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CASE REPORT

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A VPS13B mutation in Cohen syndrome presented with petechiae: An unusual presentation

Alireza Razavi[1] | **Hamed Jafarpour**[1] | **Mohammad reza Khosravi**[1] | **Ghazal Abbasi**[1] | **Abbas Dabbaghzadeh**[2]

[1]Student Research Committee, School of Medicine, Mazandaran University of Medical Sciences, Sari, Iran

[2]Department of Pediatrics, School of Medicine, Bu Ali Sina Hospital, Mazandaran University of Medical Sciences, Sari, Iran

Correspondence
Abbas Dabbaghzadeh, Department of Pediatrics, School of Medicine, Bu Ali Sina Hospital, Mazandaran University of Medical Sciences, Sari, Iran.
Email: alirezarazavi1995@outlook.com

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Abstract

Cohen syndrome (CS) is a rare autosomal recessive disorder. CS includes a range of clinical symptoms including retinal dystrophy and myopia. The new VPS13B mutation could cause CS-induced neutropenia and petechiae in patients with CS.

KEYWORDS

Cohen syndrome, mutation, petechiae

1 | BACKGROUND

Cohen syndrome (CS) is a rare autosomal recessive disorder. This case demonstrates the importance of the new VPS13B mutation in the development of CS and the development of neutropenia and petechiae and how to detect and manage it.

Cohen syndrome (CS) a rare disorder was originally identified in 1973 by Cohen Jr et al.[1] CS (MIM n.216550) is a rare autosomal recessive disorder caused by mutations in the gene COH1 on chromosome 8q22.[2] CS is a clinically heterogeneous condition with widely variable clinical manifestations such as myopia, retinal dystrophy, neutropenia, facial appearance consisting of thick hair, thick eyebrows, long eyelashes, down-slanting pupils, narrow philtrum, and prominent upper incisors, mostly marked by developmental regression, microcephaly, and hypotonic.[1] In infancy, the diagnosis is often difficult because many of the usual characteristics can be nonexistent before scholarization or upcoming years and sporadic neutropenia are not reliably detectable.[3] In this case, we reported a child girl born with neutropenia, who later developed petechiae, which is rarely reported as initial manifestations of CS.

2 | CASE PRESENTATION

A 16-month-old girl born into a distant consanguineous family, who was referred for diagnostic assessment due to frequent neutropenia in the last year, presented with a fever and vomiting to our clinic. The past medical history demonstrated a deferment in motoric milestones. At two months, she could hold her head steady. At six months, she began to sit. She needed help to stand up, and her walking was delayed at 16 months. Also, she had speech delay and received speech therapy. Her parents stated that her child had a history of a urinary tract infection (UTI) which seemed normal according

to sonography. Her parents had no underlying diseases. Her mother had a history of twice stillbirth in her pregnancy. Her temperature was 37.9℃, and other vital signs were normal. On clinical examination, few sores were observed in her gum. She was not allergic to the Bacillus Calmette-Guérin (BCG) vaccine. The growth index was normal. Her pharyngeal tonsils were normal, and no organomegaly was seen. Her facial characteristics included thick forehead hair prominent upper central incisors, thick, and long eyelashes (Figure 2). She had abdominal obesity with tenuous limbs. Moreover, the patient had cheerful mood, hypermobile joints, and tiny petechial spots on her lower limbs (Figure 3). Her eye status was checked, and no particular problems were seen. Flow cytometry, and nitro blue tetrazolium test (NBT), bone marrow aspiration, and sonography were normal. Complete blood count (CBC) checked for persistent neutropenia and revealed more severe neutropenia than eight months ago (0.30 10^3/μl vs. 0.44 10^3/μl).

In review of her laboratory results in the period of 16 months since her referral to clinic, persistent neutropenia was observed so that absolute neutrophil count (ANC) ranged from 0.30 to 2.16 (10^3/μl) (Table 1). Other components include immunoglobulins and immune markers shown in (Figure 1).

