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Received: 18 April 2024 | Revised: 3 September 2024 | Accepted: 30 September 2024

DOI: 10.1002/jdn.10384

RESEARCH ARTICLE

INTERNATIONAL JOURNAL OF DEVELOPMENTAL NEUROSCIENCE

WILEY

Cohen syndrome: Can early-onset recurrent infections and hypotonia provide early diagnosis and intervention for intellectual disability?

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Funding information
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Abstract

Introduction: Cohen syndrome is a rare disease associated with neurodevelopmental disorders, especially intellectual disability (ID), neutropenia and recurrent infections are consistently reported in cases. Neutropenia is an important part of the syndrome, as well as ID. Homozygous variants in the *VPS13B* gene, located on chromosome 8q22 and containing 62 exons, have been found to cause Cohen syndrome. Cohen syndrome is commonly diagnosed when dysmorphological findings and developmental delay become more apparent. However, the identification of some findings with increasing age has caused the diagnosis of Cohen syndrome to be delayed.

Methods: Cases diagnosed with ID were evaluated using whole-exome sequencing/clinical exome sequencing method. Family segregation analysis was performed using Sanger sequencing. We presented the clinical and genetic findings of three cases diagnosed with Cohen syndrome and their parents in detail.

Results: In this study, we presented the occurrence of symptoms in different age groups, and the prognosis of three cases carrying the *VPS13B* gene variants, including three different variant types: missense, frameshift and nonsense. Although our cases had different variant types, they shared important similarities on the onset period and prognosis of the symptoms. All cases presented hypotonia, difficulties in swallowing, recurrent respiratory tract infections, neutropenia, delay in motor development, ID and hyperactivity. Our cases did not have a diagnosis of autism spectrum disorder. All cases had increased willingness to engage in social communication.

Conclusion: We emphasize the importance of early-onset recurrent infections and hypotonia for early diagnosis and preventive genetic counselling in Cohen syndrome.

Abbreviations: AAMD, Adaptive Behavior Scale; ASD, autism spectrum disorder; Dup, duplication; GnomAD, The Genome Aggregation Database; ID, intellectual disability; IUGR, intrauterine growth restriction; VPS13B, vacuolar protein sorting 13 homolog B.

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KEYWORDS
Cohen syndrome, intellectual disability, neurodevelopmental disorder, *VPS13B*

1 | INTRODUCTION

Cohen syndrome is a rare genetic disorder that affects multiple systems. The genetic variants in *VPS13B* have been found to cause Cohen syndrome, which is characterized by neurodevelopmental disorders, neutropenia, recurrent infections, aphthous ulcers, hypotonia, obesity, characteristic facial features, myopia, retinal dystrophy and short stature (Zorn et al., 2022). *VPS13B* is localized on chromosome 8q22 and covers a genomic region of approximately 864 kb, containing 62 exons (Chandler et al., 2003). *VPS13B* encodes a transmembrane protein that plays an important role in preserving the integrity of the Golgi complex (Momtazmanesh et al., 2020). It is a transmembrane protein that is thought to play a role in the development and function of the eye, the haematological and central nervous system (Rodrigues et al., 2018).

So far, approximately 300 mutations have been detected in the *VPS13B* gene (HGMD, http://www.hgmd.cf.ac.uk/ac/index.php). Most of these are missense variants followed by small deletion-type variations (Parri et al., 2010). No major pathological findings were detected in brain imaging and EEG studies of Cohen syndrome (Kivitie-Kallio & Norio, 2001a). It has been stated that there are no facial features specific to Cohen syndrome before the age of 1. Dysmorphological facial symptoms begin to appear between 2 and 6 years of age. In the school age, characteristic facial findings become clear and the diagnosis is usually made in this age range. During this period, myopia and retinal dystrophy are detected.

