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Review Article

Cohen syndrome and neutropenia: Unveiling a novel *VPS13B* variant and literature review

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ABSTRACT

Objective: To report a novel *VPS13B* variant and to describe the prevalence of neutropenia and immunological clinical features in patients with Cohen syndrome (CS).
Study design: We conducted a comprehensive search focusing on CS and neutropenia using PubMed, Embase, Google Scholar and the Human Gene Mutation Database. The key words were "Cohen syndrome" AND "neutropenia," "*VPS13B*" AND "neutropenia," "*COH1*" AND "neutropenia." Inclusion criteria required articles to be in English, to report a confirmed *VPS13B* variant (or the previously named *COH1*) and to provide information on clinical phenotypes.
Results: The literature review identified 54 reports that met the inclusion criteria. The majority of CS patients (226/293; 77.1 %) presented with neutropenia, with notable differences according to ethnicity. Caucasians had reduced neutrophil levels in 90.6 % of cases, whereas Arabs and Asians had reduced neutrophil levels in only 58.7 % and 47.1 % of cases, respectively. There was no clear genotype-phenotype correlation with regard to neutropenia. Although few serious infections were reported, oral mucosal involvement and its sequelae were common. Dysimmune phenomena were observed in seven cases. We also report the case of a seven-year-old Italian child with a novel compound heterozygosity in the *VPS13B* gene who was previously diagnosed with isolated autoimmune neutropenia.
Conclusions: Clinical, ethnic and immunological data suggest that neutropenia in CS may be part of a complex immune dysregulation. Further immunological studies may help in the early diagnosis and treatment of autoimmune and mucosal involvement to prevent potential complications.

1. Introduction

Cohen syndrome (CS) (OMIM: 216550) is a rare autosomal recessive disorder that was first described in 1973 by M Michael Cohen Jr [1]. Early studies in the Finnish population described several cases characterized by a homogeneous clinical picture, including hypotonia, neurodevelopmental disability, motor clumsiness, ocular-cranial anomalies, mid-childhood obesity, and ligament laxity. Since then, reported cases have revealed heterogeneous clinical expression of the disease, especially in the non-Finnish population [2,3]. The description of ophthalmological abnormalities, such as progressive myopia and retinal dystrophy and the frequent occurrence of neutropenia broadened

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the clinical phenotype [4,5].

Pathogenetically, CS was shown in 2003 to be caused by homozygous or combined variants in the *VPS13B* gene (previously known as *COH1*) [6,7].

Although over three hundred cases are reported in the current literature, the clinical description of patients with neutropenia and documentation of infectious episodes are often lacking. Furthermore, few articles report haematological and immunological investigations in patients with CS, although an increased incidence of autoimmune diseases has been described [8].

Herein, we present a case of CS with clinical onset characterized by autoimmune neutropenia, and a literature review focusing on neutropenia and other immunologic features in CS.

2. Methods

2.1. Clinical data

Clinical and laboratory data were collected from the medical record review. Extensive immunophenotype analysis was performed. Informed consent for genomic analysis and clinical data collection was obtained from the patient's parents.

2.2. Genetic investigation

DNA was extracted from peripheral blood using QIAgen columns (QIAsymphony DNA minikit, Qiagen, Hilden, Germany) according to the manufacturer's instructions. Clinical exome sequencing was performed on the proband and parental genomic DNA using the Twist Human Custom Panel [Twist Bioscience] and sequenced on a NovaSeq6000 platform (Illumina, San Diego, CA). Reads were aligned to the UCSC GRCh37 reference genome using the DRAGEN Germline Pipeline and analyzed using Geneyx Analysis variant prioritisation software [9]. The variants were filtered by in silico analysis, with the presence of all suspected variants in the public database GnomAD (Genome Aggregation Database) being taken into consideration, as well as the prediction of deleterious non-synonymous SNVs for human diseases. VarSome [10] was utilized for the evaluation of the variants, with their subsequent categorization being conducted in accordance with the recommendations set forth by the ACMG [9]. The variants were also examined for coverage and Q score (a minimum threshold of 30). The results were then visualized using the Integrative Genome Viewer (IGV).

A detailed analysis was conducted on the proband and their parents' genomic DNA to ascertain microdeletions and microduplications. This analysis was performed using a Multiplex Ligation-dependent Probe Amplification (MLPA) assay kit (P321–B2/P322–C1, MRC Holland) and a capillary electrophoresis apparatus with a Genetic Analyzer automated sequencer (Applied Biosystems). The analysis was conducted in strict accordance with the manufacturer's instructions.

