Case Report

Cohen Syndrome, A Case Report

Wadah F. Elmihana[1], Abdullah T. Alshahrani[2], Ahmed Saadan[3], Basamat Eltayeb[3], Tabseem Goma[4], Abdulrahman Osman[3], Abubakr Abdelrazig[4], Arif Jamil[3]

[1]Consultant Neonatologist, Royal Commission Hospital, Jubail, KSA.
[2]Neonatology Consultant, Royal Commission Health Services Program in Jubail, Jubail, KSA.
[3]Neonatology Specialist, Royal Commission Hospital, Jubail, KSA.
[4]Neonatology Resident, Royal Commission Hospital, Jubail, KSA.

ABSTRACT

Background: Cohen syndrome is a rare genetic disorder characterized by physical, developmental, and intellectual disabilities. It is primarily considered in children presenting with microcephaly, early-onset hypotonia, neutropenia, and global developmental delay.
Results: A 16-day-old female infant with low birth weight and dysmorphic features was evaluated. This case highlights the importance of considering Cohen syndrome in the differential diagnosis of infants with similar clinical findings. Early recognition allows for timely intervention and support.
Conclusion: While there is no cure for Cohen syndrome, early diagnosis and management can improve quality of life.Genetic counseling is essential for affected families.

Keyword: Cohen syndrome, genetic disorders, developmental delay.

Introduction

A change in the VPS13B gene causes Cohen syndrome, this is inherited autosomally recessively and is found on chromosome 8q22.2. It is thought that the transmembrane protein VPS13B is involved in both the formation and operation of the eye as well as the movement and arrangement of proteins within cells, circulatory and central nervous systems [1]. Short height and low birth weight are possible, although, these qualities are not prerequisites. Reaching motor milestones, like walking on its own, is significantly delayed in children between the ages of two and five [2]. When a kid with microcephaly Experiences early-onset hypotonia, Cohen syndrome should be taken into consideration, globally delayed development and neutropenia. Physicians who treat young children with developmental delays, severe myopia, nyctalopia, and pigmentary retinopathy should take Cohen syndrome into consideration [3]. When making a diagnosis, one of the main indicators is the distinctive facial dysmorphism. Under such circumstances, a full blood count, a brain MRI, and a comprehensive ophthalmological check should be carried out [4].

Access this article online	
Quick Response Code:	Website: www.smh-j.com
	DOI: 10.54293/smhj.v4i3.117

Address for correspondence: Wadah Faisal Elmihana, Consultant Neonatologist, Royal Commission Hospital, Jubail, KSA.
E-mail: wadah4000@yahoo.com
Received: 4 Jul 2024 **Accepted:** 7 Sept 2024

Please cite this article as: Faisal Elmihana W, Thamir Alshahrani A, Ahmed Saadan, Basamat Eltayeb, Tabseem Goma, Abdulrahman Osman, Abubakr Abdelrazig, Arif Jamil. Cohen Syndrome, A Case Report. SMHJ [Internet]. 2024;4(3):211-214.

SMHJ
Saudi Medical Horizons Journal

Case study

A 16-day-old female infant was delivered via elective cesarean section at 36 weeks gestation due to concerns of low birth weight and oligohydramnios. The neonate exhibited respiratory distress immediately after delivery, necessitating prompt intervention. At birth, the patient displayed distinct dysmorphic features, including low-set ears, sloping forehead, hypertelorism, micrognathia, and a short neck characterized by residual calcaneovalgus deformity. Additionally, the infant presented with symptoms including obesity, hypotonia, mental deficiency, facial, and limb anomalies. A review of the patient's hematological profile revealed leukopenia, specifically neutropenia. Further radiological investigations were performed, and an EDTA blood sample was obtained to conduct a leukocyte count, confirming the presence and percentage of neutropenia. Due to intrauterine growth restriction (IUGR) and oligohydramnios, the patient was admitted to the neonatal intensive care unit (NICU) immediately after birth. She had an Apgar score of 7 at 1 minute and 8 at both the 5- and 10-minute marks, indicating a satisfactory recovery. The mother, a 24-year-old primigravida, had undergone dexamethasone treatment starting at 28 weeks of gestation prior to delivery. The cord blood gas analysis post-delivery showed values within the normal range. Shortly after birth, the infant developed significant tachypnea and retraction of the chest wall, leading to intubation and the administration of prophylactic surfactant therapy. The infant was later referred back through the outpatient clinic due to concerns about inadequate weight gain. During this follow-up, it was noted that the baby was losing weight compared to her discharge weight, despite reports of daily stool passage. However, she had not passed stool in the previous 24 hours. Diaper changes indicated urine output of 3-4 times per day, with no reports of fever, abnormal movements, irritability, abnormal breathing patterns, color changes, or distress during urination. The initial discharge diagnosis was recorded as a feeding problem of the newborn, unspecified. As the follow-up progressed, the baby presented with additional features of Cohen Syndrome, including external genital hypoplasia, continued hypertelorism, and ongoing intrauterine growth retardation alongside micrognathia. An ophthalmologic examination returned normal findings, with no evidence of retinal or congenital anomalies. A cardiology evaluation identified a small to moderate atrial septal defect (ASD) with a left-to-right shunt measuring 3 mm.

