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The significance of follow-up in patients with dysmorphic features: a case from clinical practice

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ABSTRACT

Background. Kabuki syndrome is a rare disorder, that is characterized by typical facial dysmorphism, hypotonia, delay in intellectual and motor development.

Case report. We present a case of a girl in whom polycystic left kidney was prenatally established. Born prematurely in 37 weeks by C section due to oligohydramnios. After birth, atresia of the anus with fistula, cysts in the left and reduced dimensions of the right kidney, were further established.
A normal female karyotype was found and targeted sequencing analysis was conducted on a panel of 81 genes associated with renal abnormalities – no pathogenic variants were detected. The child was then followed up by its general practitioner. At the age of 2 years, she was again referred for genetic counseling, which revealed the following dysmorphic signs – long eye palpebral fissuras with ectropion of the lower eyelid, sparsed lateral eyebrows, depression of the nasal bridge, brachydactyly and others characteristic of Kabuki's syndrome. The conducted molecular genetic analysis confirmed the clinical diagnosis – a likely pathogenic variant in the KMT2D gene was established.

Conclusions. Certain pathognomonic facial may not present at birth and only appear after a few years. Therefore, monitoring of the evolution of dysmorphic traits is required.

Keywords: Kabuki syndrome, KMT2D, dysmorphic features, genetic counseling

Abbreviations

Cm – centimetres	IQ – intellectual quotient
Gr – grams	KS – Kabuki syndrome

INTRODUCTION

The detection of a certain genetic disorder depends both on the physical examination and the molecular-genetic analysis. Approximately 30–40% of these conditions are associated with specific dysmorphic features, and some of them may be highly indicative of a specific disorder [1]. However, the typical dysmorphic traits may not be present at birth and develop later in life, which makes it difficult to diagnose a genetic disorder right away from the first patient's visit.

Therefore, it is not surprising that the average time for diagnosing a patient with a rare disorder is around 6 years from the first symptoms, and in the meantime, the patient would receive several wrong diagnoses [2].

Nevertheless, an early diagnosis is crucial since it makes it possible to start screening for the underlying condition's related issues, such as cardiovascular or malignant ones [3].

Kabuki syndrome (KS) is a rare disorder, which was first reported in Japan in 1980s [4]. It was named like this because of the distinctive facial features that mimic the makeup of performers in Japanese Kabuki theater [4]. It is caused by pathogenic variants in the genes KMT2D or KDM6A and its

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prevalence is around 1 in 32 000 [5]. The typical dysmorphic features of KS are long palpebral fissures with eversion of the lateral third of the lower eyelid and two or more of the following: arched and broad eyebrows with the lateral third displaying notching or sparseness; short columella with depressed nasal tip; large, prominent, or cupped ears, and persistent fingertip pads [6, 7]. Additional symptoms are short stature, microcephaly, cleft palate, lip pits, hearing loss, congenital heart defects, feeding difficulties and immunological disorders [4, 7].

Despite the striking facial features, typical for KS, the diagnosis might be delayed because these features develop in the first several years of life [4].

We present a case of a patient with KS and the course of the diagnostic process.

CASE REPORT

The patient is a 2-year-old girl born from first pregnancy. A polycystic kidney and one cyst in the other kidney were noted in the 35th gestational week. The girl was born prematurely per C section in the 37th week due to oligohydramnios, weight – 3200 gr, length – 50 cm. Anal atresia with a fistula, multiple cysts in the left kidney, decreased size of the right kidney were noted after the birth of the baby. The girl was clinically diagnosed with autosomal recessive polycystic kidney disease and was referred to genetic counseling. The karyotype of the girl was normal – 46, XX. Targeted sequencing for 81 genes, associated with kidney anomalies and polycystic kidney disease was performed, but no pathogenic or likely pathogenic variants were reported. After that, the child was followed by its general practitioner.