2.3. Literature review

The review aimed to analyze the papers describing patients with CS and their immuno-hematological signs, including neutropenia, immune dysregulation conditions, and infection rate. A comprehensive search was conducted using the search terms "Cohen syndrome" AND "neutropenia," "*VPS13B*" AND "neutropenia," and "*COH1*" AND "neutropenia" on the following databases: PubMed, Embase and Google Scholar.

Furthermore, a comprehensive search was conducted on "The Human Gene Mutation Database" [11] using the keyword "*VPS13B*," and an analysis was performed on scientific articles reporting pathogenic gene variants, in conjunction with the description of the patient's clinical picture. The corpus of articles published from 2003, the year in which the *COH1* gene was first identified as the causative gene, to January 31, 2024, was included in the study. The collection of data comprised exclusively papers or abstracts written in English and reporting at least one confirmed pathogenic variant in *VPS13B* (or *COH1*) for the purpose of screening. Subsequently, articles that did not report information on the clinical phenotypes were excluded (Fig. 2). The identification, screening and data extraction of articles that met the inclusion criteria was performed by two reviewers. The first author was responsible for finalizing all identification and data extraction steps. A second reviewer performed the same steps successively.

2.4. Statistical analysis

Statistical analyses were performed using Stata® version 13 software. Descriptive analysis has been reported as absolute frequency for qualitative data. Continuous variables were presented as the median and interquartile range (IQR) and evaluated using the Mann-Whitney *U* test. The Kruskall-Wallis test was utilized for the purpose of conducting a comparative analysis between the groups.

3. Results

3.1. Case report

A 7-year-old boy was evaluated for intermittent neutropenia at the Clinical Immunology Unit of the Bambino Gesù Children's Hospital. A diagnosis of autoimmune neutropenia had been made at the age of eighteen months, as a result of the detection of anti-neutrophils IgM (granulocyte immunofluorescence test, GIFT).

The child was born to non-consanguineous parents following a regular pregnancy. An echocardiogram performed at birth revealed a tricuspid aortic valve, a patent foramen ovale (PFO), and a patent ductus arteriosus (PDA), which resolved spontaneously after a few months. It was observed that the subject exhibited a mild delay in the acquisition of neurodevelopmental milestones during his early childhood. At the age of eighteen months, he underwent a brain MRI which documented hypoplasia of the cerebellar vermis and microcephaly. Furthermore, difficulties in feeding were reported during the first months of life. At the age of two, he underwent an endoscopic procedure for dilatation of the pylorus, owing to the presence of dysphagia and gastroparesis, as evidenced by gastric scintigraphy. Furthermore, a bone marrow evaluation revealed normal maturation of the myeloid lineage, thereby providing support for the hypothesis of the peripheral origin of neutropenia.

The mother reported that the child had experienced low vision since early childhood. The patient was diagnosed with progressive severe myopia and retinal dystrophy at the age of five. He demonstrated a visual acuity of 0.52 logMAR, accompanied by a refractive defect of −7.00 dioptres spherical equivalent (D) and −300 cylindrical (C) in both eyes. Electroretinography (ERG) revealed a significant decline in both photopic and scotopic responses. A fundus examination revealed a myopic pattern, characterized by a relatively pale optic disk, consistent vessel caliber, and mild retinal pigment epithelial (RPE) mottling. The use of Spectral Domain Optical Coherence Tomography (SD-OCT) revealed the presence of hyporeflective spaces, indicative of intraretinal cysts, within the foveal area, accompanied by thinning and fragmentation of the ellipsoid layer.

During the patient's clinical evaluation, distinctive craniofacial features were observed, including microcephaly (below the 3rd percentile), thick eyebrows, a thick head of hair, and a prominent nose. Additionally, he exhibited clumsiness, elongated extremities, and joint hyperlaxity. Moderate intellectual disability was also observed (Fig. 1).

The immunological evaluation revealed persistent moderate neutropenia, with a median absolute neutrophil count (ANC) of 925/μl. Furthermore, the inverted CD4:CD8 ratio was found to be persistent, with the normal value for naïve T cells, immunoglobulins, and T regulatory cells (CD25+CD127low FoxP3high) being observed. Immunological findings at 8 years of age are reported in Table 1.