A delay in diagnosis of Cohen syndrome has been reported in the previous literature (Seifert et al., 2006a). The age at the diagnosis of Cohen syndrome may be long after the first symptoms appear, because different multi-system findings of Cohen syndrome appear at different ages. And symptoms appearing with older age cause a delay in diagnosis. Therefore, investigating early multisystem findings and genotype–phenotype correlation in Cohen syndrome is very important for early diagnosis and genetic counselling.

Another important issue regarding Cohen syndrome is the psychiatric evaluation findings. Although intellectual disability (ID) is consistently demonstrated in all reported cases of Cohen syndrome, symptoms of autism spectrum disorder (ASD) in Cohen syndrome are inconsistent. The diagnosis of ASD in Cohen syndrome was presented in some studies while not detected in other studies (AbdelAleem et al., 2023).

In this study, we aimed to present detailed symptoms, the occurrence of symptoms in different age groups and the prognosis of three cases carrying the *VPS13B* gene variants including three different variant types: missense, frameshift and nonsense.

2 | METHOD

All the participants of the study gave their informed consent before clinical and genetic evaluation. Informed consent was obtained from all patients before the collection of blood samples. DNA extraction was performed from these 200 μL peripheral blood samples. Genomic DNA (gDNA) was extracted from peripheral venous blood samples according to the manufacturer's protocol using an Exgene TM Blood SV isolation kit (GeneAll Biotechnologie, Kore). The peripheral blood chromosome analysis revealed a normal constitutional karyotype, 46, XX. The chromosomal microarray test revealed no deletions or duplications. Clinical Exome Sequencing Libraries were prepared according to the manufacturer using the Human Comprehensive Exome Panel (Twist Bioscience, South San Francisco). Following the target process, libraries were sequenced on the DNBSEQ-G400 (MGI Tech, China). An average read depth of 20× and 95% coverage, including exon intron junction boundaries (±10 bp), were evaluated. The GeneMaster software was used for analysis with the reference human genome (hg19/GRCh37). The Human Phenotype Ontology was used for phenotypic filters, and the Online Mendelian Inheritance in Man (OMIM, https://www.omim.org/) was used for gene sets. The Human Genome Mutation Database (HGMD, http://www.hgmd.cf.ac.uk/ac/index.php), Franklin (https://franklin.genoox.com/clinical-db/home), VarSome (https://varsome.com/) and ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/), novel variants in the databases, were checked. The pathogenicity score of new variants was interpreted using the in-silico variant prediction programs Mutation Taster, CADD (Combined Annotation Dependent Depletion).

3 | RESULTS

The characteristics of three cases diagnosed with Cohen syndrome are summarized in Table 1.

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TABLE 1 Clinical and genetic findings of cases diagnosed with Cohen syndrome.

	Case 1	Case 2	Case 3
Gender	Male	Female	Female
Age	7 years	6 years	15 years
Mutation type	Missense	Frameshift	Nonsense
Exon	Exon 45	Exon 60	Exon 8
Zygosity	Homozygous	Homozygous	Homozygous
Nucleotide variation	NM_152564.5: c.8243C > T	NM_152564.5: c.11411dup	NM_152564.5: c.979C > T
Amino acid variation	p.Ser2748Leu	p.Leu3805ThrfsTer13	p.Gln327Ter
Start walking independently	18 months	27 months	4 years
Using first word	5 years	12 months	4 years
Current language ability	Several words	Several words	Sentences including two or three words
Psychiatric diagnosis	ID, ADHD	ID, ADHD	ID, ADHD
Special education	Since 2 years old	Since 3 years old	Since 4 years old
Seizure	−	−	−
Brain MRI findings	Normal	Normal	Normal
Eye anomalies	+	+	+
Hypotonia	+	+	+
Hypermobile joints	+	+	+
Neutropenia	+	+	+
Recurrent infections	Respiratory tract infections	Respiratory tract infections	Respiratory tract infections
Oral aftous	−	+	+
Truncal obesity	−	−	+
Maternal age at birth	25 years	30 years	24 years
Paternal age at birth	32 years	37 years	24 years
Consanguinity	+	+	+
Other clinical findings	Feeding problems due to swallowing problems Feeding without chewing for the first 3 years	Feeding problems due to swallowing problems PFAPA Milk allergy	Feeding problems due to swallowing problems Ongoing chewing problem Sleep problems

Abbreviations: ADHD, attention-deficit hyperactivity disorder; ID, intellectual disability.

