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Case Report

A Rare Case of Cystic Hygroma and Familial Nystagmus in a Newborn with *SHOC2* Gene Mutation

SHOC2 Gen Mutasyonu ile İlişkili Kistik Higroma ve Ailevi Nistagmus: Nadir Bir Olgu Sunumu

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ABSTRACT

Cystic hygroma (CH) is a lymphatic malformation commonly associated with various genetic disorders, including RASopathies-syndromes caused by mutations in the RAS-MAPK signaling pathway. We present a neonate referred to our center due to CH and dysmorphic facial features. During follow-up, interventricular septal hypertrophy and nystagmus were identified. Molecular analysis revealed a pathogenic c.4A>G (p.Ser2Gly) variant in the *SHOC2* gene. This mutation is associated with a rare subtype of RASopathies known as Noonan-like syndrome with loose anagen hair. Although four additional male relatives also exhibited nystagmus, sequencing of the *FRMD7* gene and whole-exome analysis did not reveal any other pathogenic variants associated with nystagmus, highlighting the clinical complexity of the case. This report emphasizes the importance of considering the possibility of dual diagnoses in cases presenting with complex clinical features. It also underscores the value of prioritizing multigene panel testing in patients with overlapping phenotypes among RASopathy subgroups, where phenotypic distinctions remain unclear.

Keywords: SHOC2, cystic hygroma, Noonan-like Syndrome with loose anagen hair, Ser2Gly

ÖZ

Kistik higroma (KH), genellikle RAS-MAPK sinyal yolundaki mutasyonlardan kaynaklanan sendromlar olan RASopatiler de dahil olmak üzere çeşitli genetik bozukluklarla ilişkilendirilen bir lenfatik malformasyondur. Yenidoğan döneminde KH ve dismorfik yüz görünümü nedeniyle tarafımıza yönlendirilen olguda, takip sürecinde interventriküler septal hipertrofi ve nistagmus saptanmış; moleküler analiz sonucunda *SHOC2* geninde patojenik c.4A>G (p.Ser2Gly) varyantı belirlenmiştir. Bu mutasyon, RASopatilerin nadir bir alt tipi olan gevşek anagen saçlı Noonan benzeri sendrom ile ilişkilidir. Olgumuz dışında ailede dört erkek bireyde nistagmus saptanmasına rağmen, *FRMD7* gen dizi analizi ve tüm ekzom dizilemesi sonucunda nistagmusla ilişkili ek patojenik varyant saptamamış ve bu durum olgunun klinik karmaşıklığını ortaya koymuştur. Bu rapor, karmaşık klinik tablolar sergileyen olgularda çift tanı olasılığının dikkate alınmasının önemini vurgulamakta ve RASopati alt grupları arasında fenotipik özelliklerin henüz net bir şekilde ayrışmadığı hastalarda multigen panel testlerinin öncelikli olarak değerlendirilmesini önermektedir.

Anahtar kelimeler: SHOC2, kistik higroma, gevşek anagen saçlı Noonan benzeri sendrom, Ser2Gly

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INTRODUCTION

Cystic hygroma (CH), is a vascular/lymphatic malformation defined by dilated lymphatic ducts resulting from inadequate communication between the lymphatic and venous systems. It can occur anywhere in the body but tend to occur mainly in the neck and axilla. It has an incidence of approximately 1 in 1,000 to 6,000 live births and 1 in 750 miscarriages[1]. CH can occur as an isolated entity, or in association with fetal structural anomalies. They have been found to be associated with

certain conditions, such as chromosomal aneuploidies, hydrops fetalis, intrauterine death or other genetic disorders[2].

