DOI: 10.4274/buchd.galenos.2023.29863
J Dr Behcet Uz Child Hosp 2023;13(2):139-141

Case Report

A Case of Waardenburg Syndrome Type 1 with Maturity-onset Diabetes of The Young Type 2

MODY Tip 2'nin Eşlik Ettiği Waardenburg Sendromu Tip 1 Olgusu

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ABSTRACT

Waardenburg syndrome (WS) is known as a group of genetic conditions associated with hearing problems and pigmentary abnormalities of the hair, skin, and eyes. The association between WS and maturity-onset diabetes of the young (MODY) is rarely reported. Herein we present a 9-year-old male patient with MODY type 2 and WS whose genetic analysis revealed a known pathogenic variant i.e. c.143G>A (p.Gly48Asp)(c.1603+2T>C) in paired box gene 3.

Keywords: Waardenburg syndrome, glucokinase gene mutation, diabetes mellitus

ÖZ

Waardenburg sendromu (WS), işitme kaybı ile saç, deri ve gözlerdeki pigment anormallikleri ile ilişkili bir grup genetik hastalık olarak bilinir. WS ile gençlerin olgunluk başlangıçlı diyabeti (MODY) arasındaki ilişki nadiren bildirilmektedir. Bu çalışmada, genetik analizi sonucu paired box gene 3'te patojenik varyantı c.143G>A'yı (p.Gly48Asp)(c.1603+2T>C) saptanan MODY tip 2'nin eşlik ettigi WS'li 9 yaşında bir erkek hasta sunulmaktadır.

Anahtar kelimeler: Waardenburg sendromu, glukokinaz gen mutasyonu, diabetes mellitus

Received: 22.12.2022
Accepted: 30.03.2023

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Cite as: Korkmaz HA, Özer L, Özkan B. A Case of Waardenburg Syndrome Type 1 with Maturity-onset Diabetes of The Young Type 2. J Dr Behcet Uz Child Hosp. 2023;13(2):139-141

INTRODUCTION

Waardenburg syndrome (WS) is known as an inherited disorder associated with sensorineural deafness and pigmentary abnormalities, affecting the skin, hair, and eyes. The incidence of this autosomal dominant disorder is estimated to be roughly 2/100,000 worldwide. This syndrome manifests itself with sensorineural deafness; pigmentation defects of the skin, hair, and iris; and various defects of neural crest-derived tissues. Paired box gene 3 (PAX3) mutations are responsible for most cases of WS type 1 cases[1]. To date, only one case of WS associated with diabetes mellitus (DM) has been reported in the literature[2].

We report a 9-year-old male patient with MODY type 2 and WS whose genetic analysis revealed a known pathogenic variant i.e. c.143G>A (p.Gly48Asp) (c.1603+2T>C) in PAX3 in this study.

CASE REPORT

A 9-year-old boy of a consanguineous family was admitted to the pediatric endocrine department because of fasting and postprandial hyperglycemia. The patient had no hypoglycemic events in postnatal history. His medical history revealed that his aunt and uncle had fasting and postprandial hyperglycemia. His auxologic measurements were as follows: height: 131.5 cm (10-25 p), height standard deviation score (SDS): -0.76, weight: 28.9 kg (25-50p), weight SDS: -0.29, body mass index:

16.72 kg/m^2, and body mass index SDS: 0.16. Physical examination revealed a brilliant blue iris with dystopia canthorum, skin hypopigmentation, synophrys, broad nasal root, hypoplasia of the alae nasi, and mild sensorineural hearing loss (Figure 1). Based on diagnostic clinical criteria of Waardenburg Consortium (1992) diagnosis of WS was made[1]. A known missense pathogenic variant i.e. c.143G>A (p.Gly48Asp) in exon 2 of PAX3 was found in the proband and this variant had been transmitted from his mother. Levels of some of his remarkable laboratory parameters were as follows: blood glucose: 148 mg/dL (75-100 mg/dL), insulin: 19.1 IU/mL (2-18 IU/mL), serum C-peptide l: 3.72 ng/mL (1.1-4.4 ng/mL). HbA1c: 6.2%, anti-insulin antibody: 0.01 U/mL (0-0.5 U/mL), anti-GAD: <1U/mL (<1U/mL), and islet cell antibody was negative. Abnormal fasting and postprandial blood glucose levels were found when blood glucose levels of our patient were monitored for 5 days (Figure 2). When our patient was evaluated for maturity-onset diabetes of the young (MODY), MODY type 2 was diagnosed with heterozygote c.313delC (p.H105TfsX11) variant in the glucokinase gene. Repaglinide (0.3 mg/kg/d po bid) was started for glycemic control (Figure 2). Glycemic control was achieved, and fasting (130-140 mg/dL), and postprandial (150-180 mg/dL) blood glucose levels (150-180 mg/dL) were lowered to their normal levels (80, and 138 mg/dL, respectively) after repaglinide treatment. The participant' parent gave written, informed consent.

