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CASE REPORT

Diagnostic difficulties in a patient with precocious puberty and short stature observed for Kabuki syndrome

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ABSTRACT

Kabuki syndrome (KS) is a rare dysmorphic syndrome characterized by multiple congenital anomalies and developmental disorders. The presented patient, who was born with weight and length too small for gestational age, was found to have multiple co-occurring disorders, including endocrinopathy – low growth and true (central, gonadotropin-releasing hormone-dependent) precocious puberty. In order to inhibit premature puberty and improve the prognosis of final height, treatment with triptorelin was initiated at the age of eight years and continued for a further 5 years. Next-generation sequencing was performed, which revealed a variant of uncertain clinical significance, which made it impossible to unequivocally diagnose KS. In this article, we describe the long process of seeking a diagnosis for rare genetic diseases.

KEY WORDS:

Kabuki syndrome, phenotype, precocious puberty, growth deficiency.

INTRODUCTION

Kabuki syndrome (KS) is a rare genetic syndrome characterized by multiple congenital anomalies and developmental disorders. Kabuki syndrome occurs worldwide with a similar frequency, estimated at 1 in 32,000 live births [1, 2]. The disorder is primarily caused by heterozygous pathogenic variants in one of two chromatin-modifying genes: *KMT2D*, located on chromosome 12 (associated with KS type 1), or the X-linked gene *KDM6A* (associated with KS type 2). In approximately 30% of patients clinically diagnosed with KS, the genetic basis of the disease remains unknown [1, 3, 4]. In 2019, international consensus diagnostic criteria for KS were established. KS diagnosis is based on phenotypic and laboratory examinations, as well as genetic analysis [1]. Typical clinical findings of KS include facial abnormalities, such as long palpebral fissures with an everted lateral part of the lower eyelid, arched eyebrows, short columella, and depressed nasal tip, as well as large, protruding, or cupped ears. Other symptoms include skeletal anomalies such as hemivertebrae, mild to moderate intellectual disability, and persistent fetal fingertip pads. Additionally, congenital heart defects, cleft lip and/or palate, gastrointestinal anomalies, urogenital anomalies, seizures, and increased susceptibility to infections and autoimmune diseases are commonly observed. KS is also associated with many endocrinopathies, including precocious puberty, short stature, diabetes insipidus, thyroid dysfunction, and obesity [5, 6]. Due to possible changes in phenotype and the delayed appearance of characteristic

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features of the syndrome and dysmorphic traits, patients should undergo long-term observation [7]. Here we present the case of a patient with features of KS, in the context of current diagnostic and therapeutic recommendations.

CASE PRESENTATION

We present the case of a 14-year-old Caucasian boy, born *via* cesarean section at 39 weeks of gestation. This was his mother's second pregnancy, and he weighed 2600 g (SD [standard deviation] = −2.43, small for gestational age [SGA]) [8], measured 50 cm in length, and had a head circumference of 34.5 cm. Prenatal examinations in the 5th month of pregnancy revealed fetal hydrocephalus, with no other anomalies detected. The child's condition at birth was assessed as good, with Apgar scores of 8 at the 1st minute and 10 at the 5th minute. There was no history of consanguineous marriage in the family, but there were reports of nicotine use by both parents. No abnormalities were found in the boy's older brother, except for diagnosed Asperger's syndrome. After birth, the child was admitted to the neonatal pathology ward due to suspected multiple congenital abnormalities. According to the medical file, the physical examination revealed numerous dysmorphic features, including long palpebral fissures with lateral downslanting, arched eyebrows, large protruding ears, preauricular tags on the right side, partial cleft palate, persistent fetal finger and toe pads, and skeletal abnormalities of the cervical and thoracic spine. During hospitalization, an interventricular septal defect, horseshoe kidney, grade IV vesicoureteral reflux, undescended testis, and hypospadias were also diagnosed. The patient underwent numerous hospitalizations due to recurrent episodes of fever, pyelonephritis, acute appendicitis, sepsis, and Meckel's diverticulum excision surgery. Verbal communication with the child was difficult due to speech impairment and tachylalia. Neurological examination revealed no abnormalities. A psychological assessment repeated at the age of 12 indicated a mild level of intellectual disability. The patient's parents reported periodic episodes of irritability, excessive psychomotor agitation, and attention disorders.

