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Phenotypic anomalies in Kabuki syndrome and their implications – an analysis of two cases in the light of scientific literature

Anomalie fenotypowe występujące w zespole Kabuki oraz ich implikacje – analiza dwóch przypadków w świetle literatury naukowej

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Abstract

Kabuki syndrome (KS1: OMIM 147920, KS2: OMIM 300867) is a rare disorder characterised by dysmorphic face and limbs, microcephaly, short stature, and concomitant multiorgan congenital defects. The prevalence is estimated at 1:32,000–86,000 live births. Most patients are also diagnosed with mild to moderate intellectual disability. Molecular diagnosis includes an analysis for the two most common mutations in *KMT2D* (KS1), also known as *MML2*, and *KDM6A* (KS2) genes. Children diagnosed with Kabuki syndrome require multidisciplinary care. This paper presents detailed case reports of two children diagnosed with Kabuki syndrome, who presented with different manifestations of kidney disease. One of the patients required kidney transplantation, which determines the length and quality of life.

Keywords: Kabuki syndrome, *KMT2D/MML2* genes, kidney defects, kidney transplantation

Streszczenie

Zespół Kabuki (*Kabuki syndrome* – KS1: OMIM 147920, KS2: OMIM 300867) jest rzadko występującym zespołem, charakteryzującym się dysmorfią twarzy, kończyn, małogłowiem, niskim wzrostem, a także współistniejącymi wadami wrodzonymi wielu narządów. Występuje z częstością 1 na 32 000–86 000 żywych urodzeń. U większości pacjentów diagnozuje się niepełnosprawność intelektualną od łagodnego do średniego stopnia. Diagnostyka molekularna obejmuje analizę dwóch najczęściej występujących mutacji w genach *KMT2D* (KS1) – znanym także jako *MML2* – oraz *KDM6A* (KS2). Dzieci ze zdiagnozowanym zespołem Kabuki wymagają interdyscyplinarnej opieki medycznej. W pracy przedstawiono szczegółowe opisy dwóch przypadków dzieci z rozpoznanym zespołem Kabuki, u których zaobserwowano odmienne manifestacje choroby nerek. Jednym z nich jest przypadek przeszczepu nerki w zespole Kabuki, warunkującego długość i jakość życia pacjenta.

Słowa kluczowe: zespół Kabuki, geny *KMT2D*/*MML2*, wady nerek, przeszczep nerki

INTRODUCTION

Kabuki syndrome (KS; Kabuki makeup syndrome, KMS; OMIM 147920 and OMIM 300867) is a rare, heterogeneous, multiple congenital malformation syndrome first described in 1981 by Niikawa and Kuroki[1,2]. Five major clinical criteria for KS have been distinguished: 1) facial dysmorphia with prominent eversion of the lateral part of the lower eyelid, arched eyebrows, flattened nasal tip, and prominent auricles, 2) skeletal anomalies, including scoliosis, clinodactyly, brachydactyly of the fifth digit, 3) dermatoglyphic abnormalities, such as increased fingerprint loops, 4) mild to moderate intellectual disability, and 5) postnatal growth disorders. Intellectual disability is not a constant symptom, with 8% of patients presenting no intellectual decline[3]. A variety of neurobehavioural problems are also observed, including behavioural disorders, learning difficulties and abnormalities related to sensory integration. Other common features of the clinical picture of KS include, among other things, muscular hypotonia (51–98% of KS patients), recurrent otitis media due to impaired humoral immunity with reduced IgA and IgG immunoglobulins (up to 70%), ocular abnormalities such as strabismus, ptosis or blue sclerae (38–61%), premature thelarche (41%), urinary defects (30–40%), cardiovascular abnormalities (40–50%; mainly aortic coarctation, ventricular and atrial septal defect, hypoplastic left heart syndrome, and tetralogy of Fallot)[4].

