Co-existence of Cohen Syndrome and Pendred Syndrome? Diagnostic Challenges Associated With Presence of Multiple Genomic Variants in the Newborn: A Case Report

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Case report

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Abstract

Background

Cohen syndrome is a multisystem autosomal recessive hereditary disease, which is caused by variants of the *VPS13B* gene. The clinical manifestations include characteristic facial features, microcephaly, trunk obesity and mental retardation. The *SLC26A4* gene encodes an anion transporter called Pendrin, the variants of *SLC26A4* lead to deafness, Pendred syndrome and enlarged vestibular aqueduct. We present a case of multiple genetic homozygous variants of *SLC26A4* and *VPS13B*.

Case presentation

In this study, we described a case of a 65-day-old female infant presenting with hearing loss and poor feeding. The deafness gene screening before admission showed that the patient carried homozygous c.919-2A>G variation of *SLC26A4* gene. The symptoms of the patient did not improve significantly after a period of targeted treatment, then the possibility of genetic diseases was considered after consultation with the different departments. Whole exome sequencing was performed, and homozygous splicing variants in intron 38 (c.6940+1G>T) of *VPS13B* and that in intron 7 (c.919-2A>G) of *SLC26A4* were identified. Later, the parent was proved as the carriers of *VPS13B* and *SLC26A4* heterozygous variations by Sanger sequencing.

Conclusions

Presence of multiple genetic homozygous variants of *SLC26A4* and *VPS13B*, it is difficult to make an early diagnosis due to early atypical symptoms. Final diagnosis depends on whole exome sequencing which plays an important role in early diagnosis of intractable neonatal cases.

Background

Cohen syndrome (CS; OMIM#216550) was first described in 1968 with the name of the patient's name for Pepper syndrome[1]. Then it was confirmed by Cohen and the colleagues in 1973 and named as CS[2]. CS is an autosomal recessive genetic multisystem disease. The clinical manifestations of different ethnic groups have been proved to be different, the classical manifestations include characteristic facial features, microcephaly, trunk obesity, mental retardation, progressive retinopathy and intermittent congenital neutropenia, etc[1, 2]. *VPS13B* gene was cloned in 2004, the germline variation of *VPS13B* gene on chromosome 8q22.2 is considered to be the hereditary cause of CS[3]. *VPS13B* contains 66 exons, spans a genomic region of approximately 864 kb[3, 4]. It mainly encodes transmembrane proteins of the golgi body, which play an important role in the transport of protein in cells. It is reported that CS can be caused by disorders of glycosylation, which is considered to be the result of the variants of *VPS13B*[4-6].

Pendred syndrome (PDS; OMIM#274600) was firstly described as a combination of deafness and goiter by V.Pendred in 1896. *SLC26A4* gene is located on chromosome 7q31, encodes a type of anion transporter called Pendrin, which was cloned in 1997[7]. The variants of *SLC26A4* can result in PDS, enlarged vestibular aqueduct (EVA) and inherited deafness. Typical clinical phenotypes of PDS include goiter, congenital sensorineural deafness and an abnormal organification of iodide[8-10]. Few cases of *VPS13B* gene

variation have been reported in China, and homozygous variants are much less. This is the first case of homozygous *VPS13B* variation combined with homozygous *SLC26A4* variation.