3.1 | Case 1

Case 1, a 7-year-old boy, applied to the outpatient clinic of the Department of Child and Adolescent Psychiatry. Genetic investigations were applied due to ID, and a homozygous variant in the *VPS13B* gene (c.8243C > T) was detected. This homozygous variant had two submissions in the ClinVAR database (Variation ID: 68093). They were classified as pathogenic and of Uncertain Clinical Significance. Also, the allele frequency in the gnomAD database was 0.000009294. His parents were first-degree relatives. At birth, the age of the mother was 25 and the age of the father was 32. Intrauterine growth restriction was detected in the sixth month of pregnancy. Caesarean section surgery was performed at 39 weeks. He started walking when he was 18 months old. Toilet training was completed at the age of 4. He received nutritional support until the age of 3 because he had chewing and swallowing problems. At the current evaluation, his eye contact and social skills were compatible with his developmental status. He was very friendly, and his desire for social communication was quite high. In addition to ID, hyperactivity and severely decreased speech content impaired his functionality.

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The parents of Case 1 gave a history of frequent hospitalization in the neonatal period. He had a history of hospitalization for 5 days after birth. The second hospitalization was due to pneumonia at the age of 40 days. Neutrophil count was 540/mm^3 in 2018, 870/mm^3 in 2022 and 1130/mm^3 in 2024.

3.2 | Case 2

Case 2, a 6-year-old girl, applied to the outpatient clinic of the Department of Child and Adolescent Psychiatry. Genetic investigations were applied due to ID, and a homozygous variant in the *VPS13B* gene (c.11411dup) was detected. This homozygous variant had one submission in the ClinVAR database (Variation ID: 638298). This was classified as pathogenic. Also, the allele frequency in the gnomAD database was not found. There was not any detected problem during pregnancy, and she was born at 39 weeks with an uneventful birth. Her height at birth was 50 cm, her weight was 2750 g and her head circumference was 33 cm. She was described as a quiet baby, and hypotonia was detected in the neonatal period. Fever and respiratory tract infections after birth caused frequent hospitalizations.

She started using her first word when she was 1 year old. She has been taking speech therapy for 3 years. She started sitting without support when she was 9 months old. She started walking at 27 months old with physiotherapy. She completed his toilet training at the age of 4. A secondary atrioventricular septal defect was detected using echocardiography.

For now, she has difficulties in using long sentences and she expresses her wishes in short sentences. She is wearing glasses because of astigmatism. Her current weight is 16.5 kg, and her height is 105 cm. In addition to ID, she had a diagnosis of attention-deficit and hyperactivity disorder. She did not present any symptoms of ASD.

For case 2, a history of infections that started shortly after birth and continued intermittently and hospitalizations due to pneumonia were reported. Also, oral aphthae have been reported since the early period. Neutrophil count was 1100/mm^3 in 2017, 700/mm^3 in 2018 and 700/mm^3 in 2023.

3.3 | Case 3

Case 3, a 15-year-old girl, applied to the outpatient clinic of the Department of Child and Adolescent Psychiatry. Genetic investigations were applied due to ID, and a homozygous variant in the *VPS13B* gene (c.979C > T) was detected. This homozygous variant had two submissions in the ClinVAR database (Variation ID: 813126). They were classified as pathogenic. Also, the allele frequency in the gnomAD database was not found. There was not any detected problem during pregnancy, and she was born with an uneventful birth. Her weight was 2500 g at birth. She had hypotonia in the neonatal period. She had difficulties in breastfeeding and swallowing. She started using her first word when she was 4 years old. She started walking at 4 years old. A secondary atrioventricular septal defect was detected using echocardiography. Neutrophil count was 1270/mm^3 in 2018, 600/mm^3 in 2019 and 820/mm^3 in 2023 for case 3.