The boy has been under constant care of the pediatric endocrinology department since the age of 8 due to diagnosed persistent growth retardation since early childhood. Gonadotropin-releasing hormone (GnRH)-dependent precocious puberty was diagnosed in the patient at the age of eight (Tanner stage: P1, G2, testicular volume – 6 ml). At the time of diagnosis, bone age assessed in March 2018 was 5 years and 6 months, indicating hard-to-explain delay. A repeat assessment 3 months later showed progression to 6 years. Additionally, the result of the triptorelin stimulation test supported the diagnosis: the luteinizing hormone level was 2.3 mIU/ml at baseline, 27.6 mIU/ml at 90 minutes, and 36.5 mIU/ml at 120 minutes after administration of the drug.

The calculation of mid-parental height (MPH) based on the father's height (160 cm) and the mother's height (155 cm) resulted in an MPH value of 164 cm. Considering the overall clinical picture, treatment with triptorelin was initiated and continued for the next 5 years. Hormonal tests conducted during treatment with triptorelin showed no deviations from norms – normal circadian rhythm of cortisol secretion, gonadotropin and testosterone concentrations were appropriate for gender and age. In the stimulation test with clonidine, the maximal growth hormone (GH) release was 18.6 ng/ml, ruling out its deficiency. Further tests did not confirm any thyroid or adrenal dysfunction. Magnetic resonance imaging of the hypothalamic-pituitary region revealed underdevelopment of the corpus callosum, blocked cerebral aqueduct and congenital bony block at C2–C4. Physical examination revealed numerous pigmented lesions on the back, scoliosis, hearing impairment, malocclusion, and speech defects. GH therapy according to the SGA (small-for-gestational age) protocol was initiated at the age of 13.1 years and is still ongoing, with a good growth response. In the patient, the initiation of GH therapy was relatively late due to a prolonged diagnostic process, including need for requalification for treatment under the national SGA therapy protocol after endocrinology follow-up. Figure 1 presents the correlation of the height standard deviation score (HSDS) on the percentile chart during growth hormone treatment. He regularly attends our outpatient clinic and receives rehabilitation as part of developmental support.

Due to short stature accompanied by congenital anomalies and dysmorphia, genetic causes were sought. Genetic testing was performed at the age of 11 using the next generation sequencing (NGS) panel for RASopathy. As a result, the variant c.7716G>C was identified in exon 32 of one allele of the *KMT2D* gene. Mutations within the *KMT2D* gene are identified in individuals with KS; however, as the detected variant is classified as a variant of uncertain clinical significance (VUS), and variant segregation in the parents was not performed, its classification remains uncertain (Figure 2). No pathogenic or potentially pathogenic variants were identified in the other genes.

In the light of the identified VUS in the *KMT2D* gene, diagnosis can still be confirmed when clinical features are present. Diagnosis can be established in any patient with a history of infantile hypotonia, developmental delay, and/or intellectual disability and typical dysmorphic features [3, 9]. The patient's phenotypic characteristics are presented in Figures 3–5.

DISCUSSION

As mentioned, some features of KS are met in our patient, but they are insufficient for a certain diagnosis (Table 1) [3]. In approximately 30% of patients, an underlying genetic cause cannot be identified. Diagnosis, both