Case Presentation

A 65-day-old girl was admitted to Tianjin Children's Hospital for hearing loss, poor feeding and slow growth. This infant was born after 38+1 weeks of gestation uncomplicated pregnancy by normal spontaneous vaginal delivery, weight 3200 g. There were no abnormalities in placenta and umbilical cord during pregnancy except premature rupture of membranes 20 h in advance. The condition of newborn was normal without history of fetal intrauterine distress and postnatal asphyxia. She Cried immediately and loudly after birth, the apgar score was 10 at 1 min. Physical examination after admission showed that the head circumference, body length and body weight were 36 cm, 53 cm and 3840 g respectively. Moreover, she presented with bilateral eye strabismus, hypertonia (both upper limbs), hypotonia (both lower limbs) and unsound original reflex. No swelling and nodule were touched in bilateral thyroid gland. Blood routine examination showed that white blood cells were 13070/ μ L and the neutrophil ratio was 13%. Thyroid function test showed that the total thyroid hormone was 160.62 nmol/L (78.38-157.4 nmol/L), and the free thyroid hormone was 20.19 pmol/L (9.92-19.54 nmol/L). No specific abnormal fatty acid metabolism was found in the blood and urine screening of genetic metabolic diseases. Other blood and urine stool results were generally normal. Cranial MRI showed that the ventricles and the extra brain space were widened. Brainstem auditory evoked potential showed moderate to severe hearing loss in the right ear and severe hearing loss in left ear. The results of deafness gene screening showed homozygous c.919-2A>G variation of *SLC26A4* gene. Then hereditary deafness was diagnosed. After a period of targeted treatment, the symptoms of the patient did not improve significantly. The possibility of other genetic diseases was considered after consultation with the rehabilitation department, ophthalmology department and neurology department. The chromosome test showed 46, XX, whole-exome sequencing (WES) showed the co-occurrence of homozygous c.6940+1G>T variation of *VPS13B* gene and homozygous c.919-2A>G variation of *SLC26A4* gene. Sanger sequencing showed that the parents of the patient were heterozygous carriers of both pathogenic genes (**Figure 1 and Figure 2**). The patient cannot be diagnosed with PDS due to the lack of parents' permission about some special examinations. CS and hereditary deafness were diagnosed according to hearing test and other tests.

At 1.5 years of telephone follow-up, the patient showed apparently growth retardation (height 76 cm, weight 6000 g). She presented with normal head circumference, a long and thin face, and two eyes (cross-eye) with normal vision. Her hearing was normal in her mother's opinion, because she could move her sight with her mother's voice and respond to small sound stimulation in life. No swelling and nodule were touched in bilateral thyroid gland. She could hold up her head, sit up and roll without the help of an adult, and could stand with the help of her parents. There is considerable muscular hypotonia and psychomotor retardation. She could only speak simple words such as BABA and MAMA. (The above was her mother's dictation.)

Discussion And Conclusions

We introduced a 65-day-old female infant with co-occurrence of homozygous variants of two pathogenic genes. In this case, the splicing-site variation c.6940+1G>T of *VPS13B* gene has been reported in some Chinese patients and its clinical significance on Clinvar was described as likely pathogenic. Because of the clinical heterogeneity and the clinical manifestations vary in different regions, the correlation between genotype and phenotype has not been determined[11]. The clinical manifestations of CS in Finnish patients are highly uniform, and there is phenotypic variability in non-Finnish patients. The common clinical manifestations are psychomotor retardation, microcephaly, characteristic facial features, progressive retinochoroidal dystrophy, hypotonia and neutropenia[12]. With the number of patients gradually increases, more cases with rare clinical manifestations are also increasing, including pulmonary hypertension, congenital defects of the genital organ, insulin resistance, diabetes, febrile convulsion, epilepsy and other clinical manifestations[13, 14]. We reviewed the medical records on the patient, including the growth, development and related examination results. We found that the clinical manifestations of this case were atypical, including hypotonia, dyspnea, poor feeding, poor weight gain, binocular strabismus, neutropenia and other clinical features. The infant was born with premature rupture of membranes 20h in advance and postnatal evaluation was normal, there was no report describing the relationship between premature rupture of membranes and CS. Other manifestations were inconsistent with the typical patients described in previous articles[13, 15, 16]. Only some mothers had oligohydramnios and decreased fetal movement during pregnancy, so we can't determine whether premature rupture of membranes is associated with CS[13]. The birth weight of patient was not significantly abnormal compared with normal newborns. The weight of patient won't increase because of the poor feeding caused by muscular hypotonia, so infant patients often show poor weight gain rather than typical facial features[17]. Just one case of bilateral strabismus in CS was reported in China[18], However, due to the absence of fundus examination and obvious clinical heterogeneity among patients with CS, it is impossible to determine whether there is damage to photoreceptor cilia and integrity of retinal structure[19]. So we can't judge whether strabismus is one of the manifestation of CS.

