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Case report

Growth hormone deficiency and hypobetalipoproteinemia in a patient with Kabuki syndrome: A case report

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Abstract. Kabuki syndrome (KS) is a rare condition characterized by facial features (eversion of the lower lateral eyelid, arched eyebrows with the lateral one-third dispersed or sparse, depressed nasal tip, and prominent ears), skeletal anomalies, dermatoglyphic abnormalities, short stature, and mental retardation. We described a case of KS clinically diagnosed at 7 years of life based on typical facial features, neurodevelopmental delay, and growth failure; the diagnosis was genetically confirmed later on in adolescence. Endocrinology investigations performed for short stature, revealed growth hormone deficiency (GHD). The treatment with rhGH from 8 years of life, initially improved height velocity and stature, however the catch-up growth was only transient and final height was disappointing. The patient investigated also for the presence of altered lipid profile showed hypobetalipoproteinemia (HBL). At the best of our knowledge, this is the first case of KS with both GHD and genetic hypobetalipoproteinemia in the literature. This case reinforces the awareness for the necessity to take in account that in many cases syndromes can combine with different unexpected genetic conditions. (www.actabiomedica.it)

Key words: Kabuki syndrome, growth hormone, growth hormone deficiency, hypobetalipoproteinemia

Introduction

KS is a rare condition (1/32000 of live births), resulting in distinctive facial features, cardiac anomalies, skeletal abnormalities, immunological defects, intellectual disability with well-known clinical heterogeneity (1). To facilitate the clinical diagnosis a score has been elaborated (2,3). The genetic basis of KS is linked to the KMT2D gene (autosomal-dominant KS type 1 - KS1), and KDM6A gene mutations (X-linked-dominant KS type 2 - KS2), therein accounting for 75% and 6% of patients, respectively (4,5). One of the hallmarks of KS is short stature which mainly arises from postnatal growth retardation (4) even if intrauterine growth retardations observed in 19% to 65% of KS subjects (6). The cause of this growth retardation is unknown, but GHD is reported in 2% to 22% of KS patients (7). We herein report a case of a patient with Kabuki syndrome associated with GHD and genetic HBL.

Case Report

XY was born at 40 weeks of gestation through spontaneous delivery (Apgar score 7 and 8 at 1st and 5th minutes, respectively; birth weight 3170 gr, 17°; length 51.5 cm, 64°. head circumference 33 cm, 5°). In the first days of life the patient suffered respiratory distress due to right anterior lacunar diaphragmatic hernia. Rachis's radiography revealed hemispondyle of the 10th dorsal vertebrae and synostosis of the head

of the 10th and 11th ribs on the right. Cardiac ultrasound showed the presence of mild aortic valve stenosis, bicuspid aortic valve, and moderate aortic coarctation. Abdominal ultrasound showed double renal district with non-functioning upper part of kidneys. The patient underwent to several surgical procedures: correction of right anterior lacunar diaphragmatic hernia, upper heminephroureterectomy, correction with percutaneous angioplasty of the aortic coarctation.

In the first 2 years of life several genetic investigations were carried out: normal standard karyotype (46, XY), negative search for the mutation responsible for the fragile X, normal telomere FISH, normal CGH-Array. The patient was referred to our pediatric endocrinology clinic at the age of 7.56 for short stature (height (H) cm 105.5, SDS -3,25). He presented facial dysmorphisms: a frontal V-shaped attachment, wide arched eyebrows, short columella with depressed nasal tip, hypertelorism, long eyelid fissures with eversion of the lateral third of the lower eyelid, large ears with thin helix and low set; thin upper and full lower lip; single transverse palmar crease and persistent of fingertip pads (Kabuki Score = 8). Tanner's stages were prepubertal PH1, B1, A0, and testes (1 ml) hypoplasic in scrotum. Complete blood counts, immunoglobulins, liver, kidney, resulted in normal range as well as baseline endocrinology values [TSH 2.56 μIU/ml (n.v. 0.35 – 4.94), cortisol 12.9 μgr/dL (n.v. 6.7 – 22.6)] except for IGF-1 values slightly below normal range [38.5 ng/mL (49 – 504)]. Celiac disease was also ruled out. The lipid profile revealed hypocholesterolemia (total cholesterol 74 mg/dL; LDL cholesterol 36 mg/dL; HDL cholesterol 31 mg/dL; triglycerides 34 mg/dL; apoA1 129 mg/dL; apoB 37 mg/dL) confirmed at subsequent controls. Genetic analysis for primitive hypobetalipoproteinemia was performed. Sequencing of the APOB gene encoding the apolipoprotein B protein revealed the presence of a sequence variant in the heterozygous state in exon 26 (c.5896 C> G, p.His1923Arg). The sequencing of the MTTP gene encoding the microsomal triglyceride transfer protein revealed the presence of a sequence variant in the heterozygous state of exon 2 (c.136 C> G, p.Arg46Gly). Therefore, we were able to diagnose primary hypobetalipoproteinemia. We monitored the lipid profile yearly and performed abdominal ultrasound which showed the presence of liver with modestly increased size and steatosis. Therefore, we advised to perform a diet low in long-chain fatty acids and instrumental monitoring over time.

