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Case Report

A Case of Sanfilippo Syndrome Type C and Wolfram Syndrome Type 1 and the Role of Next-Generation Sequencing in Diagnosis

Tip C Sanfilippo Sendromu ve Tip 1 Wolfram Sendromu Birlikteliği Gösteren Bir Olgu ve Tanıda Yeni Nesil Dizilemenin Rolü

Zehra Manav Yiğit[1], Rıdvan Savaş[1], Aydan Mengübaş Erbaş[1], Gökay Bozkurt[1], Ayşe Tosun[2]

[1]Aydın Adnan Menderes University Faculty of Medicine, Department of Medical Genetics, Aydın, Turkey
[2]Private Clinic, Pediatric Neurology, Aydın, Turkey

ABSTRACT

Mucopolysaccharidosis IIIC (MPS IIIC) and Wolfram syndrome type 1 (WS1) are rarely seen autosomal recessive disorders with overlapping clinical features. This case report aims to highlight the role of next-generation sequencing (NGS) in diagnosing complex phenotypes and the necessity of considering multiple genetic disorders, particularly in consanguineous populations. We present a 15-year-old male who priorly received the diagnosis of WS1, and currently exhibited dysmorphic features, intellectual disability, developmental delay, diabetes mellitus, diabetes insipidus, optic atrophy, and seizures. Clinical exome sequencing identified homozygous pathogenic variants in both *WFS1* and *HGSNAT* genes. While confirming WS1, these findings also implicated MPS IIIC as the underlying cause of symptoms unexplained by WS1. This is the first reported case of concurrent MPS IIIC and WS1. The findings underscore the critical role of NGS in diagnosing complex genetic conditions and emphasize the importance of comprehensive genetic evaluation, especially in cases with unexplained clinical variability.

Keywords: *HGSNAT*, *WFS1*, Sanfilippo syndrome type C, Wolfram syndrome type 1, next-generation sequencing

ÖZ

Mukopolisakkaridoz IIIC (MPS IIIC) ve Wolfram sendromu tip 1 (WS1), fenotipik benzerlikler gösteren nadir otozomal resesif hastalıklardır. *HGSNAT* patojenik varyantlarından kaynaklanan MPS IIIC, heparan sülfat birikimine ve ilerleyici nörodejenerasyona yol açarak davranış bozuklukları, gelişimsel gerilik ve motor disfonksiyonla kendini gösterir. *WFS1* patojenik varyantlarının neden olduğu WS1 ise, diabetes insipidus, diabetes mellitus, optik atrofi, işitme kaybı ve nörodejenerasyon ile karakterizedir. Bu çalışmada, WS1 tanısı bulunan 15 yaşında bir olgu sunulmaktadır. Olgu, dismorfik yüz özellikleri, entelektüel yetersizlik, gelişimsel gerilik, diabetes mellitus, diabetes insipidus, optik atrofi ve nöbetlerle başvurmuştur. Klinik ekzom dizilemeyle, *WFS1* ve *HGSNAT* genlerinde homozigot patojenik varyantlar saptanmış, WS1 tanısı doğrulanırken WS1 ile açıklanamayan bulguların MPS IIIC ile ilişkili olduğu ortaya koyulmuştur. Bu çalışmada sunulan olgu, MPS IIIC ve WS1'in eş zamanlı teşhis edildiği ilk olgu olup, yeni nesil dizilemenin karmaşık fenotiplerin belirlenmesindeki önemini ve özellikle akraba evliliği yüksek popülasyonlarda birden fazla genetik hastalığın değerlendirilmesi gerekliliğini vurgulamaktadır.

Anahtar kelimeler: *HGSNAT*, *WFS1*, tip C Sanfilippo sendromu, tip 1 Wolfram sendromu, Yeni Nesil Dizileme

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Corresponding Author
Zehra Manav Yiğit
Aydın Adnan Menderes University Faculty of Medicine, Medical Genetics Department, Aydın, Turkey
E-mail: zehra.manav@adu.edu.tr
ORCID: 0000-0002-9505-0371

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INTRODUCTION

Sanfilippo syndrome is primarily characterized by early-onset, severe, and progressive degeneration of the central nervous system, with subtype-specific variations. Clinical features include cortical atrophy, progressive dementia, motor dysfunction, hyperactivity, learning disabilities, aggressive behavior, sleep disturbances, and profound intellectual impairment[1]. This syndrome is linked to deficiencies in four distinct enzymes responsible for the lysosomal degradation of heparan sulfate and is classified into four genetic subtypes. Type C Sanfilippo syndrome results from biallelic pathogenic variants in the *HGSNAT* gene, leading to a deficiency of the enzyme heparan α-glucosaminide N-acetyltransferase, a lysosomal membrane protein. This deficiency causes the accumulation of heparan sulfate and subsequent cellular dysfunction[2].