In 2016, CS was first diagnosed by WES in China[20]. Here, we reviewed all the patients with CS confirmed by gene examinations in China (**Table 1**) and analyzed the gene variant sites and clinical features. It was found that 5 of 12 patients (including current case) carried c.6940+1G>T variant of *VPS13B* gene[20-22]. Only this patient was homozygous, and the other 4 cases were heterozygous variation. It can be found that Chinese patients with CS have a high c.6940+1G>T variant carrying rate, which may be a hotspot variation in Chinese population. The variant frequency of this site is 0.01997% in all population and that is 0.1% in East Asian population. It is obvious that the variant frequency of East Asian population is higher than other populations, and there is little reports about this variation in other populations[23-28]. The c.6940+1G>T variation was first discovered by Chinese doctor in 2016, and has been reported four times in China in recent years[20-22]. This patient is the fifth case but the first homozygous variation patient in China. Due to the early symptoms are atypical and the diagnosis is difficult, only this child is under 1 year of age, which proves the value of WES in early diagnose. Therefore, it is necessary to detect *VPS13B* gene when newborns exhibit microcephaly, hypotonia, neutropenia and developmental retardation[17].

SLC26A4 gene variation is one of the main causes of neonatal deafness in China, which can cause both syndromic deafness and non-syndromic deafness[29, 30]. The prevalence of PDS is about 10-7.5/100000,

accounting for 10% of congenital deafness cases[9, 31]. The variation of *SLC26A4* gene in this patient was c.919-2A>G (intron7), which was described as pathogenic on Clinvar. It can be manifested as PDS, EVA and hereditary deafness. As goiter mostly occurs in children and adolescents, it is easy to be affected by external iodine intake, resulting in atypical goiter in some children[9]. The patient in this study did not appear thyroid abnormalities. The parents refused the examination of CT and MRI, so we don't know whether there are abnormalities in the vestibular aqueduct and cochlea. Typical PDS patients can find inner ear malformation, EVA and Mondini cochlea[9]. The diagnosis of PDS mainly depends on the typical clinical manifestations, perchlorate excretion test, imaging findings of cochlear dysplasia and enlarged vestibular aqueduct. Therefore, the patient could not be diagnosed with PDS and was temporarily diagnosed with hereditary deafness at discharge. We found the hearing was normal at 1.5-year telephone follow up. There are two cases of double allelic deafness gene variation (both included c.919-2A>G) were reported to have normal hearing, so the possibility of false positive brainstem auditory evoked potentials was not excluded[32, 33]. It was reported that 32.7% of newborns with abnormal hearing screening were fully recovered and 9.7% were partially recovered, but the outcomes of newborns with genetic abnormalities wasn't mentioned[34]. It has been reported that non syndromic EVA is caused by 0 or 1 *SLC26A4* allele variation, while PDS is caused by two allele variants[35]. Therefore, it is a highly reliable indication of PDS.

Because the early symptoms are atypical, it is difficult to make an early diagnosis among infants with CS[36]. With the popularity of WES, the accuracy of clinical diagnosis has been greatly improved. We should consider the possibility of genetic diseases if we find that some clinical manifestations can't be explained. The patient's deafness gene screening showed *SLC26A4* variation, it can provide an explanation for the hearing loss of infants, but some symptoms couldn't be explained after admission. Hence WES was performed and homozygous *SLC26A4* gene variation combined with homozygous *VPS13B* gene variation were found, which explained other symptoms. Many diseases of the newborn are atypical, especially in some genetic diseases, that further increases the difficulty of diagnosis by neonatal pediatricians. Obviously, WES is worthwhile for early diagnosis of difficult neonatal cases and it is helpful for genetic counseling[36-39]. In recent years, the value of copy number variation analysis based on WES in phenotypic diversity of related genetic diseases has been reported[40].

Early diagnosis and early intervention are helpful to improve the prognosis of patients, and the treatment mainly relying on multidisciplinary cooperation in symptomatic support treatment. For example, insulin resistance in CS can be avoided by early nutrition education and diet control[41], early thyroid hormone replacement therapy can avoid goiter in patients with PDS, and hearing aids or cochlear implants can significantly improve the quality of life of people with hearing loss[42].