RAS-MAPK signaling pathway-related disorders should be considered when prenatal ultrasonography reveals findings such as increased nuchal translucency or CH. Noonan syndrome [(NS), OMIM 163950] is the most frequently seen RASopathy. However, NS is genetically heterogeneous, with over ten genes (such as *PTPN11, SOS1, KRAS, NRAS, RAF1, BRAF, SHOC2, MEK1,* and *CBL*) linked to this condition or closely related disorders, including LEOPARD syndrome [(LS); OMIM 151100] and Noonan-like syndrome with loose anagen hair [(NS/LAH), OMIM 607721][3]. NS/LAH syndrome, a rare type of RASopathy, shares features reminiscent of NS and is characterized by a distinct pattern of ectodermal anomalies[4]. This condition is primarily caused by mutations in the *SHOC2* gene which encodes a protein composed mainly of leucine-rich repeats (LRRs), organized in a sequence that forms a domain crucial for protein-protein interactions[5].

To date, approximately ten pathogenic or likely pathogenic variants of the *SHOC2* gene have been identified. Notably, among these variants, a recurrent activating mutation in *SHOC2* gene, ie. p.Ser2Gly, has been commonly observed in NS/LAH patients[6]. Herein, we have presented a case of a patient with excessive loose neck skin tissue and familial nystagmus, who was prenatally diagnosed with CH and found to have a mutant variant of *SHOC2* gene.

CASE REPORT

A newborn was referred to our genetic department due to her dysmorphic features. She was born via cesarean section at 35 weeks of gestation, with a birth weight of 3950 gr (2.78 SDS). She was the fourth child of healthy, consanguineous parents. During antenatal follow-up, CH was detected at 13 weeks of gestation, and chorionic villus sampling did not reveal any numerical anomalies on karyotype analysis. Additionally, polyhydramnios was noted at 34 weeks of gestation. The patient had APGAR scores of 6 and 7 at the postnatal first and fifth minutes, respectively, and was intubated for 2 days due to respiratory distress. On physical examination, her height was 49 cm (0.93 SDS), and her head circumference was 33 cm (0.44 SDS). Dysmorphic facial features included a coarse face, hypertelorism, downslanting palpebral fissures, low-set ears with prominent ear lobes, flattened and wide nasal root, long philtrum and microretrognathia. She also presented with a flat occiput, deep palmar creases, short neck and excessively loose neck skin tissue [Figure 1. (A, H)].

Ocular examination was unremarkable, and a hearing test indicated bilaterally normal hearing acuity. Abdominal and transfontanel ultrasonography (TFUS) showed no abnormalities. Echocardiography revealed a thin patent ductus arteriosus (PDA) and patent foramen ovale (PFO). Results of karyotype analysis performed to exclude sex chromosome abnormalities, were unremarkable. Based on her physical manifestations, a disorder related to the RAS-MAPK signaling pathway was considered. We conducted a targeted gene panel for RASopathies and a pathogenic mutation in the *SHOC2* gene, c.4A>G;p.Ser2Gly, was detected (Figure 1. J). Segregation analysis showed that both parents had wild type sequence.

She achieved head control at 3 months of age, and began sitting with support by six months. At 8 months of age, her weight was 6.4 kg (-1.8 SDS), her height was 65 cm (-1.4 SDS), and her head circumference was 43.5 cm (-0.17 SDS). Due to her relative macrocephaly, a repeat TFUS was performed, which showed enlargement of the lateral, third, and fourth ventricles. Cranial magnetic resonance imaging revealed no abnormalities other than a mildly enlarged ventricular system. Subsequently, echocardiography was repeated and interventricular septal hypertrophy was detected. The patient also presented with eczema, sparse hair, sparse eyebrows (Figure 1. C, F) and nystagmus. Her family history revealed that four other family members had also nystagmus (Figure 1. I). Since, all affected family members with nystagmus were male except our patient, we initially performed sequence analysis for *FRMD7* gene. However, no pathogenic variants of FRMD7 were identified. We then performed whole exome sequencing (WES) to explore other potential genetic causes of nystagmus , but this test also failed to identify any relevant gene variants.

DISCUSSION

In this study, we reported a patient presenting with familial nystagmus and excessive loose neck skin tissue, distinctive facial features, attributed to *SHOC2* gene mutation, a rare cause of RASopathy. Ensuring the integrity of RAS-MAPK signaling pathway, in which *SHOC2* gene plays a role, is essential for maintaining both early and late developmental processes, including organ formation, morphological determination, synaptic plasticity, and growth[5].