The clinical phenotype described above suggests a genetic congenital

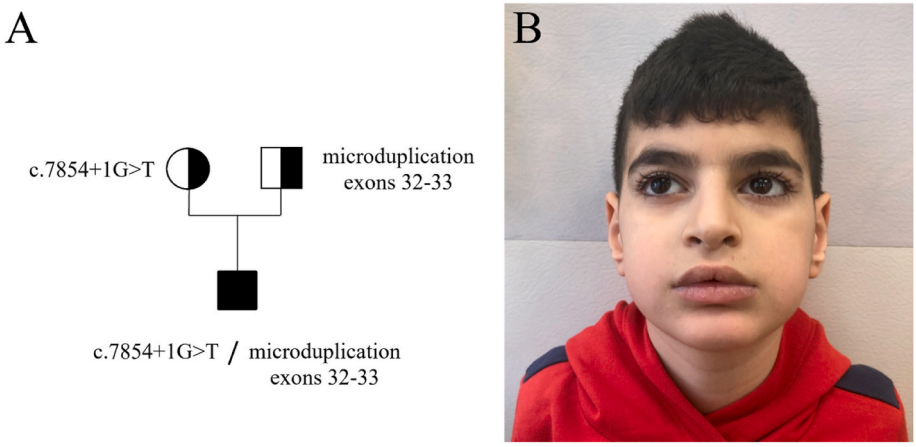

Fig. 1. A: Pedigree of the family and compound heterozygosity of the proband (black square) for *VPS13B* gene formed by the maternal segregation variant (c.7854+1G > T) (black and white circle) in a splicing site and a microduplication of exons 32–33 inherited from the father (black and white square). B: The proband at seven years of age.

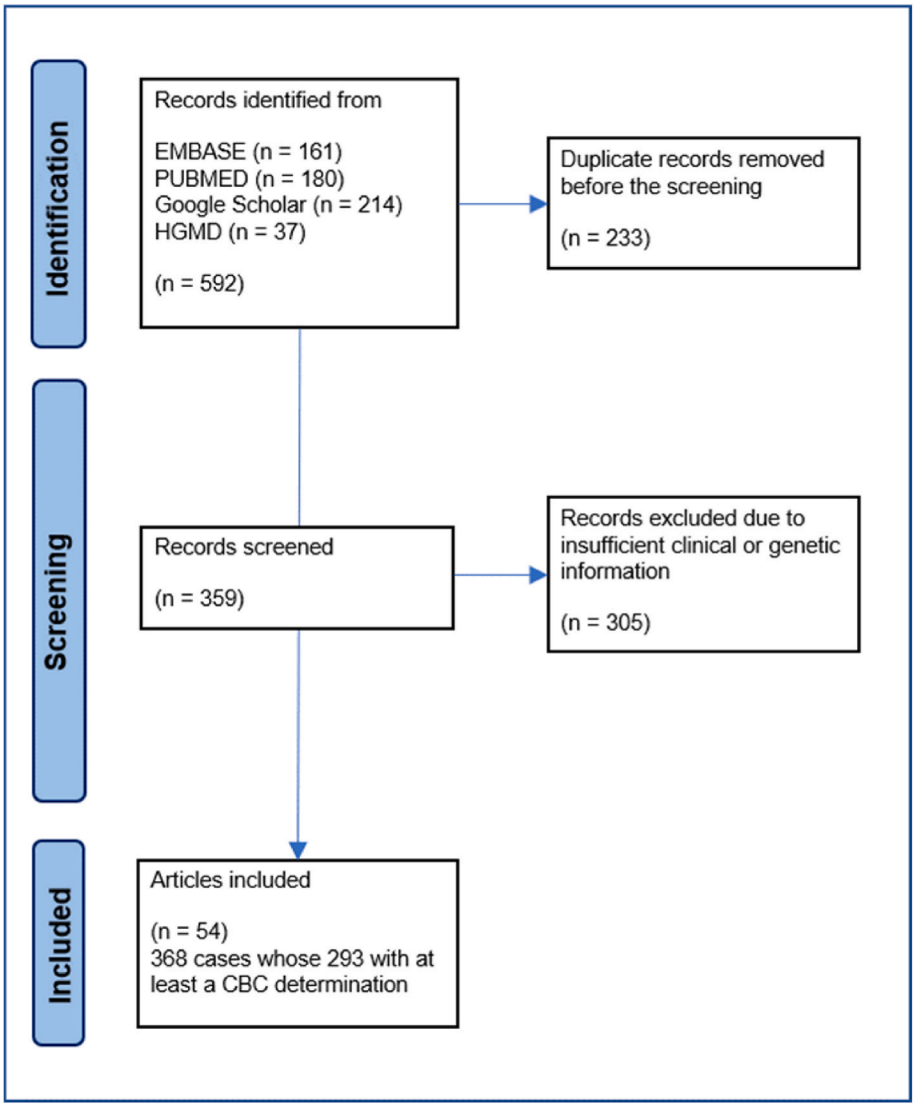

Fig. 2. Search strategy focused on neutropenia in Cohen Syndrome. PRISMA flow diagram. Adapted From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). The PRISMA Statement. PLoS Med 6(7): e1000097. https://doi.org/10.1371/journal.pmed1000097. For more information, visit www.prisma-statement.org.