The CentoXome MOx 1.0 Solo test was requested for further evaluation and yielded a positive result, identifying several likely pathogenic variants associated with the patient's clinical presentation consistent with Cohen Syndrome. Specifically, the test revealed a variant in the AHDC1 gene (c.326C>T, p.Arg109Cys), which has been implicated in the characteristic symptoms of this syndrome, including hypotonia and developmental delays. Additionally, a nonsense mutation in the EHF gene (c.1158G>A, p.Trp386Ter) was detected, indicating a premature stop codon that likely disrupts normal protein function. Furthermore, a missense mutation in the OCRL gene (c.1187A>G, p.Lys396Arg) was identified, which is associated with neurological and renal manifestations observed in similar syndromic conditions. Specifically, In the ANKRD17 gene, a heterozygous probable pathogenic variation was discovered, compatible with the autosomal dominant Chopra-Amiel-Gordon syndrome genetic diagnosis. Furthermore, a deletion affecting VPS13B gene exon 28 was found, resulting in the complete absence of this exon from the transcript. This deletion disrupts the reading frame of the mRNA, leading to a premature stop codon and a truncated protein. The loss of exon 28 significantly impairs VPS13B function, likely contributes to the developmental delays and dysmorphic features observed in the patient, which is in line with the genetic diagnosis of autosomal recessive Cohen syndrome.

Discussion

An uncommon genetic condition known as Cohen syndrome causes a range of physical, intellectual, and developmental abnormalities. It's a highly uncommon illness that affects an estimated 1 in 1,000,000 people globally. [4]. Dr. first characterized the condition. Michael Cohen back in 1973. Neutropenia was subsequently shown by Norio et al. to be a consistent hallmark of Cohen syndrome. More than 100 instances of Cohen syndrome have been reported since then, 35 of which are from Finland, a country with a more uniform distribution of the disorder. Beyond the Finnish group, Cohen syndrome has a broad range of phenotypic diversity [5]. Despite the fact that a number of people exhibiting clinical symptoms similar to Cohen syndrome were first identified as having "Mishosseini-Holmes-Walton syndrome," it is now believed that these patients really had Cohen syndrome, indicating variability within the same condition [3]. Changes in the VPS13B gene are the cause of CS. The proband, who was born to healthy heterozygous parents, contains a unique compound