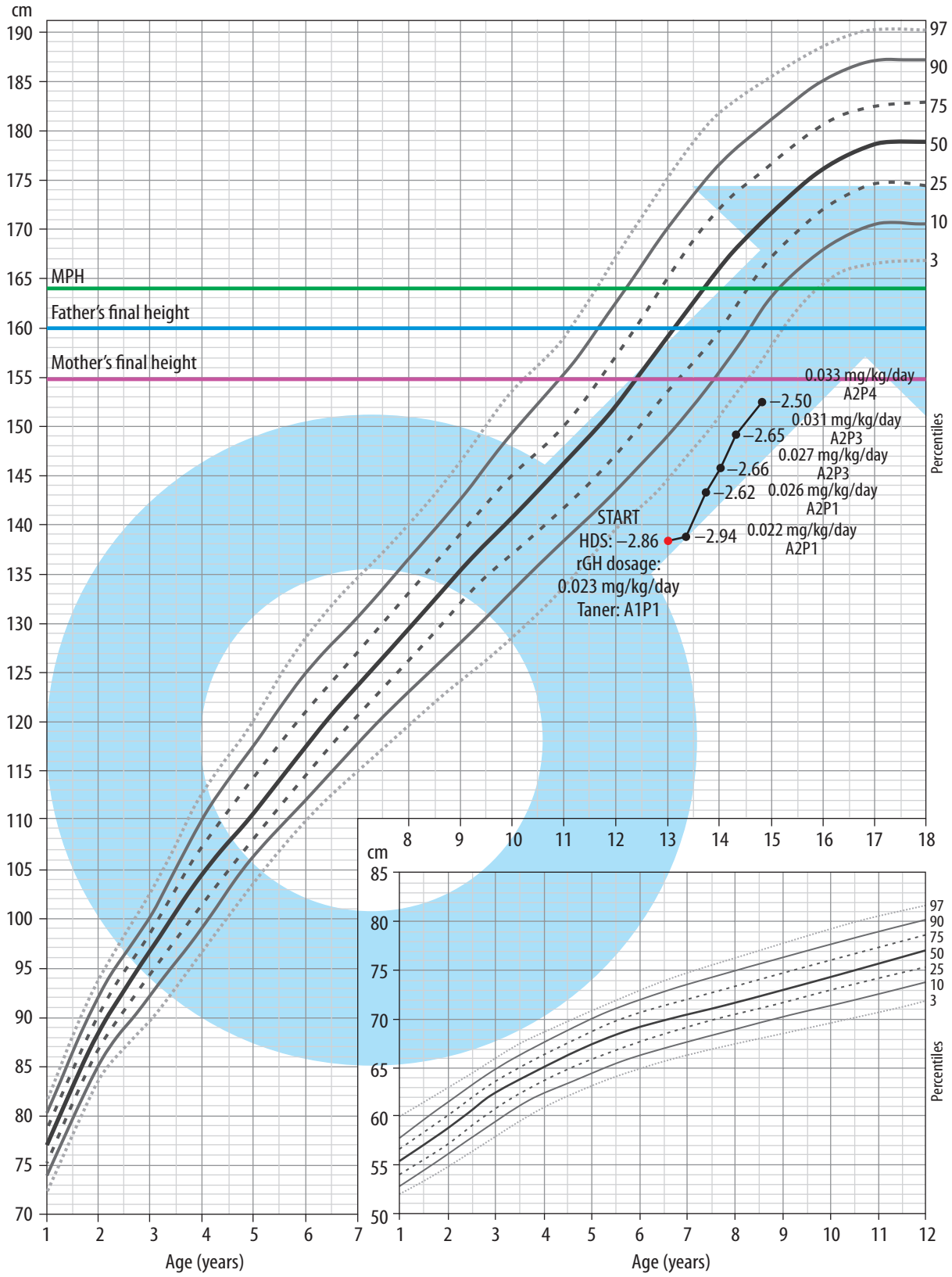

FIGURE 1. Correction of height standard deviation score during growth hormone treatment

MPH – mid-partition: eight, rGH – recombinant growth hormone humamp
Source: http://i.wp.pl/a/i/szkola2/pdf/siatki_centylowe.pdf (date of access: 27.01.2025)

clinical and molecular, can be complicated by significant clinical variability, the genetic heterogeneity of the disorder, and the presence of mosaicism [10]. It is known that phenotypic characteristics may change with age, which requires further observation. The genetic testing performed does not allow determination of the origin of the identified variant; it is unclear whether it was inherited or occurred *de novo*. What is more, in a situation

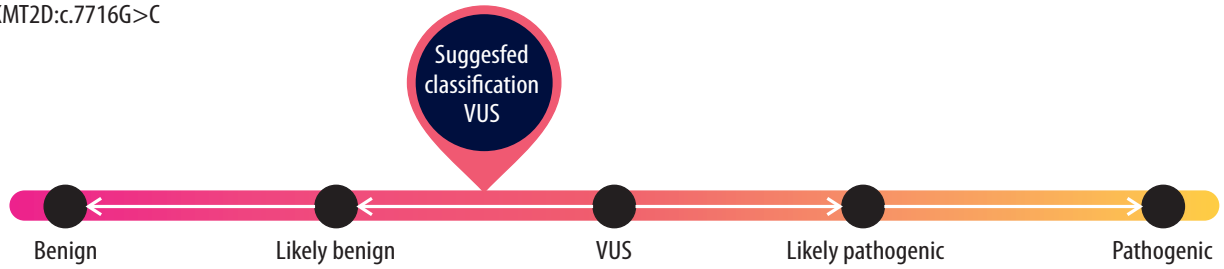

FIGURE 2. Classification of the patient's genetic variant according to Franklin by Genoox

VUS - variant of uncertain clinical significance
Source: https://franklin.genoox.com/clinical-db/variant/snp/chr12-49433837-C-G?app=acmg-classification (date of access: 27.01.2025)