The global prevalence of KS is unknown. The number of confirmed cases depends on the geographic region and available diagnostic tools. KS has an estimated incidence of 1:32,000 (Japan) to 1:86,000 live births (Australia and New Zealand)[5,6]. Mutation in the *KMT2D* gene, which, according to the available literature, accounts for 56–78% of cases, is the most common aetiology[7–9]. KS generally arises sporadically, but cases with autosomal dominant inheritance have been described. A dominant autosomal mutation in the *KMT2D* gene (*MLL2*) is responsible for about 64% of KS cases, while a dominant mutation in the *KDM6A* gene on the X chromosome accounts for a milder and much less common phenotypic expression of KS, which accounts for about 5–8% of cases. The *KMT2D* gene (OMIM 147920), whose mutation causes Kabuki syndrome 1 (KS1), is located on chromosome 12 and encodes a specific methyltransferase. A mutation in the KDM6A gene (previously known as *UTX*, OMIM 300128) is responsible for Kabuki syndrome 2 (KS2) (OMIM 300867). The gene locus is on the X chromosome and encodes a histone demethylase, which interacts with *KMT2D*. These genes are responsible for transcription activation and chromatin stability. Both genes are postulated to mediate histone methylation modification and to have an epigenetic function in both prenatal and postnatal development. Studies in a murine model of KS with methyltransferase dysfunction (Kmt2d+/bGeo) appear promising, suggesting that the disorder can be treated with epigenetic modulation.

Previous analyses failed to provide sufficient data on urinary disorders in KS[10]. According to Cheon and Ko, urinary anomalies occur in 30–40% of KS patients. These include hydronephrosis, ectopy, and renal hypoplasia or dysplasia. Renal malformations are more common among patients with *KMT2D* mutations[4].

CASE REPORTS

We present descriptions of two clinical cases: a 3.5-year-old boy and a 6-year-old girl both diagnosed with KS. The children presented typical dimorphic facial features, including elongated eyelid crevices with lower eyelid eversion, high eyebrow arches and large dysplastic ears.

Case 1

The boy was born in 1994 from third uncomplicated pregnancy and delivery to healthy, unrelated parents. The child was born naturally at 39 weeks gestation. He had birth weight of 3,200 g, body length of 51 cm, and head circumference of 34 cm. The newborn's condition at birth was considered good; he received an Apgar score of 8 at minute 1. Medical history showed an unremarkable maternal obstetric history. Psychomotor development was significantly delayed from birth. The boy was able to sit up independently after the first year of life, and started walking at the age of 3 years. Speech was and still is dysarthric. The neurological condition was characterised by upper and lower limb hypotonia. Until the age of 2.5 years, the patient remained under outpatient care due to the presence of dysmorphic features and hypotonia, and a diagnosis of delayed psychomotor development. At the age of 2 years, the boy was observed to have bilateral renal hypodysplasia.

Physical examination revealed dysmorphic facial features: swarthy complexion, distinctive facial features resembling the makeup of Kabuki actors (a traditional Japanese theatre), as well as short stature, convergent strabismus of the right eye; other phenotypic findings in the boy are summarised in Tab. 1. Kidney function parameters were indicative of renal failure: elevated creatinine (4.4 mg/dL; eGFR 5.97 mL/min/1.73 m^2); urea 174 mg/dL. Cardiac echo showed atrial septal defect (ASD), left ventricular hypertrophy and mild mitral regurgitation. Brain magnetic resonance imaging showed advanced atrophic changes in the frontal lobes. Electromyography showed slowing of axonal conduction. The boy was also evaluated by a psychologist, who diagnosed mild mental disability. The clinical picture described raised a suspicion of KS1 (OMIM 147920). The boy required further diagnosis in the Department of Genetics. Routine cytogenetic analysis led to the diagnosis of male karyotype 46,XY,inv(9)(p11q13). Based on a scoring system proposed by Makrythanasis et al., molecular testing for *KMT2D* mutation was performed and the boy was diagnosed with KS at the age of 9 years.

