients with stridor who were admitted to the hospital and misdiagnosed, such as croup, laryngitis or asthma. We aimed to emphasize their remarkable characteristics in the differential diagnosis in the light of literature.

Written informed consent from the patients' parents or guardians was obtained to publish cases in this study.

CASE REPORTS

Case 1

A 45-day-old male infant presented with respiratory distress. He had been intubated for 31 days following birth. On physical examination (PE), tachypnea, stridor and long expiration time were detected. No pathological finding was found at ear, nose, and throat (ENT) examination and direct laryngoscopy. Flexible endoscopy, performed under general anesthesia, revealed 95% stenosis in the subglottic region (Figure 1-A).

Case 2

An 8-month-old male patient was admitted to our clinic with difficulty sucking during an upper respiratory tract infection. Stridor and wheezing were noted when the patient was crying and excited. He was hospitalized for bronchiolitis three times. A hemangioma, which narrowed the airway passage by 50% in the subglottic region, was detected through flexible endoscopy during ENT examination (Figure 1-B).

Case 3

A 2-month-old female patient presented with respiratory distress and wheezing. Her wheezing and stridor increased when she cried since she was born, and she was more comfortable when she slept. On PE, tachypnea, stridor, intercostal and substernal retractions, and bilateral rales in lungs were observed. Laryngomalacia was assessed by flexible bronchoscopy in ENT examination (Figure 1-C).

Case 4

A 3-month-old male was referred for investigation of the etiology of stridor. Despite three direct laryngoscopic examinations and one bronchoscopic examination in another hospital, the exact cause of the stridor could not be elucidated.

On PE, wheezing and stridor were detected. No pathology was detected via direct laryngoscopy during the ENT examination. A hyperintense region was detected at the rima glottides level by computed tomography (CT) of the neck. A hemangioma covered with normal mucosa at the subglottic level was detected just below the vocal cords during the flexible laryngoscopic examination performed under general anesthesia (Figure 1-D).

Case 5

A 45-day-old male was intubated at birth due to wheezing and respiratory distress. The infant stayed in neonatal intensive care unit NICU for 30 days, 11 days of which he was intubated. On PE, he had mild stridor, wheezing and suprasternal retractions. Weight gain was at the lower threshold. In the ENT examination, which was performed under anesthesia, the glottic level was normal during flexible bronchoscopy; however, irregular web and stenosis were detected in the subglottic region (Figure 1-E).

Demographic and clinical data of all patients are given in Table 1.

DISCUSSION

Stridor arises from the turbulent airflow through the narrowed airway. Usually, it is heard during inspiration, and stridor that also occurs on expiration is termed biphasic stridor. It suggests severe, constant airway obstruction at the level of the subglottis, glottis, or upper trachea.

Stridor due to congenital anomalies may be present from birth or develop with time. In the event of narrowing at lower degrees, there might be no stridor during rest; however, due to increased activity (e.g., excitement or crying) and increased airflow rate, stridor may occur [4].

The feature of the sound heard provides further and very important insights. Hoarseness indicates an abnormality in the vocal cords. The stertor, another form of noisy breathing, evokes snoring, and essentially it is an inspiratory, low-pitched, secretory, and snoring-like sound. Pathologies that may lead to obstruction of the oropharynx, nasopharynx, and hypopharynx may usually cause stertor [5].