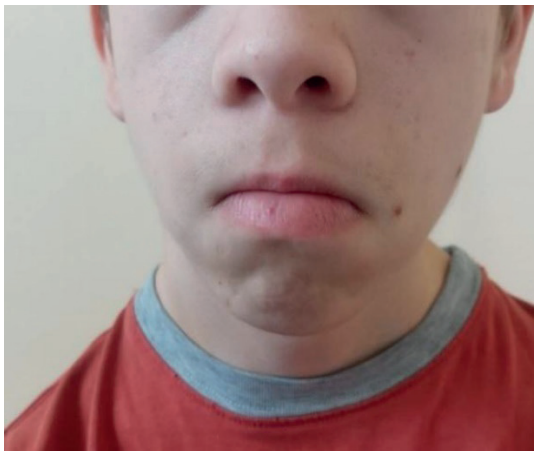

FIGURE 3. Prominent lower lip, the corners of the mouth turned downward

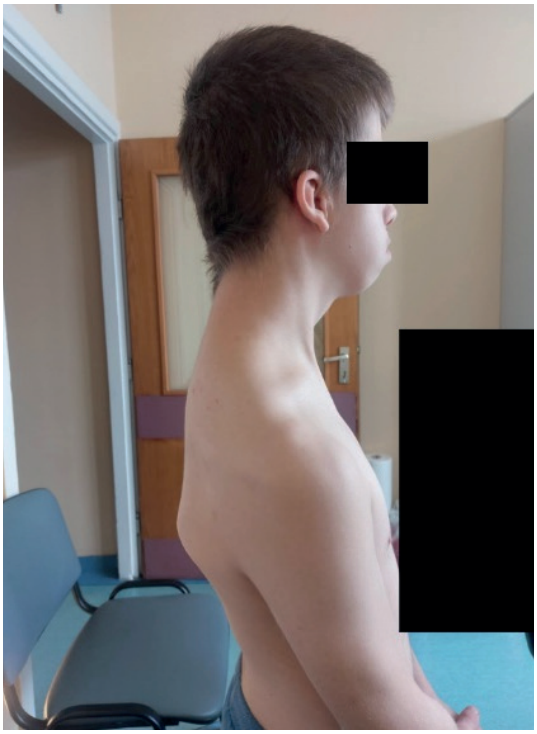

FIGURE 5. Protruding ear

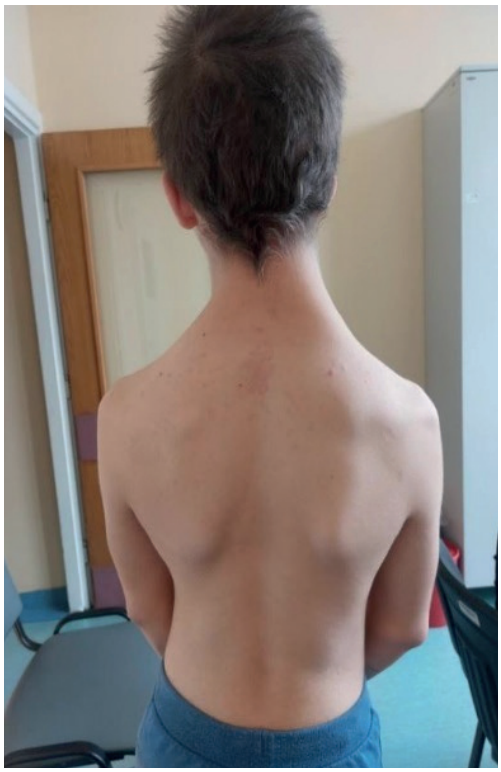

FIGURE 4. Scoliosis

where diagnosis is uncertain and VUS is detected in a molecular test, the segregation of the variant should be verified in the biological parents of the patient. The next step should include array comparative genomic hybridization (aCGH), particularly due to the presence of dysmorphic features, intrauterine growth restriction, intellectual disability, and organ anomalies. This test enables the detection of submicroscopic chromosomal abnormalities, such as copy number variations. If the aCGH results are inconclusive, the next recommended diagnostic step is whole exome sequencing, preferably performed as a trio analysis (the child and both biological parents). In addition, reanalysis of the NGS study in 12–24 months is recommended because the pathogenicity of the described VUS may change as genetics progresses and the same variant can be described in subsequent patients.