At two years of age, the girl was again referred to genetic counseling due to the presence of dysmorphic features and intellectual disability. The girl presented with long palpebral fissures with eversion of the lower eyelid, sparce lateral eyebrows, depressed nasal bridge, anteverted nares, low set ears with overfolded helix and linear creases of the left earlobe, high-arched palate, brachydactyly, ulnar deviation of both thumbs, and persistent fingertip pads (Figure 1). The suspected diagnosis was Kabuki syndrome, based on the similarity with the cardinal features of KS.

Targeted sequencing of 1902 genes reported a likely pathogenic variant p.(Arg1709Hisfs*25) in KMT2D gene, which was associated with KS. In our case there was no family history of other affected members and the pathogenic variant occurred de novo.

The child was referred to a pediatric department, specialized in patients with rare disorders and is regularly screened for the manifestation of additional symptoms, typical for KS.

DISCUSSION

KS is a heterogeneous disorder, which involves various systems. The phenotypic features vary over time and the cardinal dysmorphism may manifest later in life, like it was in our case. That is why the patients should be reevaluated for the presence of

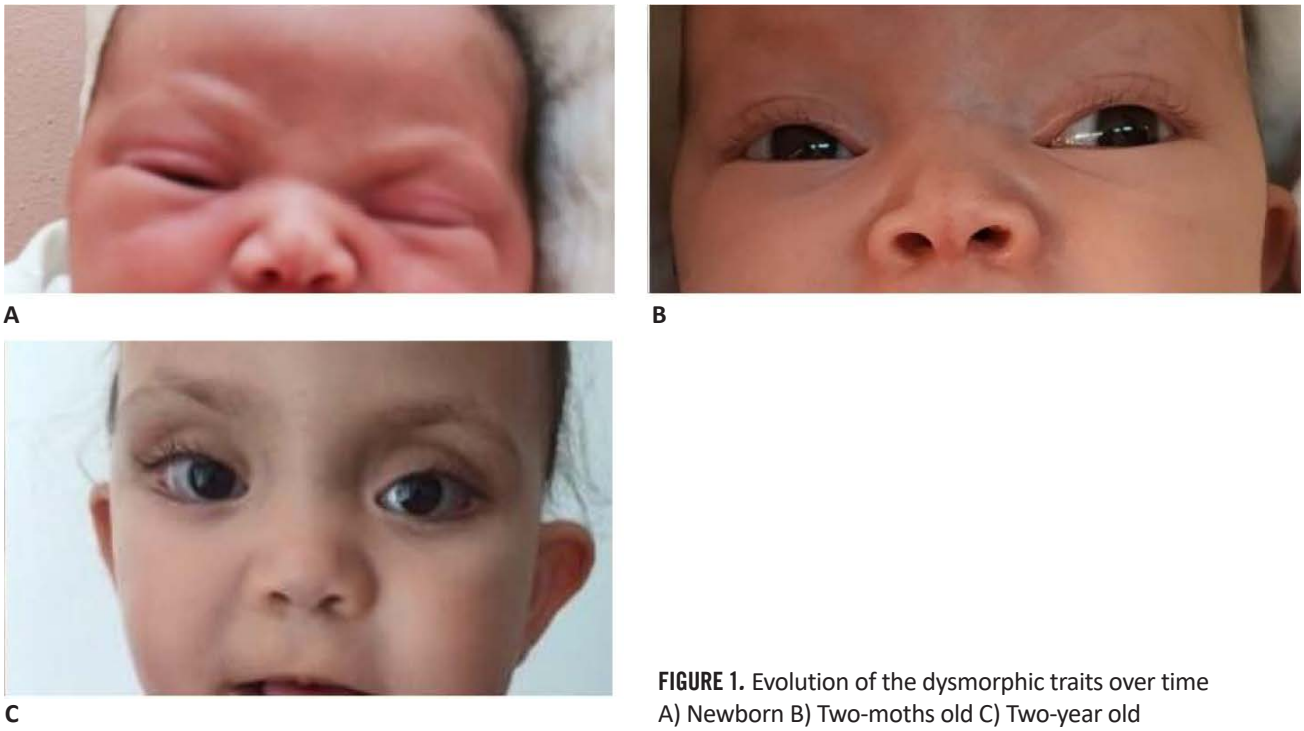

FIGURE 1. Evolution of the dysmorphic traits over time
A) Newborn B) Two-moths old C) Two-year old