Wolfram syndrome type 1 is an autosomal recessive disorder caused by pathogenic variants in the *WFS1* gene. It is characterized by diabetes mellitus (DM), optic atrophy, hearing loss, and neurodegenerative symptoms. *WFS1* encodes Wolframin, a transmembrane protein localized in the endoplasmic reticulum (ER). Wolframin plays critical roles in maintaining ER homeostasis, regulating intracellular calcium levels, and ensuring the proper folding of secretory proteins. A deficiency in Wolframin leads to cell death through ER stress and reduced insulin secretion, particularly affecting pancreatic beta cells[3,4].

The coexistence of two or more syndromes in a single individual is extremely rare. Advances in next-generation sequencing (NGS) technologies have facilitated the simultaneous diagnosis of multiple monogenic disorders by elucidating their genetic basis. In this study, we report a case initially followed with a clinical diagnosis of Wolfram syndrome. However, due to the presence of additional findings suggestive of a comorbid condition, a clinical exome panel was analyzed for other potential diseases which identified a homozygous pathogenic variant in the *HGSNAT* gene, in addition to the *WFS1* gene variant. To the best of our knowledge, this is the first documented case in the literature in which these two syndromes coexisted. This case report aims both to highlight the diagnostic challenges associated with the co-occurrence of rare syndromes and to underscore the critical role of genetic analysis in such cases.

CASE REPORT

A 15-year-old male, the third child of a consanguineous marriage (1.5-degree cousins) was referred to our clinic due to dysmorphic features, neuromotor developmental delay, moderate intellectual disability, DM, diabetes insipidus, and bilateral optic atrophy (Figure 1).

At 18 months of age, he was admitted to the hospital with an upper respiratory tract infection, where incidental hyperglycemia was detected. Further investigations revealed negative diabetes autoantibodies, and he was subsequently diagnosed with DM.

His developmental milestones were delayed, with head control achieved at 6 months, sat without support at 12 months, and walked without assistance at 18 months. Although he initially developed meaningful speech at 12 months, language regression was observed after onset of his DM. Currently, he utters nonsensical words and is unable to form complete sentences.

At age 14, an electroencephalogram revealed mild epileptic abnormalities, and magnetic resonance imaging showed increased signal intensity in the peritrigonal white matter, suggestive of prior hypoxic-ischemic injury, along with prominence of the mega cisterna magna and the occipital horns of both lateral ventricles. Fundoscopic examination confirmed bilateral optic atrophy. A visual evoked potential test indicated an absence of significant responses in the bilateral anterior visual pathways.

Whole abdominal ultrasonography showed stage 0-1 liver parenchymal echogenicity, results of hearing tests and echocardiography were unremarkable. The patient's current medications include levetiracetam, desmopressin, insulin, and melatonin.

His physical examination revealed short stature (<3rd percentile, -5.8 standard deviation score), coarse facial features, hard and dry hair, thick eyebrows, synophrys, upslanting palpebral fissures, epicanthus, long eyelashes, a depressed nasal root, macrotia, thickening of the helices, anteverted nostrils, and hypertrichosis. The patient has difficulty walking and is not independently mobile. For the past year, he has been consuming only liquid foods due to dysphagia. He has poor social interactions and academic performance, along with irritability and sleep disturbances. The patient has received four years of special education to improve his speech, cognitive development, and social skills.

His older brother, diagnosed with Wolfram syndrome type 1, exhibited symptoms of DM, diabetes insipidus, and optic atrophy but had normal motor and cognitive development.

Informed consent was obtained from the patient's parents for genetic testing and the publication of test results and clinical findings. Exome sequencing was performed on leukocyte-derived genomic DNA using the SOPHIA™ Genetics Clinical Exome Solution V2 Kit, covering 4490 genes. Sequencing was conducted on the Illumina NextSeq platform, and data analysis was performed using the SOPHIA™ DDM V4 analysis platform. Variant annotation was based on the GRCh37/hg19 human genome reference.