DISCUSSION

High fasting and abnormal postprandial levels of glycemia detected during the follow-up should suggest the presence of type 1 or 2 DM, MODY, mitochondrial diabetes, and Wolfram syndrome[3]. The work-up should include measurements of serum glucose, insulin, C-peptide, HbA1c levels, and diabetes insulin autoantibodies. In our patient mitochondrial diabetes, type 1 DM should be considered due to congenital rubella infection, and Wolfram syndrome due to the discordance between the serum glucose and insulin levels, lower C-peptide levels accompanied with family history, and hearing loss[3]. The immunodiagnostic autoantibodies in the present case were not detected during the period when non-immune diabetes was diagnosed. Our patient, did not present with diabetic ketoacidosis, low insulin, and C-peptide levels compatible with his blood glucose levels, thus type 1 DM was not considered. This study aimed to explain diabetes and hearing loss and to present signs under a single entity and WS that was rarely reported in association with DM, and different disease states that were not initially considered in the literature. The patient's hearing loss and diabetes and family history suggested Wolfram syndrome or mitochondrial diabetes. However, these diseases were excluded for the following reasons: lack of family history suggesting hereditary mitochondrial diabetes, normal optic and retinal examination, and absence of clinical findings suggestive of endocrine dysfunction and neuromuscular diseases. His physical examination revealed a brilliant blue iris with dystopia canthorum, skin hypopigmentation, synophrys, broad nasal root, hypoplasia of the alae nasi, and mild sensorineural hearing loss, thus WS was diagnosed associated with c.143G>A (p.Gly48Asp) pathogenic variant in exon 2 of PAX3 gene. With only one case report of WS with DM in the literature, concomitant presence of two different diseases were considered and MODY type 2 was diagnosed with heterozygote c.313delC (p.H105TfsX11) variant in the glucokinase gene.

Dystopia canthorum, brilliant blue iris, and synophrys were present in our patient, which are the most distinguishing diagnostic features of WS1[4]. Two or one major and two minor criteria must be present to

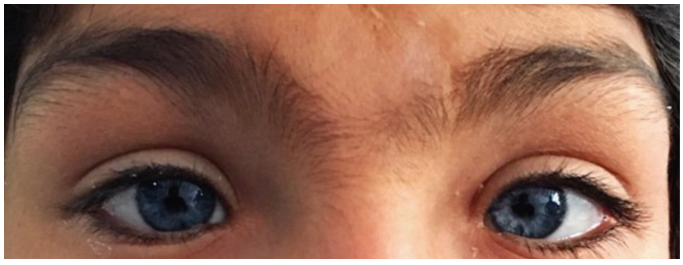

Figure 1. Dysmorphic features of the patient with Waardenburg syndrome

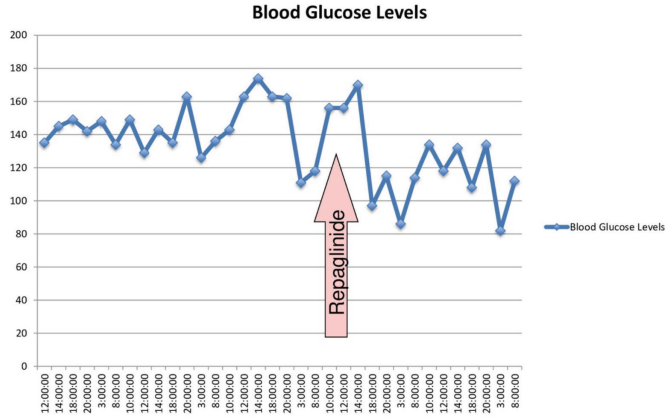

Figure 2. Decreasing trend in blood glucose levels after treatment with repaglinide

diagnose WS according to diagnostic criteria proposed by the Waardenburg consortium[1]. Evaluation of our patient based on these criteria revealed WS type 1 with four major and four minor diagnostic criteria. Galler et al.[5] reported the presence of MODY in 2.4% of their patients with newly diagnosed DM. Additionally, the Search for Diabetes in Youth study investigated MODY genes in 586 patients according to the MODY diagnostic criteria and found glucokinase gene mutation in 2.3% of their study participants. This study also reported the presence of MODY patients with an incidence rate of 8.0% in their cohort[6]. Herein we present a case of WS accompanied by glucokinase gene mutation, which was believed to be the first reported WS associated with this concomitant disorder. According to literature data, Kashima et al.[2] reported WS with diabetic retinopathy. A 30-year-old female patient presented with physical examination findings of vitreous hemorrhage and hypochromic iris, and hypopigmentation of the fundus. The *PAX3* gene homeobox domain mutation was revealed because of hypopigmentation of the fundus associated with the diagnosis of WS type 1. This patient presented with a microvascular complication of type 2 DM, such as diabetic retinopathy. After initiation of treatment with repaglinide, normal fasting and postprandial blood glucose levels were achieved and the risk of microvascular complications of DM was reduced. Kashima et al.[2] reported the association between the severity of diabetic retinopathy and the degree of hypopigmentation in the posterior fundus. The authors speculated that the hypopigmentation of the fundus in WS induced the aggravation of diabetic retinopathy. No relationship was found between WS and MODY in the literature. To our knowledge, this is the first report of a case of WS with concomitant MODY in the literature. Further observations are needed to disclose the association between DM and WS.

Ethics

Informed Consent: The participant' parent gave written, informed consent.

Peer-review: Externally peer reviewed.

Author Contributions

Surgical and Medical Practices: H.A.K., B.Ö., Concept: H.A.K., B.Ö., Design: H.A.K., B.Ö., Data Collection or Processing: L.Ö., Analysis or Interpretation: L.Ö., Literature Search: H.A.K., B.Ö., Writing: H.A.K., B.Ö.

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

Financial Disclosure: The authors declared that this study has received no financial support.

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