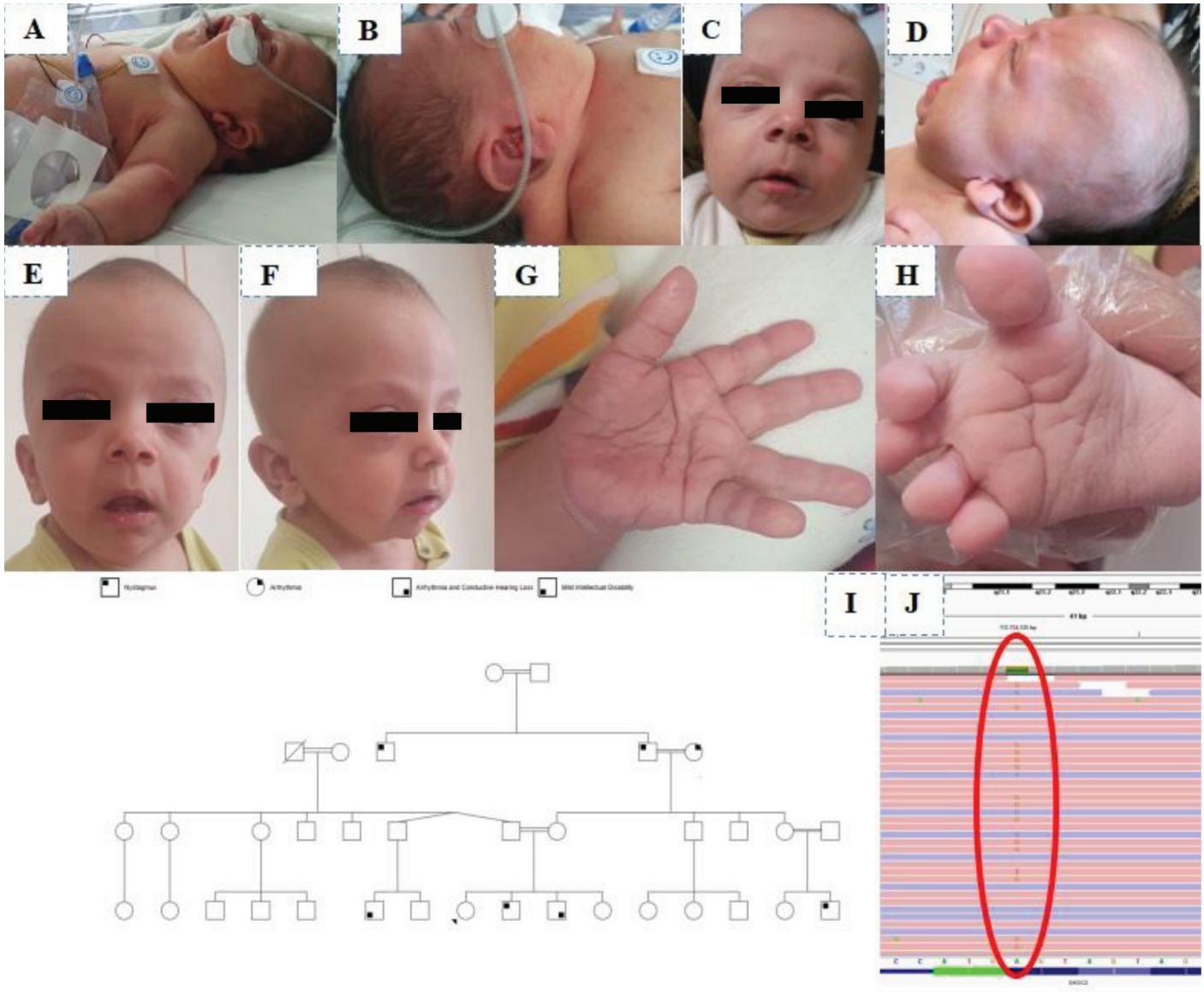

Figure 1. The main characteristic facial features of the patient, the patient's pedigree, and an IGV image of the genomic region corresponding to the *SHOC2* gene (c.4A>G; p.Ser2Gly) are shown. A photograph of the patient on the second day demonstrates low-set ears with prominent earlobes, a short neck, and excessive loose skin tissue around the neck **(A, B)**. Photographs of the patient at the fifth months **(C, D)** and eleventh months **(D, E)** of age show sparse hair, sparse eyebrows, hypertelorism, down-slanting palpebral fissures, low-set ears with prominent earlobes, a flattened and wide nasal root, a long philtrum, microretrognathia, and a short neck. Deep palmar and plantar creases are also visible **(F, G)**. The pedigree of the patient and family members with nystagmus are shown **(I)**. An IGV image of the genomic region corresponding to the *SHOC2* gene (c.4A>G; p.Ser2Gly) is provided **(J)**

IGV: Integrative genomics viewer

Mutations in *PTPN11* coding gene are identified in 2% of fetuses with increased nuchal translucency and in 16% of those with CH. Additionally, *de novo* mutations in *PTPN11*, *KRAS*, or *RAF1* genes were detected in 17.3% of fetuses with a normal karyotype and abnormal prenatal ultrasound findings such as increased nuchal translucency, hydrothorax, polyhydramnios, CH, cardiac anomalies, hydrops fetalis, and ascites[7]. In our patient, prenatal assessments revealed CH and polyhydramnios. Postnatally, the patient exhibited dysmorphic facial features including coarse facial findings, hypertelorism, downslanting-palpebral fissures, low-set ears with prominent ear lobes, flattened and wide nasal root and a webbed neck compatible with the diagnosis of NS.

A targeted gene panel for RASopathy-related disorders identified a pathogenic *SHOC2* gene variant (c.4A>G; p.Ser2Gly), which is commonly observed in NS/LAH patients. Clarifying ectodermal findings associated with SHOC2 mutations in the neonatal period remains challenging. Given the clinical overlap and molecular heterogeneity in RASopathy patients, we recommend the use of multigene panels for the establishment of a faster and more accurate diagnosis when phenotypic features suggest NS.