Table 1
Immunological findings at 8 years of age.

		Results	Range
Hb	g/dl	12.1	9.5–14.0
WBC	10^3/uL	4.31	6.0–17.5
Neutrophilis	10^3/uL	0.77	1.5–8.0
Lymphocytes	10^3/uL	2.56	4.5–13.5
Monocytes	10^3/uL	0.26	0.2–1.9
PLTs	10^3/uL	227	150–450
IgG	mg/dL	1287	633–2016
IgG1	mg/dL	1150	377–1131
IgG2	mg/dL	383	68–388
IgG3	mg/dL	58	15.8–89.0
IgG4	mg/dL	55	1.2–169.9
IgA	mg/dL	226	41–315
IgM	mg/dL	66	56–261
IgE	kU/L	13.2	<90
$CD3^+$	%	75.1	58–75
$CD3^+$	10^3/uL	1922	
$CD3+CD4^+$	%	33.4	29–47
$CD3+CD4^+$	10^3/uL	412	
$CD3+CD8^+$	%	35.6	17–33
$CD3+CD8^+$	10^3/uL	911	
$CD19^+$	%	15.1	14–30
$CD19^+$	10^3/uL	386	
CD16 + 56+	%	8.8	4–17
CD16 + 56+	10^3/uL	225	
CD4+CD45Ra+	%	26.7	
CD4+CD45Ro+	%	6.7	
CD8+CD45Ra+	%	31.7	
CD8+CD45Ro+	%	3.9	
T regulatory cells (CD25+CD127low FoxP3high)	%	6.18	IQR 3.7–9.0

disorder, with Cohen syndrome being the primary but not the sole clinical hypothesis. We therefore performed a clinical exome panel that detected a maternally inherited c.7854+1G > T splicing variant and a paternally inherited microduplication involving exons 32–33 of the *VPS13B* gene. The microduplication had previously been documented in the literature in homozygous status and associated with Cohen syndrome [12], while the c.7854+1G > T variant was a novel change. According to the criteria established by the Clinical Genetics Community (ACMG), both variants were classified as pathogenic (class 5) [9].

Patient is currently undergoing regular follow-ups, with periodic logopedic and psychomotricity treatments, as well as immunological monitoring with annual screening for autoimmune diseases.

3.2. Review

3.2.1. Neutropenia

Following the elimination of duplicates and the exclusion of papers lacking essential information, 54 papers were selected from a total of 592 results found on Pubmed, Embase, Google Scholar and the Human Gene Mutation Database (HGMD®) (Fig. 2).

Totally, 293 subjects were investigated for presence of hematological abnormalities in clinical descriptions of patients found in the literature. Of these, 226 (77.1 %) showed chronic neutropenia. The median age of subjects at the time of evaluation was nine years (interquartile range: 6–18 years).

Complete follow-up with median ANC values for individual patients was available in only forty-five cases. A comparison was made between patients of Caucasian (n = 31) and Asian (n = 14) origin, revealing no significant differences in median ANC values [700 cells/uL (IQR 600–900) vs. 660 cells/uL (IQR 555–990); $p = 0.8$].

A geographical analysis reveals that patients of Caucasian ethnicity frequently exhibit neutropenia (164/181; 90.6 %), with the highest prevalence observed among Finnish patients (39/40, 97.5 %). Patients of Asian and Arab ethnicity were less affected by neutropenia (27/46; 58.7 % and 25/53; 47.1 %, respectively) (Fig. 3) [13–15].A statistically significant difference was identified between the three groups ($p < 0.0001$).

3.2.2. Infections and autoimmunity

Few severe cases of infectious diseases were reported, including one cerebral abscess, one deep mucosal *Pseudomonas aeruginosa* infection and two cases of recurrent pneumonia in children. Conversely, seven authors described oral mucosal involvement in a total of thirty patients (Supplementary Table 1). In a total of five cases, the occurrence of premature tooth loss was documented [16–22].