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Symptoms	Boy	Girl
Facial dysmorphia	Long almond-shaped palpebral fissures	Narrow palpebral fissures, ptosis, arched eyebrows Depressed nasal tip, short philtrum, high-arched (gothic) palate
Hair	Long thick eyelashes	Thin eyelashes, alopecia
Auricles	Large and low-set	Long, prominent
Dentition	Enamel defects, decay	Normal
Head circumference	Microcephaly	Normal
Skeletal disorders	Clinodactyly of the fifth phalanx, shortening of the third phalanx, brachydactyly, scoliosis	Shortening of the fifth phalanx, valgus knees, hip dysplasia
Dermal papillae	Deep	Deep
Skin	*Café au lait* spots	Normal
Reproductive system	Bilateral cryptorchidism, hypogonadism	Normal
Neurological disorders	Waddling wide-based gait	Wide-based gait, motor stereotypes, ataxia
Immune disorders	None	IgA and IgG deficiency
Comorbidities	Iron deficiency anaemia, hypercholesterolaemia, obesity, hypertension	Recurrent otitis media

Tab. 1. Comparison of phenotypic features in the described patients

Due to renal failure, the patient underwent peritoneal dialysis for 3 years. The treatment was complicated by secondary hyperparathyroidism, venous thrombosis and osteoporosis with a femoral neck fracture in 2005. High doses of alfacalcidol (2 μg/day) were used for secondary hyperparathyroidism with rising parathormone (PTH) levels, achieving PTH normalisation as early as one week after the treatment onset.

The boy underwent kidney transplantation at the age of 5 years. The kidney was transplanted from a 35 kg 7-year-old donor. The recipient's body weight at the time of transplantation was also 35 kg. Renal structure and function were normal, and single vessels (one artery and one vein) were visualised in the renal hilus. A full human leukocyte antigen (HLA) tissue match was not achieved, with two compatible DR antigens and four incompatible A and B antigens. During the procedure, an end-to-side anastomosis of the external iliac vein and the external iliac artery was performed. Standard immunosuppression regimen (steroids, cyclosporine and mycophenolate mofetil) and standard anticoagulation (subcutaneous low-molecular-weight heparin, SC LMWH) was used. After 4 days of normal graft function, symptoms of extensive venous thrombosis involving the graft vein, the iliac vein and the inferior vena cava were observed. Due to complications, an attempt was made to revise and remove the blood clot. Ultimately, graftectomy was performed. Histopathological examination showed no acute graft rejection; signs of venous thrombosis were evident. Post-transplant laboratory workup in the child showed no hypercoagulability. The boy again required dialysis therapy. At the age of 11 years, he underwent another kidney transplantation. The procedure involved a venous anastomosis with the inferior vena cava in the subhepatic segment, where no blood clot was observed. Standard anticoagulation (LMWH) was used. Due to the mismatch of histocompatibility antigens between the donor and the recipient, 4-drug immunosuppression (daclizumab, steroids, mycophenolate mofetil, tacrolimus) was included. Immediate normal graft function was noted, with no major complications. Serum creatinine was 0.4 mg/dL.

Graft function was regularly monitored, maintaining serum creatinine in the range of 0.7–0.9 mg/dL, until the boy reached adulthood.

Case 2

The girl was born in 1996 from second pregnancy, second vaginal delivery at 35 weeks gestation, with a birth weight of 2,550 g and an Apgar score of 6/10. She had a perinatal history of congenital pneumonia. The child's parents were unrelated and had no significant family history. Delayed psychomotor development was observed: the girl was able to sit up at 1 year of age, and started walking after the age of 2 years. Single words were uttered by the child at 7–8 months of age, while perfunctory speech occurred around 2 years of age. At the age of 5 months, she developed pneumonia with secondary bacteraemia. Laboratory workup performed at that time revealed hypoglycaemia and hyperammonaemia. Since then, the patient remained under the care of the Department of Metabolic Diseases. From the age of 6 months, she was treated conservatively for congenital hip dysplasia and, due to unsatisfactory therapeutic effect, underwent a surgery at 21 months of age. The postoperative period was complicated by *Mycoplasma pneumoniae* with high acute phase markers. The patient was repeatedly hospitalised for recurrent upper and lower respiratory tract infections. A cardiac defect in the form of an accessory chorda tendinea was also observed on echocardiography. The girl was repeatedly diagnosed with otitis media and sensorineural hearing loss; she underwent bilateral tympanostomy at 5 years, followed by adenotomy.