For now, she has difficulties in using long sentences and she expresses her wishes in short sentences. She is wearing glasses because of myopia and suffering from retinitis pigmentosa. Her current weight is 63 kg, her head circumference is 44 cm and her height is 146 cm. In addition to ID, she exhibited symptoms of sleep problems, truncal obesity, oral ulcers and hyperactivity.

4 | DISCUSSION

In this study, we presented detailed clinical findings from cases carrying three different homozygous *VPS13B* gene variants. At the same time, these three different homozygous variants had different variant classifications: missense, frameshift and nonsense. We aimed to investigate genotype–phenotype correlation and discuss the effect of symptom progress on the prognosis of cases.

We emphasize that the clinical findings of cases carrying the homozygous *VPS13B* gene variant are useful in establishing the genotype–phenotype correlation. Although our cases had different variant types, they shared important similarities on the onset period and prognosis of the symptoms. All cases presented hypotonia, difficulties in swallowing, recurrent respiratory tract infections, neutropenia, delay in motor development, ID and hyperactivity. We performed the genetic testing for all of three cases, and the diagnosis of Cohen syndrome occurred following the diagnosis of ID. Some studies in the literature indicate that the diagnosis of Cohen syndrome, determining the *VPS13B* gene variant, is generally made at the school age when visual disorders occur including retinal dystrophy (El Chehadeh-Djebbar et al., 2013). Some studies also emphasize the importance of early ophthalmological tests and neutrophil count in diagnosis in preschool children (El Chehadeh-Djebbar et al., 2013). Delayed diagnosis prevents appropriate genetic counselling. This may be due to a small number of studies on Cohen syndrome, and the lack of awareness may cause this delay.

The symptoms of the cases started in the neonatal period, and the symptoms presented in a similar order.

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Although the symptoms of this disease were consistent in all three cases, symptom severity varied from case to case. Symptom progress of our cases showed that earlier diagnosis between the ages of 0 and 2 is possible. Some important symptoms of Cohen syndrome have been recognizable in the neonatal period with hypotonia, difficulty in swallowing and recurrent respiratory tract infections requiring hospitalization. In conclusion, we emphasize the importance of the earlier diagnosis of Cohen syndrome to manage other symptoms that will occur in the following developmental periods. We emphasize that the findings occurring in the 0–2 age period are important evidence for providing genetic testing for these cases. Although age at diagnosis is important for early intervention, there is a small number of reported patients diagnosed under 1 year of age with Cohen syndrome (Kivitie-Kallio & Norio, 2001a).

In the following period (2–6 years), most children diagnosed with Cohen syndrome need physical therapy for delayed walking and commonly start walking between the ages of 2 and 5 as in our cases. All patients had isolated granulocytopenia (Kivitie-Kallio & Norio, 2001a). Frequent infections may occur but are not fatal. The aetiology of neutropenia is unknown (Kivitie-Kallio et al., 1997). In this period, ID becomes more recognizable and requires special education support in the following developmental periods. For this reason, we suggest that early special education interventions may be beneficial at the age of 0–2 when brain development has important acceleration.

In a recent study, the natural history of Cohen syndrome was investigated (Güneş et al., 2023). Authors suggested that a differential diagnosis of Cohen syndrome in infancy should be made with Prader–Willi syndrome based on facial features and hypotonia especially in in consanguineous families. Early recognizable facial features were reported as round faces, almond-shaped eyes, small mouths with down-turned corners and small hands and feet.