Structural cardiac anomalies and hypertrophic cardiomyopathy have been frequently reported in cases with RASopathies. Most patients with NS/LAH have congenital heart defects, particularly mitral valve dysplasia and septal defects[5,8]. An initial echocardiography of our patient revealed the presence of a PFO and a thin PDA. Follow-up echocardiography showed closure of both the PFO and PDA, but also identified thickening of the interventricular septum. This finding underscores the importance of regular and periodic systemic evaluation in such cases, with particular attention to monitoring for the likely presence of hypertrophic cardiomyopathy and its potential complications.

Emerging evidence suggests that patients with NS may present with a wide spectrum of ocular manifestations. However, refractive errors are the most prevalent ocular abnormalities in patients with NS. In a recent study, nystagmus was observed in 16 out of 105 patients, with 2 of these patients carrying a SHOC2 mutation[9]. In our study, both the patient and many of her family members exhibited nystagmus. Given the family history, the nystagmus observed in this case was considered more likely to be associated with a different etiology than the SHOC2 mutation.

Unfortunately, FRMD7 sequence analysis and WES analysis did not identify any likely pathogenic/pathogenic variant that could be linked to the nystagmus. Therefore, follow-up reanalysis of the patients WES data and further molecular studies for the affected family members were planned.

CONCLUSION

In conclusion, abnormalities of the lymphatic system, including CH and lymphedema, in conjunction with hypertrophic cardiomyopathy, should prompt consideration of a RASopathy. During the neonatal period, due to the absence of distinctive phenotypic features across RASopathy subgroups, the use of a targeted gene panel analysis should be prioritized as the primary diagnostic tool. Moreover, although concomitant findings such as nystagmus have been reported in association with RASopathies, it is imperative to thoroughly ascertain whether similar clinical manifestations are present in family members to avert the potential oversight of a dual diagnosis.

Ethics

Informed Consent: Written consent was obtained from the patients' parents for the use of their medical data and photographs.

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Footnotes

Author Contributions

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

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