In this study, we describe a patient with co-occurrence of homozygous variants *SLC26A4* and *VPS13B* gene. The high frequency of c.6940+1G>T in Chinese population with CS indicates that may be a hotspot variation, and it is helpful to clarify the pathogenicity of this site. It is difficult to make early diagnosis due to the atypical symptoms. WES can effectively help clinical neonatologist make an early diagnosis. The early diagnosis and treatment can significantly improve the quality of life and prognosis of patients. Therefore WES has important diagnostic value in neonatal miscellaneous cases.

Abbreviations

CS: Cohen syndrome

PDS: Pendred syndrome

EVA: enlarged vestibular aqueduct

WES: whole-exome sequencing

DD: Developmental Delay

MC: Microcephaly

TFG: Typical Facial Gestalt

TO: Trunk Obesity

OS: Overly Sociable Behavior

JH: Joint Hypermobility

HM: High Myopia

RD: Retinal Dystrophy

IN: Intermittent Neutropenia

Declarations

Ethics approval and consent to participate

This study involving human participants were reviewed and approved by the ethics committee of Tianjin Children's hospital. Written informed consent was obtained from minor's legal guardian for publication of this case report and any accompanying images or data included in this article.

Consent for publication

Written informed consent was obtained from the patient/parents/legal guardians for publication of this Case Report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Authors Contributions

Yang Liu and Jianbo Shu designed this study and made data interpretation. Guoxu Li prepared the manuscript. Yu Mu and Chao Sun presented the clinical information of the patient and performed literature review. Jie Zheng, Xiaowei Xu, Xiaodan Yan and Fang Zhang performed the bioinformatics analyses. All authors provided their feedbacks on final manuscript.

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Tables

TABLE 1: 12 patients with CS confirmed by gene examinations in China

References	Sex	Age	Variations	DD	MC	TFG	TO	OSB	JH	HM and/or RD	IN
Yin L et al. [20]	male	2 years	c.5086C>T c.6940+1G>T	+	+	-	-	+	+-	-	+
Zhang F et al.[43]	male	1 year	c.8868-1G>A c.11624-11625del	+	+	+	-	+	+	-	+
Zhao S et al.[18]	male	8 years	c.3666+1G>T	+	+	+	-	+	+	+	+
	female	5 years	c.9844A>T	+	+	+	-	+	+	-	-
Yang C et al.[21]	male	2 years	c.5086C>T c.6940+1G>T	+	+	+-	-	+	+	-	+
	male	5 years	c.3203C>T c.8016+7G>C	+	-	-	-	-	-	-	-
	male	3 years	c.2199C>A c.553T>C	+	+	+-	-	+	+-	-	-
	male	3 years	c.6940+1G>T c.9852-9855del	+	+	+-	-	+	+-	-	-
Liao X et al.[44]	male	4 years	c.9259-1G↔C c.11104-11105de1	+	+	-	-	+	+	-	+
	male	1 year	c.9259-1G↔C c.11104-11105de1	+	+	-	-	+	-	-	+
Zhou J et al.[22]	male	1 year	c.6940+1G>T c.8531delG	+	+	+-	-	+	+-	-	+
This case	female	65 days	c.6940+1G>T c.919-2A>G	+	-	+-	-	-	+-	-	+

+: Typical symptom, +-: Atypical symptom, -: No symptom

DD: Developmental Delay

MC: Microcephaly

TFG: Typical Facial Gestalt

TO: Trunk Obesity

OS: Overly Sociable Behavior

JH: Joint Hypermobility

HM: High Myopia

RD: Retinal Dystrophy

IN: Intermittent Neutropenia

Figures

Figure 1

Pedigree: VPS13B and SLC26A4 variations in a Chinese family. The newborn was multiple genetic homozygous variants of SLC26A4 and VPS13B, the parents were heterozygous carriers of both pathogenic genes.

Figure 2

Chromatograms of VPS13B and SLC26A4 variations. Sanger sequencing showed that the patient was homozygous c.6940+1G>T variation of VPS13B gene and homozygous c.919-2A>G variation of SLC26A4 gene, the parents of the patient were heterozygous carriers of both pathogenic genes.

Supplementary Files

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- [CAREchecklistEnglish2013.docx](#)