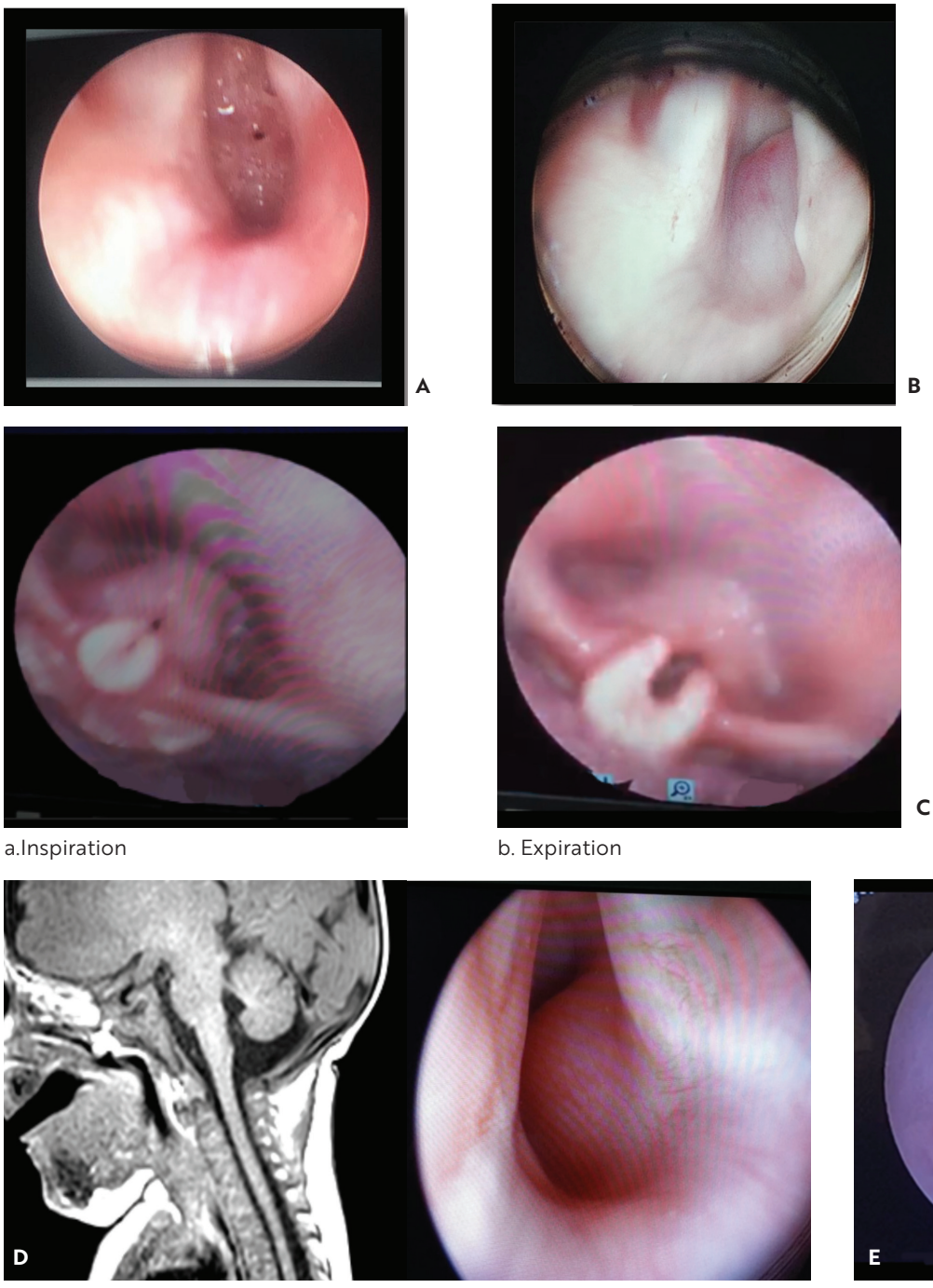

Figure 1. (A) Flexible bronchoscopy subglottic stenosis causing 95% stenosis, **(B)** Hemangioma, observed via flexible bronchoscopy, causing 50% stenosis. **(C)** Laryngomalacia, in the first picture (a), the epiglottis and arytenoids collapse during inspiration and close the glottic opening, causing inspiratory stridor. In the second picture (b), the glottis is open during expiration, and no abnormal sound is heard, **(D)** Hemangioma in neck tomography and bronchoscopy, **(E)** Subglottic stenosis and web in bronchoscopy

Table 1. Demographic and clinical findings of the patients

	Case 1	Case 2	Case 3	Case 4	Case 5
Diagnosis	Subglottic stenosis	Subglottic hemangioma	Laryngomalacia	Subglottic hemangioma	Laryngeal web, stenosis
Age/gender	45 days/male	8 months/male	2 months/female	2,5 months/male	45 days/male
Time of birth	On term	On term	On term	34 GW	On term
Birth weight (grams)	3,300	3,200	3,000	2,100	3,340
Onset time of the complaints	At birth	2.5 monts	Since birth, it has increased for the last 1 month	2.5 monts	Since birth
Complaints and symptoms	Tachypnea, stridor, longer expirium	Bronchiolitis attacks, snoring, stridor when excited or crying	Stridor when crying and lying down, snorre reflux	Stridor, wheezing	Wheezing, mild stridor, suprasternal retraction
Symptom severity	Severe	Mild, worsens with infection	Mild, worsens with infection	Moderate	Severe
Comorbidity	Mild MR, ASD	Absent	Physiological GER	Absent	Absent
Growth arrest	Slow weight gain	Absent	Absent	Absent	Slow weight gain
Duration of hospitalization	Constant	Short-term hospitalization for bronchiolitis 3 times	Absent	Neonatal pneumonia for 10 days in the neonatal period	30 days
Intubation	Intubated for 31 days	Absent	Absent	Absent	Intubated for 11 days
Treatment	Tracheostomy	Beta-blocker theraphy	Follow-up	Beta-blocker therapy	Tracheotomy
Health condition of the patient during follow-up	Tracheostomy cannula Acceration of growth	Partial recovery	Decrease in complaints	Partial recovery	Tracheostomy cannula Acceleration of growth

GW: Gestational Week, MR: Mitral regurgitation, ASD: Atrial septal defect, GER: Gastroesophageal reflux

Laryngomalacia is the most common cause of congenital stridor. It typically resolves spontaneously at the age of 12 to 24 months. Children with cor pulmonale, pulmonary hypertension, hypoxia, apnea, recurrent cyanosis, growth retardation, pectus excavatum, stridor causing respiratory failure, or laryngomalacia with severe neck/chest retractions are potential candidates for surgical treatment [6].