Based on the patient's history, her laboratory results and physical examinations such as her facial features and developmental delay, CS was our first diagnosis. Therefore, a whole-exome sequencing test was performed for sure. According to the test, a homozygous frameshift variant in the VPS13B gene was found, and finally, our diagnosis was confirmed. Hence, Bardet-Biedl syndrome, Prader-Willi syndrome, Cri-du-chat syndrome, Alström syndrome, Angelman syndrome, Williams syndrome, MORM syndrome, and monosomy were ruled out because of the homozygous frameshift variant in the VPS13B gene. Prophylaxis of cotrimoxazole 80 mg/400 mg has been prescribed. In the follow-up, the patient has not been symptomatic and no severe problems were seen. Speech therapy and occupational therapy have been continued, and fortunately, her verbal and motor abilities have improved. Also, in the last visit, eye and nephrology consultations were requested due to the likelihood of abnormalities that were normal. Cotrimoxazole has been discontinued since 3 months before her last referral.

3 | DISCUSSION

We reported a novel homozygous frameshift variant in the VPS13B gene in an Iranian 16-month-old girl born to a distant consanguineous family with recurrent infections and neutropenia, which are rarely reported as initial manifestations of CS.[4] The diagnosis of CS is difficult, even for an accomplished clinician. This condition is essentially a rare autosomal recessive disorder, and CS diagnosis is mostly unlikely before middle or late childhood. The phenotypic characteristics are therefore very variable, some may be missing before scholarization or upcoming years.[3] Actually in this case, neutropenia was the most important manifestation. Moreover, we indicated some facial features regardless of ethnic background including thick hair and eyebrows and long eyelashes. Also, we discovered some rare skin manifestation in this case as a tiny petechial spots with no itching on her forearms. So neutropenia and facial appearance and some skin manifestation can be a red sign of CS. Unlike most of other cases, our patient did not present any ophthalmologic or nephrological abnormality. She also did not present any cardiologic abnormality, which may be seen in some cases of CS.[4]

Neutrophils are first-line defense innate immune cells which represent two thirds of blood leukocytes. In controlling bacterial and fungal infections, neutrophils are necessary, and neutrophil deficiency, neutropenia, is predisposed to serious

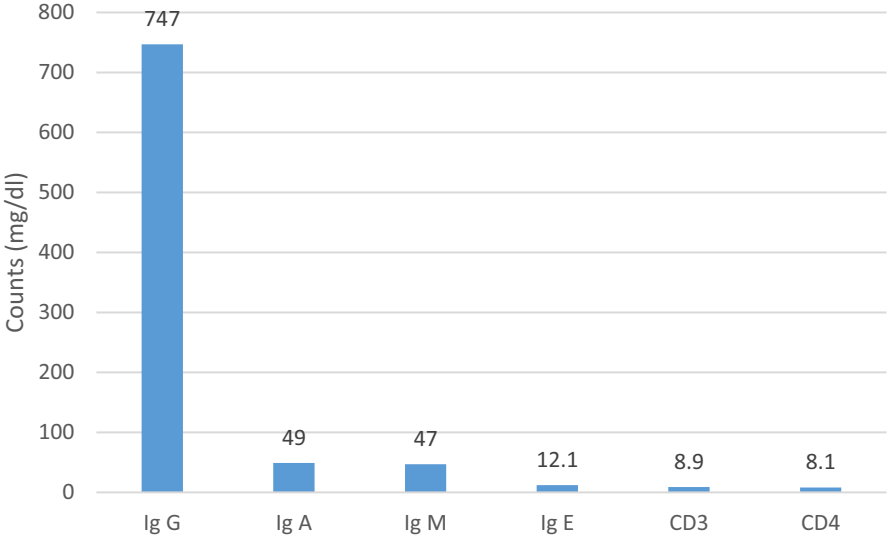

FIGURE 1 Immunoglobins and Cluster of Differentiation (CD Markers) levels at 16th month