On physical examination, there was marked facial dysmorphia with hypertelorism, strabismus, and oblique palpebral fissures. Phenotypically, facial dysmorphia characteristic of KS was present in the child (Fig. 1). The patient also

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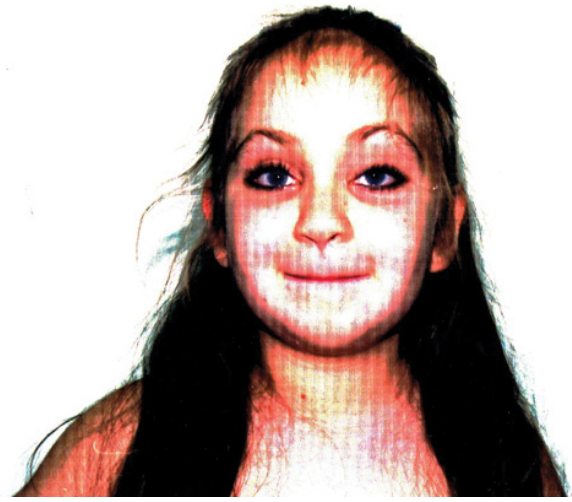

Fig. 1. KS patient's face

Fig. 2. A side view of a KS patient

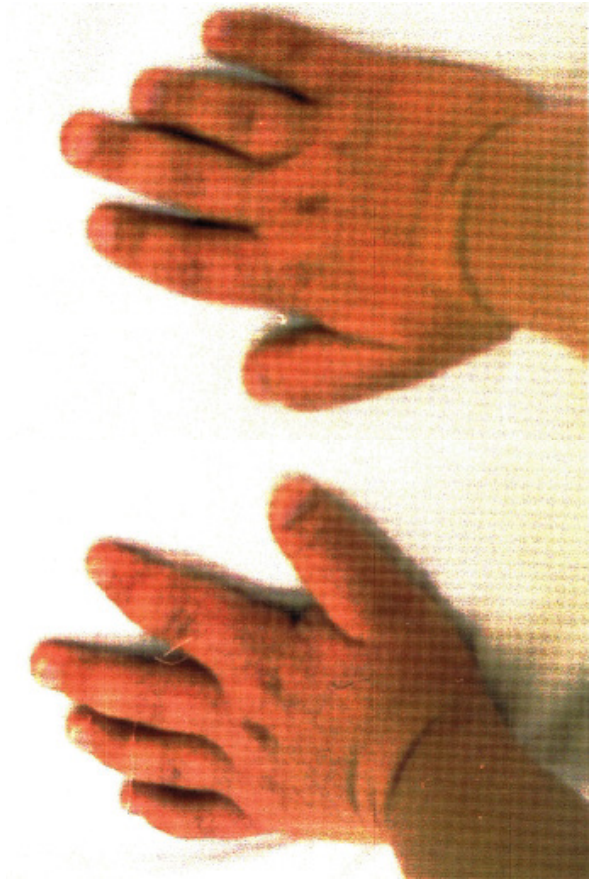

Fig. 3. Hands of a KS patient

exhibited brachydactyly of the hands and feet, barrel chest, hip deformity and short stature (91 cm – <3 percentiles) (Figs. 2, 3). Laboratory workup showed abnormal humoral immunity: low IgA antibodies (47.3 mg/dL) and high IgM antibodies (313.2 mg/dL). Ultrasound of the urinary tract showed a small ectopic right kidney (35 mm), located at the upper edge of the left kidney (80 mm). Micturition cystography showed no features of vesicoureteral reflux. On renal scintigraphy, the contribution of the hypoplastic right kidney to total function was 20% (left – 80%); loss of active parenchyma of the right kidney was observed.

The child met the clinical criteria for the diagnosis of KS. The diagnosis was confirmed in the Department of Genetics. At the age of 8 years, according to the opinion of a psychologists, the girl achieved general intellectual performance with an intelligence level below the lower limit of the average age range and was qualified for school education. Until coming of age, the patient remained under the care of the Department of Nephrology. Renal parameters evaluated at follow-up were normal.

DISCUSSION

Specific data on the prevalence of KS in the Polish population are missing. The cases presented above are characterised by a heterogeneous clinical course of KS (Tab. 2).