In relation to the phenotypic characteristics of the patient we requested exome sequencing; a likely pathogenic variant was detected in KMT2D gene, confirming the clinical suspicion of KS. The heterozygous variant c.11584C>T on KMT2D creates a stop codon at codon 3862 in exon 39. Arginine stimulation test (0,5 gr/kg) revealed impaired growth hormone secretion (GH peak at 60 min: 9.2 ng/mL) which was confirmed by an L-Dopa test (GH peak 3.6 ng/mL). Neuroradiological MRI showed features compatible with isolated type 1 Arnold Chiari malformation. Bone age was retarded and corresponded to a male of 6 years and 9 months. In consideration of the clinical, instrumental and laboratory data, we started treatment with rhGH (0.0346 mg/kg/day). After the first year of therapy, the patient gained 0.57 SDS in height (SDS -2.68, perc. 0.4 °) with an improvement in growth rate 8.2 cm/year. The patient continued the treatment, but the dose/kg/week was progressively reduced (from 0.242 to 0.125) due to the increase of IGF-1 t and of weight (from BMI of 23 kg/m2 to BMI 28.5 kg/m2). The initial positive effect of GH treatment progressively decreased until discontinuation of the GH therapy, at the chronological age of 17.82 years (Table 1). Final height SDS resulted not significantly different from the beginning of the treatment.

Discussion

KS, for the first time described in Japan in 1981, is characterized by five cardinal manifestations. They include postnatal growth restriction, dysmorphic facial features (long palpebral fissures with eversion of the lateral third of the lower eyelid; arched and broad eyebrows with the lateral third displaying notching or sparseness; large, prominent or cupped ears; and short columella with depressed nasal tip), skeletal anomalies, dermatoglyphic abnormalities and intellectual disability.

The facial features of KS change over time as our patient clearly showed (Figure 1).

Table 1. Auxological, laboratory parameters and bone age study and body proportions during rhGH therapy.

	Age (year)	Height cm (SDS)	BMI mg/kg2 (SDS)	Growth velocity (cm/year)	rhGH therapy (mg/kg/week)	IGF-1 (ng/mL)	Bone age (Greulich and Pyle tables)
Time 0 (start of therapy)	7.56	105.5 (-3.25)	23 (1.89)	3.9	0.242	81.7	6 years and 6 months
After 1 year of therapy	8.53	113.4 (-2.68)	23.3 (1.71)	8.2	0.210	250	8 years
After 2 years of therapy	9.49	120 cm (SDS-2.34)	22.6 (1.38)	7.1	0.215	388	8 years and 6 months
After 3 years of therapy	10.49	126.2 cm (SDS-2.09)	25.1 (1.64)	7.0	0.175	327	10 years
After 4 years of therapy	11.45	130.4 cm (SDS-2.15)	28.5 (2.02)	4.4	0.144	290	11 years
After 5 years of therapy	12.47	134.8 cm (SDS-2.22)	30.8 (2.26)	4.3	0.150	351,2	/
After 6 years of therapy	13.56	138.7 cm (SDS-2.67)	32 (2.40)	4.3	0.136	378,1	13 years and 6 months
After 7 years of therapy	14.60	142.9 cm (SDS-3.50)	31.4 (2.32)	4.0	0.130	406,8	14 years
After 8 years of therapy	15.63	147.5 cm (SDS-3.63)	31.3 (2.27)	4.5	0.123	480	14 years and 6 months
After 9 years of therapy	16.67	151.2 cm (SDS-3.42)	31.0 (2.18)	3.6	0.118	588.4	15 years and 6 months
At the end of therapy	17.82	153.1 cm (SDS-3.24)	28.5 (1.73)	1.7	0.125	597.6	17 years