Identified variants were filtered according to a 1% allele frequency threshold using population databases such as dbSNP142, Human Reference Genome, 1000 Genomes Project, OMIM database, and an internal database of exomes from 3,206 individuals of

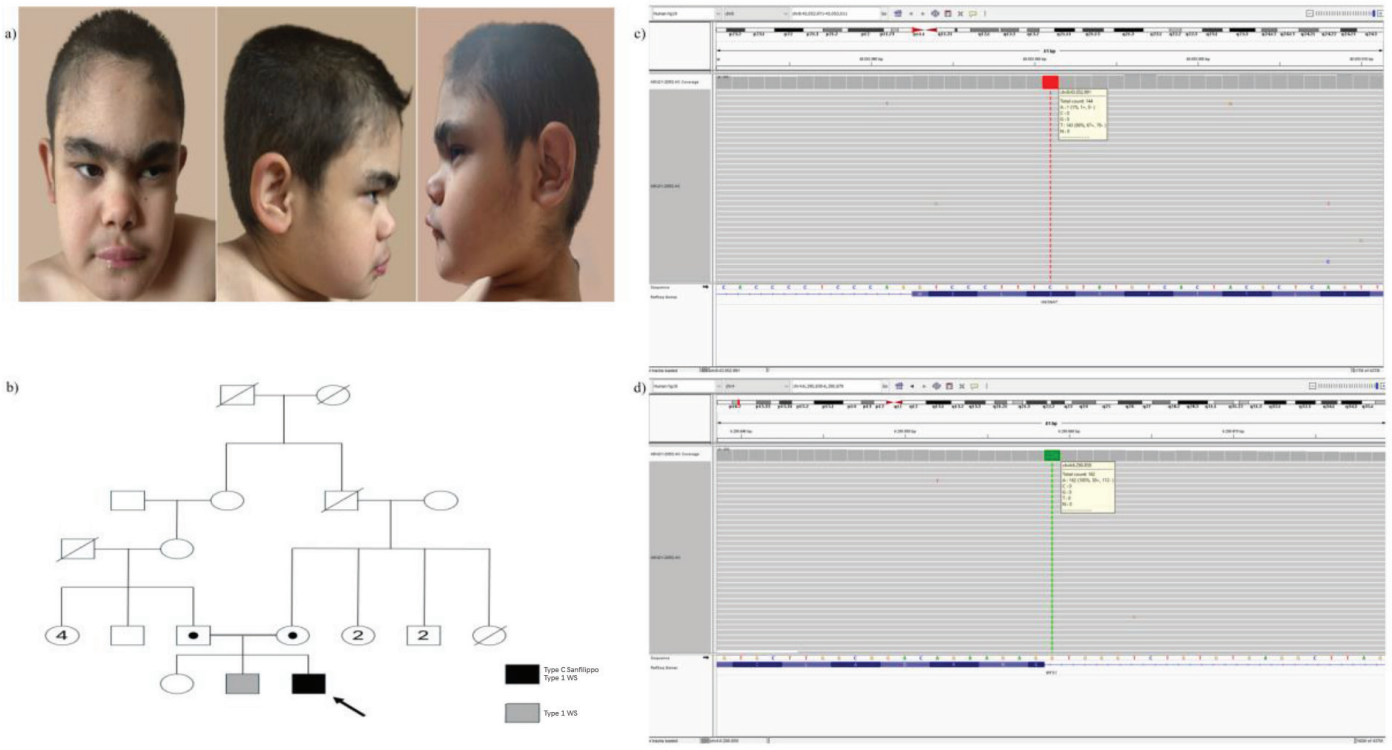

Figure 1. a) Dismorphic features of the proband. b) Proband's pedigree. c) *HGSNAT* NM_152419.2:c.1622C>T p.(Ser541Leu). d) WFS1 NM_001145853.1:c.460+1G>A

Turkish ethnicity. Sequence variant classification followed the guidelines set by the American College of Medical Genetics and Genomics.

RESULTS

As a result of NGS analysis, *HGSNAT* NM_152419.2:c.1622C>T; p.(Ser541Leu) and *WFS1* NM_001145853.1:c.460+1G>A variants were identified in homozygous form in our case (Figure 1c and d). Segregation analysis using Sanger sequencing method revealed that both parents were heterozygous carriers of these variants.

DISCUSSION

This case report highlights the coexistence of Sanfilippo syndrome type C and Wolfram syndrome type 1, two distinct autosomal recessive disorders. With the expanding use of NGS, the simultaneous identification of multiple hereditary diseases has become more feasible, offering a rapid and cost-effective diagnostic approach for complex phenotypes.