heterozygous mutation in VPS13B, acquired from the mother and father, respectively, are c.3582delT (p.A1149fs) and c.6295_6296delAT (p.M2124 fs), correspondingly, and her brother generates a premature stop codon by a frameshift [6]. This frameshift mutation results in the early generation of a stop codon, which can lead to the production of a functional null-allele through non-sense driven mRNA decay or a truncated protein lacking several functional domains of the VPS13B protein. [5]. The cis-Golgi matrix protein GM130 and the peripheral membrane protein VPS13B co-localize. Two genes involved in retinitis pigmentosa illness are found in the Golgi apparatus, RP2 and RPGR. Golgi dysfunction and abnormal protein transport in the photoreceptor are brought on by decreasing RP2 [7]. This indicates that the normal functioning of the photoreceptor depends on regular Golgi-associated protein activity, specifically VPS13B. It has been determined by recent study that VPS13B mutations, which cause COH1, induce an impairment in endosomal-lysosomal trafficking and a defect in glycosylation unique to a certain tissue. This suggests that the maintenance of lysosomal-endosomal pathways and the glycosylation and structure of the Golgi apparatus depend on VPS13B [8]. The ANKRD17 gene encodes a protein involved in various cellular processes, and pathogenic variants in this gene have been associated with disorders that can manifest as feeding difficulties and inadequate weight gain. In our patient, the identified pathogenic variant in ANKRD17 is likely contributing significantly to her primary complaint of inadequate weight gain and feeding problems. These issues may arise from metabolic dysfunction or disruptions in appetite regulation linked to the genetic alteration. Recognizing and emphasizing the impact of this genetic variant is essential to provide a comprehensive understanding of the patient’s condition and to guide potential management strategies aimed at addressing her nutritional needs and overall health [9]. The existence of a characteristic facial look is one of the defining characteristics of Cohen syndrome, which includes thick hair, high arched eyebrows, long eyelashes, a prominent nose, and a small chin. Individuals with Cohen syndrome may also have microcephaly, which is a smaller than average head size, as well as hypotonia, which is low muscle tone. These physical characteristics can help doctors diagnose the syndrome, nonetheless, genetic testing is frequently required to validate the diagnosis [1, 7]. In addition to the physical features, individuals with Cohen syndrome may also experience developmental delays and intellectual disabilities. They may have delayed challenges with fine and gross motor abilities, as well as speech and language development, Some individuals may also have vision problems, such as nearsightedness or retinal dystrophy. These challenges can make it difficult for individuals with Cohen syndrome to fully participate in school, work, and other activities of daily living [4, 6]. Although Cohen syndrome does not yet have a cure, there are interventions and therapies that can help control the symptoms and enhance quality of life. Physical, occupational, and speech therapy are examples of early intervention treatments, may assist individuals with Cohen syndrome develop the skills they need to communicate, move, and learn. In some cases, individuals may also benefit from special education services and assistive devices to support their learning and independence [1]. Because Cohen syndrome is a genetic condition, it can be inherited from a person's parents. Changes in the COH1 gene are the cause of it, it has a role in the growth and upkeep of cells. Sometimes, there may be no family history of the disease, indicating that the syndrome only sometimes manifests. Genetic counseling can be helpful for families who have a history of Cohen syndrome or who are concerned about passing the condition on to their children [5, 9].

Conclusion

Cohen syndrome is a complex and challenging condition that requires ongoing support and care. By raising awareness about the syndrome and investing in research and treatments, we may make a positive difference in the lives of those who have Cohen syndrome and their families. It is important for healthcare professionals, educators, and the general public to be informed about this rare disorder so that individuals with Cohen syndrome can receive the care and support them need to thrive.

Conflict of Interest

None

Funding

None

References

1. Rodrigues JM, Fernandes HD, Caruthers C, Braddock SR, Knutsen AP. Cohen Syndrome: Review of the Literature. Cureus. 2018;10(9):e3330.

2. Spoor J, Farajifard H, Rezaei N. Congenital neutropenia and primary immunodeficiency diseases. Critical reviews in oncology/hematology. 2019 Jan 1;133:149-62.

3. Gong J, Zhang L, Long Y, Xiao B, Long H. Cohen syndrome in two patients from China. Mol Genet Genomic Med. 2022;10(12):e2053.
4. Momtazmanesh S, Rayzan E, Shahkarami S, Rohlfs M, Klein C, Rezaei N. A novel VPS13B mutation in Cohen syndrome: a case report and review of literature. BMC Medical Genetics. 2020 Dec;21:1-6.
5. Kraus RF, Gruber MA. Neutrophils—from bone marrow to first-line defense of the innate immune system. Frontiers in immunology. 2021 Dec 23;12:767175.
6. Guillén-Samander A, Leonzino M, Hanna IV MG, Tang N, Shen H, De Camilli P. VPS13D bridges the ER to mitochondria and peroxisomes via Miro. Journal of Cell Biology. 2021 Apr 23;220(5):e202010004.
7. Nachury MV, Mick DU. Establishing and regulating the composition of cilia for signal transduction. Nature reviews Molecular cell biology. 2019 Jul;20(7):389-405.
8. Awadh Hashem S, Georgiou M, Ali RR, Michaelides M. RPGR-related retinopathy: clinical features, molecular genetics, and gene replacement therapy. Cold Spring Harbor Perspectives in Medicine. 2023 Nov 1;13(11):a041280..
9. Leonzino M, Reinisch KM, De Camilli P. Insights into VPS13 properties and function reveal a new mechanism of eukaryotic lipid transport. Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids. 2021 Oct 1;1866(10):159003.