Five patients required treatment with granulocyte-colony stimulating factor (G-CSF), with a favorable response observed in terms of both neutrophil count (ANC) values and infection rate. However, it should be noted that one patient showed no clinical improvement [19].

Autoimmune diseases were reported in seven patients, six of whom presented with neutropenia; and in one case the available data did not include ANC. Two patients demonstrated thrombocytopenia. One patient had been diagnosed with inflammatory bowel disease (IBD) and juvenile idiopathic arthritis (JIA). As illustrated in Supplementary Table 1, three distinct cases of rheumatoid arthritis, autoimmune hepatitis and psoriasis were documented. In one case, positive antiphospholipid antibodies (APA) were detected, suggesting antiphospholipid syndrome (APS).

4. Discussion

In this work, we report the case of a seven-year-old male patient diagnosed with CS who carries a novel compound heterozygous variant in the *VPS13B* gene. To the best of our knowledge, the maternally inherited c.7854+1G > T variant has not been previously described in the scientific literature. In contrast, the paternally inherited microduplication of exons 32–33 has been reported in a single case, involving a Moroccan girl born to consanguineous parents [12]. The female patient presented with intermittent neutropenia and a clinical phenotype characterized by intellectual disability, microcephaly, thin extremities, chorioretinal dystrophy, myopia, joint laxity, and friendly behavior. It is noteworthy that the subjects in both cases exhibited the absence of trunk obesity.

4.1. Genotypic and phenotypic variability in CS

The initial substantial research on CS was undertaken on Finnish patient groups, revealing that the c.3348_3349delCT founder mutation accounts for approximately 75 % of mutant alleles and it is linked to a relatively homogeneous phenotype [6]. In contrast, non-Finnish patients demonstrate elevated levels of both genotypic and phenotypic variability [6,12,16,17,23,24]. The literature includes cases of subjects without intellectual disability or obesity, such as the present patient, thereby providing further documentation that confirms the variable expressivity of CS [25]. It has been posited that this variability may be attributed to partial protein expression [19].

Based on the identification of distinctive features of CS, several authors have proposed diagnostic criteria for this syndrome. Among them, chronic or intermittent neutropenia has been identified as a recurrent clinical feature [16,26,27]. It is important to note the assertion made by El Chehadeh et al. that molecular analysis should only be considered when there is evidence of neutropenia or chorioretinal dystrophy [12]. Furthermore, while the combination of intellectual disability and retinopathy is found in various syndromes catalogued in the London

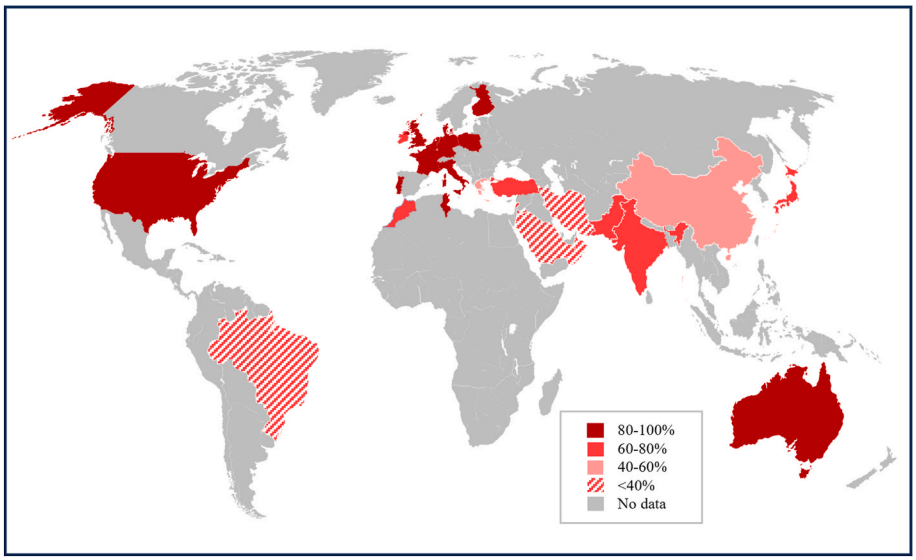

Fig. 3. Prevalence of neutropenia in patients with Cohen syndrome based on geographic origin.

Medical Databases (LMD, https://www.face2gene.com/lmd-history/), few syndromes include both intellectual disability and neutropenia. This observation suggests that *VPS13B* pathogenic variants are more likely to be found in patients with neutropenia and psychomotor retardation and/or intellectual disability, regardless of the presence of retinopathy or dysmorphic features, which may develop later (Fig. 4).