specific dysmorphic features in certain time intervals with the application of the international diagnostic criteria for KS [7]. However, molecular-genetic testing is required to further prove the suspected underlying condition. The pathogenic variant in the KMT2D gene, which is also present in our case, has been reported in about 75% of Kabuki patients. In three to five percent of patients, there is a pathogenic variant found in another gene, KDM6A. Kabuki-like syndrome is a term used to describe patients who do not have pathogenic variants in either of the two genes that typically cause the condition. In total, they account for about 30% of cases of KS, suggesting that this is a very heterogenous disorder. Furthermore, the inheritance pattern may differ based on the gene involved: autosomal dominant for KMT2D variants and X-linked dominant for KDM6A variants [8, 9].

The intellectual disability is typical for this condition and the intellectual quotient (IQ) of the patients is usually below 70, but there are also cases described of mild and moderate intellectual disability [10]. Infantile hypotonia and epilepsy are also reported in patients with Kabuki syndrome [7, 10]. KS patients with pathogenic truncating mutations in the first half of the gene or whole-gene deletions of KMT2D may be more severely disabled intellectually. Individuals with KS caused by a whole-gene deletion of KMT2D gene or pathogenic truncating variants that occur in the first half of the gene may have more severe intellectual disability than patients with other type of pathogenic mutations [11].

A congenital heart defect affects about 80% of people with KS, the most common being atrial septal defect, ventricular septal defect and coarctation of aorta [4]. Patients with KS typically present with poor feeding, which may be due to severe reflux. Chronic diarrhea is also described [4]. As was the case in our instance, anorectal anomalies such as atresia of the anus are possible. Involvement of the kidneys is typical for KS, however, cysts are not a typical finding (described in our case). More than 40% of afflicted people with KS have present with hydronephrosis, renal dysplasia, and horseshoe kidney [4].

Endocrine issues include hypothyroidism, short stature with unknown etiology, obesity, cryptorchidism in boys are described [10, 12]. KS is associated with immune dysfunction. This could be explained by the fact that the responsible genes KMT2D and KDM6A participate in B-lymphocyte differentiation. Hypogammaglobulinemia is a typical finding and patients with KS may present later with common variable immune deficiency. There is also an increased risk of autoimmune disorders such hemolytic anemia, vitiligo, and immune thrombocytopenia [4,10]. KS may also predispose to malignant diseases and the patients should be regularly screened for such complications [4].

Over one-third of the affected individuals have ocular abnormalities, such as blue sclerae, strabismus, nystagmus, nocturnal lagophthalmos and dry eye, refractive error, and coloboma [4]. Hearing loss affects up to 50% of affected individuals, and it may be linked to chronic otitis media [4]. Numerous dental anomalies are also described in more than 60% of KS patients, most frequently hypodontia, widely spaced teeth, irregularly formed teeth, missing lateral, upper, and lower incisors, and malocclusion [4].

Differential diagnosis of Kabuki syndrome involves distinguishing it from other conditions with some overlapping features such as CHARGE syndrome, 22q11.2 deletion syndrome, IRF6-related disorders, Branchiootorenal syndrome, Hypermobile Ehlers-Danlos syndrome, Larsen syndrome,

Hardikar syndrome. However, Kabuki syndrome is characterized by distinct facial features, which could help identify this diagnosis [6,7].

Regular evaluations are required for cardiac, endocrinologic, immunologic, renal, and other problems following the initial diagnosis of Kabuki syndrome. Hearing and vision testing should be perfomed, as well [6,7].

CONCLUSION

Some of the dysmorphic syndromes are characterized by typical facial features, which are pathognomonic. However, it is possible that they are not present at birth, but develop after a few years. This requires sustainable monitoring of undiagnosed patients and, if necessary, reanalysis of the clinical diagnosis.

Thorough follow-up of phenotypic traits and their documentation are key in the evaluation of patients with rare dysmorphic traits.

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