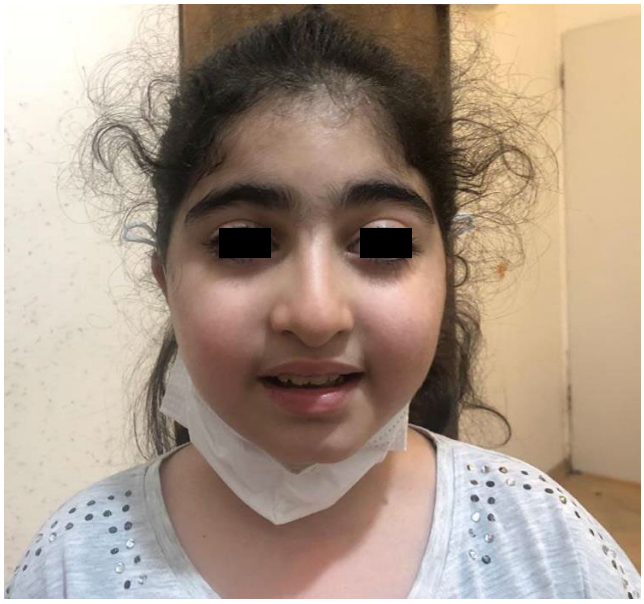

FIGURE 2 Thick forehead hair prominent upper central incisors, thick and long eyelashes in CS patient

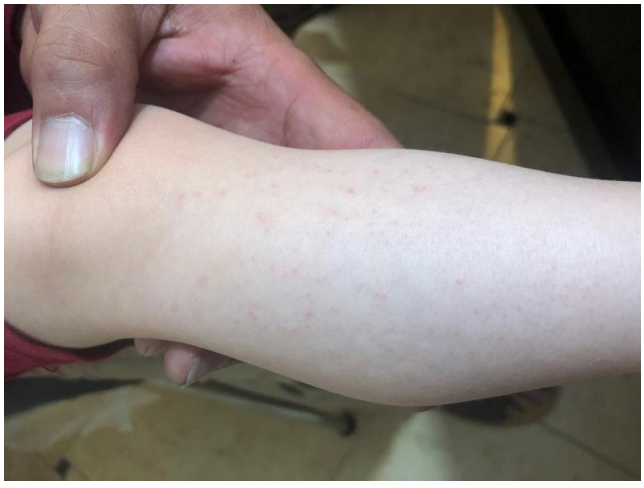

FIGURE 3 Tiny petechial spots on her lower limbs in CS patient

or fatal infections. In a variety of conditions, neutropenia may occur. It may be caused by serious types of bone marrow failure or malignant disease or arise as a manifestation of illness secondary to other diseases.[5] Recurrent CS neutropenia may be caused by a VPS13B gene mutation that is associated with increased neutrophil apoptosis and decreased SerpinB1 expression, which is a critical component of neutrophil survival.[4] Both neutrophil functions seemed to be regular in addition to this increased cell death, which occurs in the absence of any endoplasmic reticulum stress or neutrophil elastase (ELANE) expression or localization defect. In CS neutrophils precursors, it had been demonstrated disorganization of the Golgi apparatus, as observed by the migration change of the protein, which coincides with the altered glycosylation of ICAM-1 in those cells. In addition, in CS neutrophils, a substantial decrease in the expression of the SERPINB1 gene, which encodes a critical component of neutrophil survival, was observed. The excessive apoptosis of neutrophils leading to CS neutropenia may account for these abnormalities.[6] Hypotonic facial expression with an open mouth is conspicuous in the facial appearance of the baby and young child with CS. Typically, the mouth has corners that are downturned and the lower lip is often thick and pouting. Not always is the philtrum so obviously short. The eyes are a striking feature and give the baby an almost "china doll" look. They are wave-shaped and downward slanting with thick eyebrows and eyelashes.[7] In few cases such as a Chinese patient with CS, hyperlinear palms or palms with extra skin creases displayed a hand phenomenon with atopic dermatitis or ichthyosis Vulgaris.[8] But in our case, skin manifestations have been demonstrated in a different shape in a way that we discovered some tiny petechial spots on her lower limbs without any itching and irritation. Additionally, no allergic manifestations have been discovered in this case. So this skin manifestation could be considered as a diagnostic symptom of CS. Although neutropenia has been shown to cause petechiae in some cases,[9] the exact mechanism is unclear in CS.