Neutropenia, therefore, stands out as an important clinical sign because it is very frequent and easy to demonstrate. However, a systematic review based on hematological and immunological signs of CS has not yet been performed.

We conducted the first comprehensive literature review on the frequency of neutropenia and its infectious and immunological implications in CS patients.

4.2. The role of ethnicity

The first notable finding from our review is the different prevalence of neutropenia based on geographic origin. Caucasians exhibited reduced neutrophil counts in 90.6 % of cases, whereas Arabs (58.7 %) and Asians (47.2 %) displayed lower frequencies of neutropenia. This

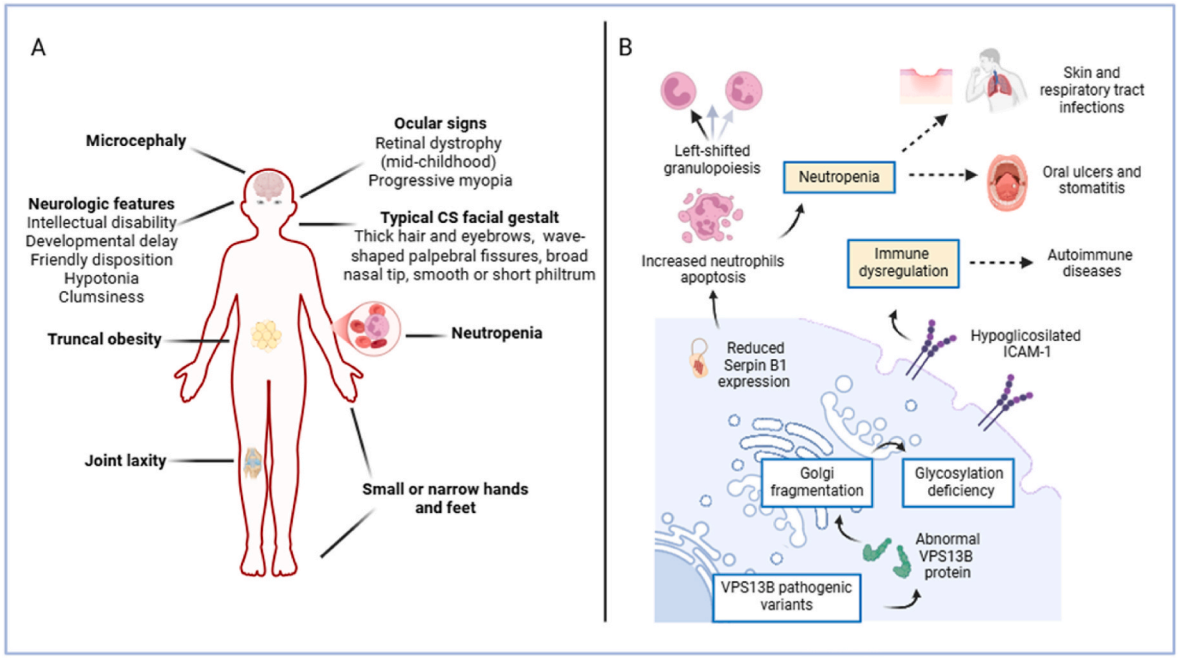

Fig. 4. (A) Common clinical signs of CS. (B) Proposed pathogenetic mechanism of immune system involvement in Cohen syndrome. The VPS13B protein has been shown to play a pivotal role in Golgi apparatus function. However, the precise location and function of this protein remain to be fully elucidated [57]. Models of VPS13B-depleted cells show fragmentation of the Golgi [58]. Furthermore, a glycosylation defect has been observed in the serum of CS patients. Glycosylation of ICAM-1, a key molecule in the activation and interaction of immune cells, has been observed to be reduced in patients with systemic sclerosis (SSc). This finding suggests a potential for immune dysregulation, which may in turn increase the risk of developing autoimmune diseases [31]. Reduced expression of Serpin B1, a cytoplasmic serine protease essential for neutrophils survival, indicates that the elevated apoptosis of neutrophils in peripheral blood is the primary cause of neutropenia and its clinical consequences [39]
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result suggests a potential influence of ethnicity on neutrophil levels in CS patients, as illustrated in Fig. 3.

The influence of ancestral nationality on CS phenotype has been previously investigated. Firstly, a number of authors put forward a classification of CS into two distinct types, namely "Jewish" and "Finnish", based on the presence of a unique clinical phenotype [27]. However, with the advent of molecular diagnostics, this rigid dichotomy has become obsolete, although clinical heterogeneity among different ethnic groups remains apparent.