KS patients are typically born with normal growth but fail to thrive during infancy [11, 12]. In about 35–85% of KS patients, postnatal growth restriction is observed [13]. Due to the perinatal history, our patient meets the criteria for qualification for recombinant GH treatment un-

TABLE 1. Comparison of the patient's characteristics with features necessary to make a diagnosis of Kabuki syndrome

Features necessary to diagnose KS	Features in presented patient
Infantile hypotonia	+
Developmental delay	+
One or both of the following:	
A heterozygous pathogenic variant in *KMT2D* or a heterozygous or hemizygous pathogenic variant in *KDM6A*	–
Long palpebral fissures with eversion of the lateral third of the lower eyelid	–
≥ 2 of the following:	
Arched, broad eyebrows with the lateral third displaying notching or sparseness	+/–
Short columella with depressed nasal tip	–
Large, prominent, or cupped ears	–
Persistent fingertip pads	+

+ symptom present, – symptom absent

der the National Health Fund drug program for short-statured children with SGA. A study conducted by Schott *et al*. in 2017 [14] on 18 genetically verified prepubertal children with KS (9 females and 9 males), aged 3.8 to 10.1 years, showed that after one year of GH treatment, the average height improved from –2.40 to –1.69 SD. In our patient's case, the correction of HSDS after one year of treatment was much smaller (Figure 1). In the above case, the growth potential inherited from the parents may also be important, because the father was below the 3rd percentile in terms of height.

Our patient was diagnosed with GnRH-dependent precocious puberty at the age of 8, based on pubertal levels of gonadotropins in the triptorelin stimulation test and elevated testosterone concentration. Due to premature puberty, there was a high risk of additional decrease in adult height due to a disproportionate increase in skeletal age [14]. However, at the time of diagnosis, bone age was significantly delayed (5 years and 6 months) relative to calendar age (8 years), which is atypical for GnRH-dependent precocious puberty, where advanced bone age is usually a key diagnostic indicator and the basis for initiating treatment. Nevertheless, within a short period, accelerated bone maturation was observed, suggesting a rapidly progressing process. The patient presents with a difficult-to-explain disturbance in otherwise harmonious biological development, requiring further observation. Since June 2018, the patient has been treated with the GnRH analog triptorelin (Diphereline 3.75 mg intramuscularly every 28 days). Continuation of triptorelin therapy was justified by the patient's persistently low height (< 3rd percentile) and the need to preserve growth potential. According to current recommendations, GnRH analog therapy can be continued until at least one of the following criteria is met: bone age exceeds 13 years, pubertal development is appropriate for chronological age, growth velocity falls below 4 cm/year, or acceptable predicted adult height is reached [15–17]. However, the decision to discontinue therapy should be individualized, considering factors such as actual and predicted height, age, psychosocial context, stage of puberty, and family preferences. In this case, treatment was continued until the patient's bone age exceeded 13 years due to unfavorable growth prediction, at a chronological age of 13 years and four months. In KS, isolated benign forms of puberty (e.g., premature thelarche in girls) are more commonly observed than generalized precocious puberty [12]. Nevertheless, the picture of this disease may be significantly different, because cases where puberty is delayed have also been described [18].

The results of the thyroid profile were normal, but it would still be necessary to perform follow-up tests in the future due to the increased risk of thyroid diseases, especially autoimmune thyroiditis [13]. Antithyroperoxidase and antithyroglobulin antibody testing will be useful in detecting thyroid diseases earlier [19]. KS is also associated with an increased risk of other autoimmune diseases such as vitiligo, type 1 diabetes, type 3 membranous glomerulonephritis, or immune thrombocytopenic purpura [13, 20].

A balanced diet and maintaining a healthy weight are recommended, because infants may experience failure to thrive, while adolescents and adults may develop obesity [13]. Despite the correct result of the oral glucose tolerance test, regular glycemic control should be recommended, because the risk of developing type 2 diabetes in early adulthood is estimated to be approximately 20% [13, 20]. In the case of the youngest patients with KS, particular attention should also be paid to the occurrence of hypoglycemia due to hyperinsulinemia, because if it is untreated it can lead to developmental delay and permanent neurologic damage [21]. About 1% of neonates with hyperinsulinism have a diagnosis of KS [22]. In the case of our patient, insulin and glucose levels were within normal ranges.

There is no therapy to prevent multisystem and progressive organ involvement in KS. The care of pa-

tients with KS emphasizes the importance of its multidisciplinary nature from an early stage of development. Life expectancy usually remains unchanged, and daily functioning may depend on the severity of symptoms, including the degree of intellectual disability and behavioral disorders. Sleep problems are also common among patients with KS; they strongly correlate with anxiety and can exacerbate behavioral disorders, negatively affecting the quality of life of patients and their caregivers [23]. Intensive rehabilitation therapies and ongoing psychological care are needed to alleviate developmental problems.

CONCLUSIONS

Despite the lack of a certain genetic diagnosis, it is important to treat diseases that we can recognize, such as short stature, premature puberty, and scoliosis. Nevertheless, it is worth being vigilant and observing the patient for certain symptoms if we suspect a specific genetic disease.

DISCLOSURES

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4. Conflicts of interest: None.

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