In a separate Finnish study, it was suggested that the diagnosis of CS with at least 6 of 8 clinical manifestations including (1) facial features of CS, (2) developmental retardation, (3) microcephaly, (4) cheerful mood, (5) hypermobile joints, (6) neutropenia, (7) abdominal obesity with tenuous limbs, and (8) chorioretinal dystrophy and/or myopia.[10] Our patient had 6 of the 8 items mentioned above, in addition to the fact that the skin manifested petechiae in her lower extremities. However, in addition to these clinical diagnostic criteria, due to the variety of clinical signs, it has been suggested that genetic evaluation should be performed when a CS diagnosis is suspected. It is beneficial to note that enlargement of the corpus callosum in magnetic resonance imaging (MRI) of the brain in infancy and early childhood can aid in the early diagnosis of this complication.[11] Moreover, in our case, the homozygous frameshift variant in the VPS13B gene finalized the diagnosis of CS, as several reports have shown an association between the VPS13B variant and CS occurrence.[4] Therefore, due to the presence of 6 of the 8 clinical manifestations along with the VPS13B variant detection, the diagnosis of CS in our patient was confirmed and differential diagnoses, including Bardet-Biedl syndrome, Prader-Willi syndrome, Cri-du-chat syndrome, Alström syndrome, Angelman syndrome, Williams syndrome, MORM syndrome, and monosomy, were ruled out.

Although cotrimoxazole can increase the risk of neutropenia,[12] it disappeared after the onset of prophylaxis during the follow-up period. It is noteworthy that our patient had neutropenia before the prescription of cotrimoxazole and it seems the VPS13B gene mutation underlined this complication.

TABLE 1 Laboratory results at intervals with the first visit

	1st week	2nd week	3rd week	4th week	2nd month	8th month	16th month
White Blood Cells (WBCs), 10^3/μl	8.7	8.3	6.4	9.5	7.5	6.7	7.9
ANC, 10^3/μl, (%)	0.5 (6.6)	2.16 (26)	0.77 (12)	1.12 (11.8)	0.36 (4.8)	0.44 (6.6)	0.30 (3.1)
Lymphocyte, 10^3/μl, (%)	7.4 (86)	5.48 (66)	5.24 (82)	7.8 (82)	6.6 (88)	5.96 (89)	7.1 (89)
Monocyte, 10^3/μl, (%)	0.5 (6.4)	0.49 (6)	–	–	0.45 (6)	0.27 (4)	–
Hemoglobin, g/dl	9.8	9.6	10.1	10.9	10.7	10	9.5
Platelets, 10^3/μl	309	–	–	–	202	290	–

Management of CS includes regular monitoring and rehabilitation. For monitoring neutropenia, serial ANC is recommended. Furthermore, speech and physical therapy can help in improving the speech and motor developmental delay. In addition, laboratory tests include the measurements of WBC, WBC diff, hemoglobin, and platelets should be monitored. Also, blood pressure, fasting blood sugar levels, lipid metabolism, and A1C levels of hemoglobin should be checked each year.[4] In our case, prophylaxis of cotrimoxazole 80 mg/400 mg had been prescribed since her first visit but it has been discontinued since 3 months before her last visit. Moreover, eye examination, cardiac, and nephrological monitoring should be prescribed because of being high-risk factors in CS.[2]

4 | CONCLUSIONS

Mutations in VPS13B can induce CS. CS can cause a range of clinical manifestations, including neutropenia and petechiae. The diagnosis of this disease is a combination of clinical symptoms along with genetic test. Detection of VPS13B mutation can be very helpful in diagnosing this disease.

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CONFLICTS OF INTEREST

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

AUTHOR CONTRIBUTIONS

AR: first operator in the case, planned and performed the procedure, and took decisions on hardware and technique used. HJ, MK, and AD: assisted in procedure and drafted the manuscript. GA: assisted in procedure. All authors read, revised, and approved the final manuscript.

ETHICAL APPROVAL

Written informed consent was obtained from the patient for the publication of this case report as well as accompanying images. A copy of the written consent is available for review by the editor-in-chief of this journal.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

ORCID

Abbas Dabbaghzadeh https://orcid.org/0000-0001-9017-3041

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