It is interesting to note that the geographical distribution of neutropenia in CS patients does not correspond with that of benign "ethnic" neutropenia. The latter is linked to Duffy antigen expression and it results in physiologically lower neutrophil counts in specific populations in Africa, South America and the Middle East [28,29]. Paradoxically, cases of CS from these regions exhibit higher neutrophil levels (Fig. 3), suggesting that ethnic neutropenia does not contribute to CS-associated neutropenia.

4.3. CS: a congenital disorder of glycosylation with neutrophil apoptosis

The pathophysiology of neutropenia in CS has been investigated in a limited number of studies. Overall, CS patients do not present with significant bone marrow abnormalities, and few studies describe their immunological and hematological characteristics in detail. Kivitie-Kallio et al. found no abnormalities in bone marrow cellularity among 16 patients, although 8 exhibited left-shifted granulopoiesis. It was observed that a positive response to G-CSF administration was exhibited by three patients [4]. Gueneau et al. reported a case of a child with recurrent infections and oral aphthosis, whose bone marrow analysis was normal. Notwithstanding a period of two years during which the patient was treated with G-CSF, no substantial clinical improvement was observed [19].

It is generally accepted that G-CSF therapy is both safe and effective; however, it should be noted that side effects have been reported. A recent case study documented the case of a 26-year-old male patient who exhibited acute bleeding as a result of oesophageal varices, a condition that may have been induced by G–CSF–correlated splenomegaly [30].

The relationship between *VPS13B* variants and neutropenia remains to be elucidated. However, Duplomb et al. demonstrated that neutrophil precursors in CS patients exhibit Golgi apparatus disorganization, which is likely due to altered glycosylation of intercellular adhesion molecule 1 (ICAM-1) [31], a known biomarker of hypoglycosylation [32]. This finding suggests that CS may be classified as a congenital disorder of glycosylation (CDG).

ICAM-1 is a transmembrane protein belonging to the immunoglobulin superfamily. It is expressed on the surface of a range of immune cells, with a key function in the trafficking of leukocytes and the activation of T-cells [32,33]. It can thus be concluded that an impaired expression or activity of this protein could play a key role in immune dysregulation and autoimmune disorders, as was previously investigated (Fig. 4) [34,35].

It is interesting to note that other CDGs are also characterized by constitutional neutropenia, including syndromes caused by glucose-6-phosphatase catalytic subunit 3 (*G6PC3*) and Jagunal Homolog 1 (*JAGN1*) variants [36]. The resultant immune system imbalance gives rise to chronic inflammatory conditions, including periodontal disease and recurrent aphthous lesions (which are also prevalent among CS patients), as well as autoimmune phenomena. As demonstrated in the existing literature, there is a reported correlation between the presence of anti-neutrophil autoantibodies, autoimmune thyroiditis, coeliac disease, and chronic inflammatory bowel disease in patients with G6PC3 variants [36].

Moreover, other hallmark symptoms of CS, such as retinitis pigmentosa and microcephaly, are likewise identified in cases of CDGs [37,38].

Concerning potential etiologies of neutropenia in CS, a recent study by Duplomb et al. demonstrated reduced expression of Serpin B1, a pivotal protein in the survival of neutrophils, in patients carrying a pathogenic *VPS13B* variant. This finding serves to substantiate the hypothesis that the genesis of neutropenia in CS patients stems from heightened apoptosis of neutrophils, which nevertheless manifests normal functionality [39].

However, further studies are required to elucidate the mechanisms by which *VPS13B* variants result in diminished neutrophil survival and to determine whether the presence of autoantibodies contributes to this process.

4.4. Immunological phenomena

Confirming the immune system's involvement in CS, the patient herein described exhibited signs of immune dysregulation, including a reduction in $CD4^+$ T cells. Moreover, initial haematological evaluations resulted in a diagnosis of autoimmune neutropenia (AIN) due to the presence of positive autoantibodies.

Although AIN is generally considered to be a benign condition that resolves spontaneously within three years, some atypical cases may become chronic and they may be associated with systemic autoimmune manifestations [28,40,41].

The presence of extra-hematologic symptoms is crucial for distinguishing syndromic forms of neutropenia that may mimic atypical AIN.