The *HGSNAT* c.1622C>T variant leads to misfolding of the heparan α-glucosaminide N-acetyltransferase enzyme, disrupting lysosomal targeting and enzymatic activity, ultimately resulting in cognitive decline[1,2,5-7]. Studies on *HGSNAT* variants have shown that misfolding-induced glycosylation defects, leading to intracellular retention and loss of function[5]. Glucosamine treatment has been suggested to partially restore enzymatic activity in some missense variants, including S541L[5].

The *WFS1* c.460+1G>A variant disrupts splicing, leading to a truncated or absent wolframin protein[8,9]. Deficiency of Wolframin protein impairs protein folding and calcium homeostasis, triggering ER stress, defective insulin secretion, and neuronal apoptosis[3,4]. The absence of diabetes autoantibodies in this case suggests diabetes is more consistently associated with Wolfram syndrome rather than classical type 1 diabetes.

A study of 24,164 cases with type 1 diabetes and 50 cases with Wolfram syndrome found that diabetes was the initial presentation in Wolfram syndrome, manifesting with optic atrophy, motor retardation, and dysphagia among the most common neurodegenerative findings. The study further reported that hearing loss and neurological/psychiatric symptoms are less frequently observed in patients with Wolfram syndrome-associated

diabetes when glycemic control is maintained (HbA1c ≤7.5)[10]. In our study, neurocognitive decline was not observed in the patient's older brother, who was diagnosed with WS1, and this was attributed to his strict glycemic control (HbA1c ≤7.5). However, in our patient, as the HbA1c level could not be kept under control as effectively as in his brother.

Hyperactivity, cognitive impairment, speech delay, and epilepsy are common in patients carrying a variant in the *HGSNAT* gene, while macrocephaly, hepatomegaly, and dysostosis multiplex are seen in more severe cases[7]. Our patient exhibited developmental and neurological symptoms but lacked several common *HGSNAT*-associated features, such as macrocephaly, sphincter control problems, recurrent infections, hepatomegaly, dysostosis multiplex, and diarrhea. Epilepsy was diagnosed approximately two years after the patient's initial presentation. Furthermore, less common findings, including hypoacusis, inguinal and umbilical hernias, and mitral insufficiency, were not observed in our case. Both Wolfram syndrome and MPS IIIC may induce neurological impairments. Literature suggests that Wolfram syndrome commonly presents with optic atrophy and hearing impairment, while MPS IIIC is associated with neurocognitive decline, hyperactivity, and speech regression. The coexistence of both disorders complicates the attribution of specific neurological findings. The fact that the same *WFS1* variant was homozygous in the patient's older brother, who had not neurological symptoms suggests that the neurological manifestations in our patient may be associated with Sanfilippo syndrome. However, there is a difference in the clinical management of Wolfram syndrome-associated diabetes between the two siblings, and it is thought that poor glycemic control in our patient may have contributed to the development of neurological findings. Naturally, individuals carrying the same variant may exhibit phenotypic variability. Therefore, further histopathological, and genetic studies on different tissues are necessary to clearly determine the underlying cause of the neurological findings.

In a study published by Çelmeli et al.[11] DM, progressing to partial central diabetes insipidus, sensorineural hearing loss, optic atrophy and bladder dysfunction have been reported in three Turkish children with *WFS1* variants. However, our case had not hearing impairment and urinary tract anomalies. Other homozygous *WFS1* cases have shown diverse urological findings[8,9,12]. Although neurogenic bladder dysfunction is frequently associated with Wolfram syndrome due to brainstem involvement[13], our patient did not manifest any signs and symptoms of remarkable bladder dysfunction. Intellectual disability of the patient may have limited the assessment of subtle urological symptoms, necessitating further urodynamic studies.

This case underscores the diagnostic challenges in distinguishing overlapping phenotypes in rare genetic syndromes. Our findings emphasize the role of NGS in identifying coexisting disorders and highlight the need for multidisciplinary approaches in evaluating complex clinical presentations.

CONCLUSIONS

This case represents the first reported coexistence of Sanfilippo syndrome type C and Wolfram syndrome type 1, emphasizing the diagnostic challenges associated with overlapping of rare genetic disorders. Our findings underscore the importance of genetic testing in cases with atypical presentations and suggest that a multidisciplinary approach is essential for optimal patient management.

Ethics

Informed Consent: Written informed consent was obtained from the parents of the child.

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Footnotes

Author Contributions

Concept: G.B., A.T., Design: Z.M.Y., G.B., A.T., Data Collection or Processing: A.M.E, Analysis or Interpretation: R.S., A.M.E., Literature Search: Z.M.Y., R.S., Writing: Z.M.Y., R.S.

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