	At first visit ***(5.21 years)***	**Time 0 - start of therapy** ***(7.56 years)***	**After 5 years of therapy** ***(12.47 years)***	**At the end of therapy** ***(17.82 years)***
SPAN/H	1.03	1.03	1.06	1.04
HS/H	0.56	0.56	0.53	0.52

Most of subjects diagnosed with KS have a heterozygous pathogenic variant in lysine-specific methyltransferase 2D gene (KMT2D) identified in 2010, located on chromosome 12q12 (KS1). Later, in 2012, another causative variant in lysine-specific demethylase 6A (KDM6A) gene, located on chromosome Xp11.23, were identified (KS2) (7). The clinical consequences of KMT2D/KDM6A gene mutations seem to have a global effect on development and growth, both craniofacial, cardiac, neural and musculoskeletal tissue (8). The role of KTM2D in cancer has been described in a lot of studies, especially, gene mutations are common in gastric cancer, lymphoma and medulloblastoma (9). KTM2D also plays a critical role in regulating HOX genes; in particular HOXC6 plays a fundamental role in breast carcinoma development (10). A causative association of the KS syndrome and malignancy should be taken into consideration. White showed in 27 patients with Kabuki syndrome more than 50% of patients are overweight or obese during childhood or adolescence with reported normal caloric intake. Different studies described the presence of obesity in KS, but the exact cause is still unknown (10). The estrogen receptor (ER) is associated with obesity, playing a role in adipogenesis, adipose deposition, lipogenesis, lipolysis, and adipocyte proliferation (10).