Laryngeal webs are rare congenital anomalies that arise from failure to dissolve the epithelial layer that shelters the laryngeal opening in normal development. Moreover, it can also be induced by trauma to the airway (intubation). These webs should be considered a lighter version within the spectrum of laryngeal atresia. 90% of the congenital laryngeal webs have been anterior glottic, while 2% are supraglottic, and 7% are subglottic. Patients with the laryngeal web generally present respiratory distress and a weak or high-pitched cry during infancy. Treatment of the laryngeal web depends on the degree of airway obstruction, whereas anterior webs in the vocal cords can be treated with simple dissection; a laryngeal stent or tracheotomy might be required in some cases [7]. Case 5 had complaints starting from birth and had 30 days of hospitalization, 11 days of which he was intubated. Although his complaints from birth onwards and the absence of adhesions in the vocal cords primarily suggested a congenital laryngeal web, it was also considered that it could have developed secondary to trauma as he was intubated for 11 days. Tracheotomy was conducted due to the presence of the web in the subglottic region and partial stenosis. Accelerated weight gain and amelioration in respiratory symptoms were detected during the follow-ups after the treatment.

Congenital subglottic stenosis is the constricting the lumen of the trachea in the cricoid area that is considered to be caused by incomplete canal formation of the

cricoid ring. It may cause biphasic stridor if it is severe in the newborn. We should note that congenital subglottic stenosis is distinguished from gained subglottic stenosis because of the lack of a history of trauma or instrumentation and relatively less severe symptoms. Less than half of the children with congenital subglottic stenosis need the administration of tracheostomy [8]. Stenosis may develop due to injury to the glottis and surrounding structures following endotracheal intubation in neonates. Acquired subglottic stenosis is more common among infants who have been intubated for a week or ≥3 times.

Endoscopy is required to identify the underlying reason and also to determine the level of the airway obstruction. Children with severe subglottic stenosis may require a tracheostomy for treatment. Decannulation may be possible as the child grows up or following reconstructive surgery [9]. Although acquired causes seem to be more common, the patient (case 1) had severe hypoxia and respiratory distress that started with birth. Very severe stenosis was detected during the flexible endoscopy of the ttic and cannulated by tracheotomy. A recovery in respiratory symptoms and accelerated weight gain were observed throughout post-cannulation follow-ups.

Subglottic hemangiomas may lead to airway obstruction. They usually become apparent around three months and cause biphasic stridor. Nowadays, the first option in treatment is propranolol. Twelve to 18 months of treatment is adequate, but it is necessary to be careful against potential adverse effects [10].

Case 2 and case 4 are the cases that we diagnosed with subglottic hemangioma. The complaints of case 2 started when he was two months old, and his stridor became permanent with the gradual growth of the subglottic hemangioma. During this period, the patient was hospitalized due to respiratory distress and received treatment for bronchiolitis. The fact that subglottic hemangiomas lead to biphasic stridor and cause expiratory manifestations makes differential diagnosis challenging for physicians.

Although the laryngoscopic examination was performed four times and one flexible bronchoscopic examination was performed due to the chronic stridor of case 4, the hemangioma, which usually looks bluish and red, could not be detected since it was covered with normal mucosa. As the current clinical manifestations indicate airway obstruction, neck CT was performed, and a hyperintense region was observed at and below the glottis level. The diagnosis could be achieved through flexible endoscopic examination, performed under general anesthesia.

Causes of congenital stridor are frequently evaluated with the misdiagnosis of croup, laryngitis, asthma, and wheezing infants [1,2,11,12]. Congenital causes of stridor can be life-threatening. Therefore, patients with chronic and recurrent symptoms should be evaluated carefully.

In conclusion, the medical history, including type and time of onset of stridor, whether it is inspiratory or biphasic, the progression of symptoms over time, the increase in breathing need in infants, such as crying, excitement, and eating, sleep-wakefulness relationship, perinatal problems and endotracheal intubation, should be questioned for differential diagnosis. Patients with intermittent respiratory problems coexisting with stridor can be diagnosed typically through an adequate medical history, a well-enough PE, and radiological methods. Flexible endoscopy provides a safe and complete examination of the children's airway and should be conducted under general anesthesia on cases with suspected airway pathology if it is indispensable.

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