The manifestation of clinical signs indicative of CS (predominantly retinal dystrophy from the age of five) and the persistence of neutropenia for a period exceeding three years (termed "long-lasting neutropenia") permitted us to overcome the initial suspicion of AIN and attain a genetic diagnosis in our patient. Antineutrophil antibodies have been demonstrated to be a useful diagnostic tool in the discrimination of peripheral forms of neutropenia [28,42]. Nonetheless, even though the most widely employed indirect method (GIFT) exhibits a high degree of specificity, it is increasingly evident that several patients suffering from complex chronic neutropenias (including both congenital and syndromic forms) may also exhibit positive antineutrophil antibodies [43]. It is therefore vital to consider other possible diagnoses and meticulously monitor the patient in the event of warnings suggesting atypical neutropenia [41].

Of particular interest is the report of autoimmune diseases in both children and adult CS patients. These include thrombocytopenia, rheumatologic diseases, and IBD [23,44,45, 46, 47, 48, 49]. Furthermore, frequent uveitis and recurrent pericarditis were observed [personal observation by Wang H] (Supplementary Table 1) [48].

Given the rarity of CS, even a small number of cases of autoimmune diseases require further investigation. Immunological studies could have the potential to elucidate whether autoimmune phenomena are coincidental or they represent an integral component of the syndrome.

4.5. Infections and periodontal disease

The patient presented herein experienced one episode of pneumonia and three episodes of acute bronchitis in early childhood, but he had no significant recurrent infections. This finding is consistent with the extant literature, which demonstrates that severe infections are uncommon and that neutropenia is frequently mild (Supplementary Table 1). However, there are some documented cases of serious and life-threatening infections, including a brain abscess. [50]

Conversely, the presence of periodontal disease is a frequent occurrence. A number of studies have indicated the repercussions of chronic neutropenia on oral mucosal inflammation, which can result in tooth loss [51,52]. A recent study by Lafon et al. discovered a correlation between the severity of neutropenia and the occurrence of tooth loss in a cohort of 12 patients diagnosed with CS [53]. It is therefore recommended that a preventative approach be given particular consideration,

including periodic examinations with a view to delaying or avoiding sequelae such as premature tooth loss.

4.6. *VPS13B* gene variants and neutropenia

An evaluation of all variants reported in the literature was conducted, with the presence or absence of neutropenia serving as the primary outcome measure (see Supplementary Table for details). It has been observed that only specific variants in the *VPS13B* gene appear to be more closely associated with neutropenia. The most striking case is that of the c.3348_3349delCT founder mutation in the Finnish cohort, which has been associated with neutropenia in all reported cases.

In the other most prevalent variants, the frequency of neutropenia was never so elevated.

In the Chinese population, the c.6940+1G > T variant was identified in five patients in a state of compound heterozygosity. Three of the compound patients exhibited neutropenia, and one homozygous case also demonstrated neutropenia. In subjects of Greek origin, an intragenic deletion spanning from exon 6 to exon 16 was observed to be associated with neutropenia in two out of four individuals [18]. Furthermore, in a cohort of Irish patients carrying c.4471G > T (p.Glu1491X), neutropenia was observed in three out of five cases [54]. Moreover, the present study found no evidence that neutropenia was associated with a specific *VPS13B* variant in siblings. This finding was suggested by three case reports. Out of three pairs of siblings carrying the same variant, only one of them developed neutropenia [20,55,56].

5. Conclusions

This study presents a novel compound heterozygous *VPS13B* variant in a seven-year-old male patient diagnosed with CS, thereby broadening the existing knowledge of the genetic and clinical spectrum of the disorder. The literature review highlights high genotypic and phenotypic variability, particularly concerning neutropenia, which manifests inconsistently across patients with the same variants, including siblings and twins.

The role of ethnicity in the prevalence of neutropenia is a subject of interest, with Caucasian patients exhibiting a higher frequency of occurrence in comparison to Arab and Asian populations. Emerging evidence suggests that CS is a CDG, with immune system involvement due to impaired ICAM-1 glycosylation and Serpin B1 downregulation leading to increased neutrophil apoptosis. The immunological findings in this case, in conjunction with the various autoimmune comorbidities reported in the literature, serve to confirm the link between CS and immune dysregulation.

Although severe infections are uncommon, periodontal disease is prevalent; and there is a documented correlation between the severity of neutropenia and tooth loss. This correlation underscores the necessity for preventive dental care.

To summarize, the present study offers novel insights into the clinical spectrum of CS, with particular regard to neutropenia and immune involvement. The study underscores the necessity for additional research to elucidate underlying mechanisms and optimise clinical management.

Informed consent

Informed consent was obtained from the patient and his family.

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Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pedneo.2025.08.010.

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