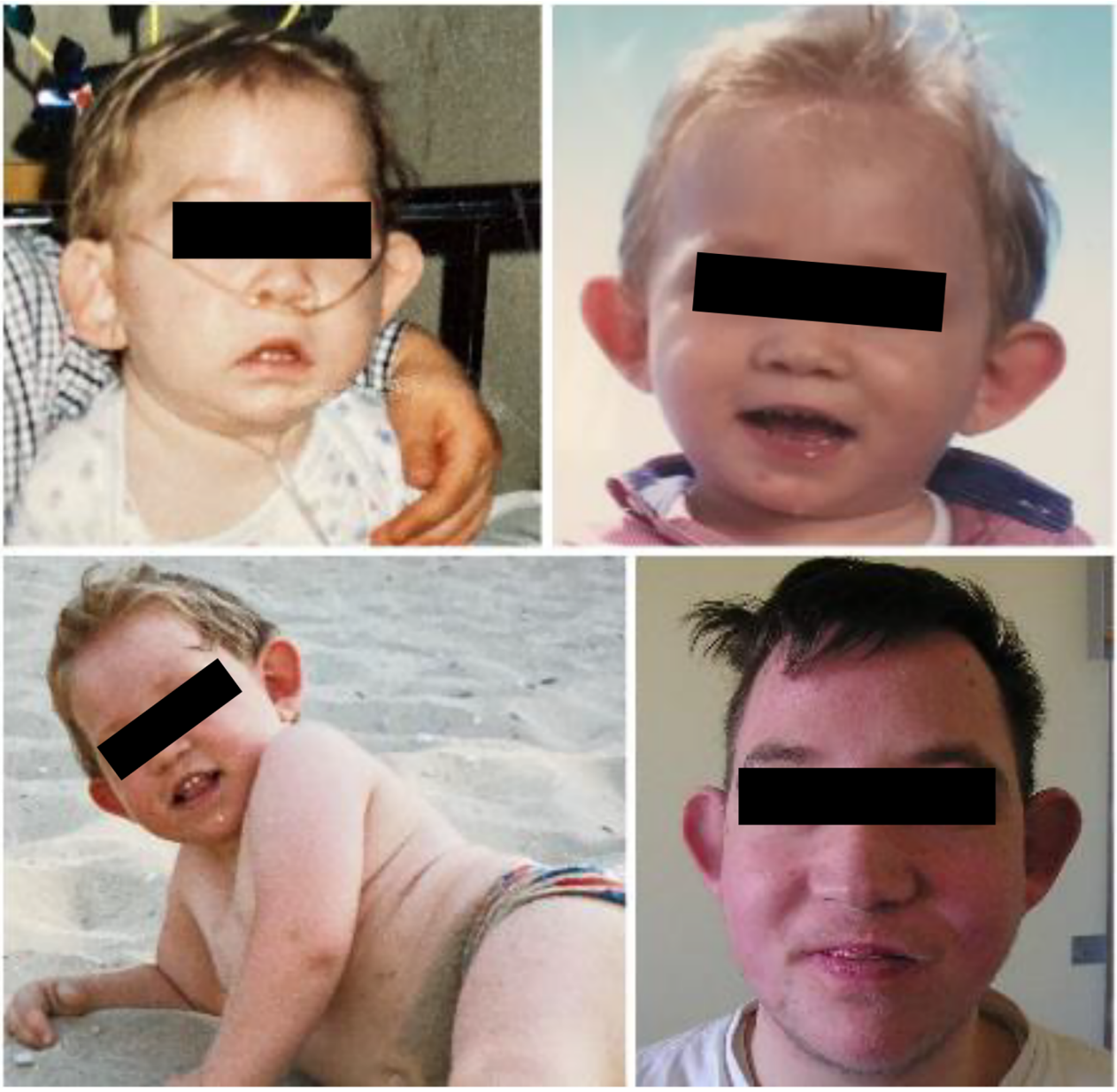

Figure 1. The patient aged about 18 months (top left), 3 years (top right), 5 years (lower left) and 19 years (lower right) respectively.

Because KMT2D (MLL2) is involved in ER-dependent gene regulation, it is feasible that a mutation in KMT2D may be linked to obesity (10). KS patients have a postnatal growth retardation and a decrease of the growth spurt6. Since KS present many features like Turner syndrome and Prader-Willi syndrome, different studies hypothesized that KS children would experience the same positive growth effects of rhGH treatment as these children (11). In 21 KS children treated with GH therapy achieved an increase in height SDS from −3.41 to −2.58 SDS after 1 year of treatment (12). However, these are pre-2010 data, before the genetic basis for KS was known and thus not a proven syndrome in all cases. Subsequently in 2017, Schott et al., instead evaluated the growth response after 1 year of rhGH therapy in children whit

KS genetically validated (12). The results of this study indicate a normalization of height during childhood in 72% of the KS patients, with a mean increase in height SDS from −2.40 to −1.69 for the entire study group.4 Recently, a study reported 18 pre-adolescent children with KS experienced catching-up growth one year after receiving recombinant human growth hormone (rhGH) treatment, but the proportion of their body did not change (4). here are currently no studies on definitive height after growth hormone therapy in a patient population with genetically determined KS. Our patient reached a positive result in the first 3 years of treatment, subsequently the positive effect of treatment vanished and SDS final height was not different from the SDS pre-treatment height. This could be attributed to low dose of GH used. On the other hand, the treatment was titrated based on IGF-1 levels taking in account the obesity of our patient. Treatment with GH reduces insulin sensitivity and elevates blood glucose. In the study of Florakis et al. (13) conducted in 90 patients on GH treatment, a significant increase in both glucose and hemoglobin A1c levels was demonstrated, these changes were evident at six months and persisted after two years of treatment. In many studies has emerged that the treatment with GH was associated with a worsening of glucose tolerance and the appearance of diabetes or carbohydrate intolerance (13). In consideration of developing obesity in patients with KS, it is useful to follow-up these patients from a nutritional team, setting up a correct diet and lifestyle. It will also be careful to evaluate the glucose and lipid metabolism in routine exams. This approach allowed us to perform the diagnosis of hypo-betalipoproteinemia. The association of hypo-betaliproteinemia in patients with KS has not been described before. Familial Hypo-betalipoproteinemia is an autosomal codominant disorder characterized by ApoB < 5th percentile and LDL-C usually between 20–50 mg/dL. The result of this decreased secretion of ApoB from the liver is an insufficient triglyceride export from the liver, which in turn leads to the development of fatty liver. Subsequently, the mild elevation of liver enzymes and fatty liver, are the main clinical manifestations of heterozygous FHBL. Therefore, early diagnosis is important so that treatment can be started including a low-fat diet, supplementation with essential fatty acids and high oral doses of fat-soluble vitamins, vitamins A and E, when necessary.

Conclusion

Our case demonstrated the short stature in patients with KS has to be investigated to ascertain the possible existence of GHD even if the result of treatment with rhGH in our case was disappointing,

More studies with a greater number of patients with genetically determined KS would be necessary to evaluate the efficacy of rhGH therapy. Finally, it should be remembered that even the diagnosis of a genetic disease such as KS does not exclude the possible association with other genetic pathologies. Therefore, a careful look at the patient is always useful in medicine, in order to highlight any conditions associated with the principal disease, which in our case has allowed us to diagnose GHD and hypo-betalipoproteinemia in a patient with KS.

Ethic Approval: In our institution case reports don't are submitted to examination of Ethical Committee.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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