A previous study investigated the phenotype–genotype correlation of 24 cases from 16 families diagnosed with Cohen syndrome (Seifert et al., 2006b). The missense variant of c.8243C > T that we detected in the results of case 1 was reported in three cases presented in this study. Although the age at first walking was highly variable among all patients diagnosed with Cohen syndrome, the age at first walking in these three patients carrying c.8243C > T variant was similar (2 years). Similarly, our patient was able to walk at the age of about 2 years. There were significant differences in the speech skills of the three patients reported in the previous study. Since the previous study did not provide information on neutropenia and recurrent infections, no comparison could be made with our case. Other variants of case 2 (c.11411dup) and case 3 (c.979C > T) were reported in the ClinVar database with the Variation ID (638298) and Variation ID (813126), respectively. However, there needs to be more detailed clinical information on these variants.

We suggest the importance of early recognized hypotonia and neutropenia accompanied by recurrent infections that start earlier than developmental delay signs. In the previous literature, hypotonia was implicated starting in the prenatal period with reduced foetal movement. Hypotonia was presented in all cases diagnosed with Cohen syndrome between 0 and 1 years (Kivitie-Kallio & Norio, 2001b). The neutropenia pattern was described as mild to moderate (ranging from 500 to 1200/mm^3 for all age groups), non-cyclic and not fatal (Falk et al., 2004). In our patients, neutropenia persisted consistently and we did not detect any normal neutrophil count in the previous investigations. Increased rates of otitis media, pneumonia and aphthous ulcers were reported in cases diagnosed with Cohen syndrome (Falk et al., 2004). In our cases, pneumonia requiring hospitalization before the age of 1 year was described.

We examined the psychiatric symptoms of the cases in our study, all three cases suffered from hyperactivity in addition to ID. Our cases did not have a diagnosis of ASD. All cases had increased willingness to engage in social communication. In the previous literature, Cohen syndrome has been placed in syndromes associated with ASD (Richards et al., 2015). On the other side, parents of patients with Cohen syndrome typically characterize their behavioural characteristics as loving children and peaceful newborns, affectionate children and cooperative, socially interactive individuals (Chandler et al., 2003). Another study investigated behavioural characteristics of cases diagnosed with Cohen syndrome using an adaptive behaviour scale (AAMD). This study found high scores on the positive domains (self-direction, responsibility and socialization) accompanying cheerful disposition, but there were not any higher scores on maladaptive behaviour (Kivitie-Kallio & Norio, 2001a). The results of our study are also in the same line with these findings.

Based on the results of our cases and previously reported cases in the literature, we emphasize the importance of genetic testing in the presence of hypotonia and neutropenia starting in the first year of life. In our patients, the diagnosis of Cohen syndrome was applied after the diagnosis of ID. Early diagnosis of Cohen syndrome before ID and ocular findings occur is important for early intervention. In conclusion, a multidisciplinary approach in the early stages is important; evidence reports are important for early diagnosis of these rare diseases. In addition, the prevalence of social, academic, communication and behavioural problems requires further research.

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AUTHOR CONTRIBUTIONS

Gül Ünsel Bolat and Ezgi Keskin Çelebi provided psychiatric evaluation. Hilmi Bolat provided genetic evaluation. Gül Ünsel Bolat, Ezgi Keskin Celebi and Hilmi Bolat designed the study, then wrote the manuscript.

ACKNOWLEDGEMENTS

The authors would like to thank the families contributing to the study. Also, authors would like to thank the the editor and the reviewers for their valuable comments.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

ETHICS STATEMENT

All the participants of the study gave their informed consent before clinical and genetic evaluation. All procedures performed in this study were in accordance with the declaration of Helsinki.

CONSENT TO PARTICIPATE STATEMENT

Informed consent was obtained from participants or their parents/legal guardians to participate in the study.

CONSENT TO PUBLISH DECLARATION

All the participants of the study gave their informed consent to publish declaration.

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How to cite this article: Ünsel-Bolat, G., Keskin-Çelebi, E., & Bolat, H. (2024). Cohen syndrome: Can early-onset recurrent infections and hypotonia provide early diagnosis and intervention for intellectual disability? *International Journal of Developmental Neuroscience*, *84*(8), 918–923. https://doi.org/10.1002/jdn.10384

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