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Phenotypic features	Boy	Girl	Typical KB patient – incidence rate [%][11,12,20]
Facial dysmorphia:			
• long palpebral fissures	+	+	100
• eversion of the lateral third of the lower eyelid	+	+	100
• hypertelorism	+	+	100
• long, thick eyelashes	+	+	100
• arched eyebrows	+	+	25
• thinning of the eyebrows in the outer segment of the eyebrow arch	+	+	31
• epicanthic folds	+	+	50
• large protruding auricles	–	+	80–84
• thick earlobes	+	+	85
• gothic palate	+	+	68
• cleft lip and palate	–	–	33
• dental dysplasia	–	–	80–100
Postnatal weight deficiency	–	–	83
Delayed growth	+	+	+
Obesity	+	+	–
Urinary tract defects	+	+	+
Heart defects (ASD, VSD, ToF, CoA)	+	–	31–58
Renal failure	+	–	–
Hypertension	+	–	–
Intellectual disability	+	+	+
Microcephaly	+	-	+
Hypotony	+	–	50–80
Impaired hearing	–	+	+
Cryptorchidism	+	–	+
Phimosis	+	–	+
Hypogonadism	+	–	+
Neurological manifestations:	+	+	80
• gait disorders	+	+	10–82
• epilepsy	–	–	10–82
• microcephaly	+	–	10
• dysarthria	+	+	40–50
• brain structure disorders	+	–	rarely
• strabismus	+	+	19
• ptosis	–	–	22–50
• hearing impairment	–	+	>50
Abnormal dermatoglyphics	+	+	93
Persistent foetal fingertip pads	+	+	93
Difficulty feeding	–	–	67–75
Gastroesophageal reflux	–	–	12
Skeletal disorders:			
• brachydactyly of the fifth finger	+	+	92
• rib defects	–	–	79–88
• thoracic defects	–	+	32
• scoliosis	+	+	Missing data
• spina bifida	–	–	37
• ligamentous laxity	–	–	50–90
Hirsutism	–	–	18
Cellular immune disorders	–	–	79
Humoral immune disorders	–	+	Missing data
Recurrent respiratory infections	–	+	72
Otitis media	–	+	63
Intellectual disability	+	+	84–92
Normal intellectual development	–	–	8–16

ASD – atrial septal defect; **CoA** – coarctation of the aorta; **ToF** – tetralogy of Fallot; **VSD** – ventricular septal defect.

Tab. 2. Comparison of KS clinical expression in presented patients in relation to incidence reported in literature

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The prevalence of the syndrome can only be estimated based on the available literature, which refers to the populations of Japan, Australia and New Zealand. There have been isolated reports of 12 cases in China, 94 in France and 25 in the Czech Republic[13–15].

There is little data on the prevalence of the syndrome in Europe; therefore, it is important to report each new case of the disease to more accurately determine its prevalence among Caucasians[16]. KS is mainly inherited in an autosomal dominant manner, and anticipation of the degree of expression of the disorder in subsequent generations is possible[17]. The current state of knowledge and the availability of advanced diagnostic tools have allowed for diagnosing KS not only based on the phenotypic expression. Based on the characteristic phenotypic features, specific molecular testing of *KMT2D* and *KDM6A* genes is performed. Pathogenic *MLL2* variants are the most common cause of KS[18]. Makrythanasis et al. assessed the genotype-phenotype correlation for mutations in the *MLL2* gene[19]. A phenotype scoring system, known as the "*MLL2*-Kabuki Score", has been developed and is currently used to assess phenotypic changes in patients with clinical features of KS in correlation with an analysis of *MLL2* mutations based on DNA sequencing. Further potential mutations in KS are currently being investigated. To date, *HUWE1*, *EFTUD2*, *GRIN1* mutations and 14q11.2 deletion been detected, which require detailed analysis using advanced bioinformatics methods and next-generation sequencing (NGS)[20–23]. Due to insufficient data on genetic variants, further studies are needed to evaluate *de novo* variants in the *KMT2D* or *KDM6A* genes. In the case report presented here, the patients did not consent to further genetic testing to evaluate the type of mutation.

Kidney abnormalities in KS can lead to a reduced nephron number and subsequent kidney failure[24]. Urinary tract defects occur at a rate of 0.3–1.6 per 1,000 births, unilateral renal dysplasia at 1:3,000–5,000 live births, bilateral renal dysplasia at 1:10,000, and renal ectopy at 1:1,000 live births[24,25].

A cohort study in 94 patients in France assessed the incidence and complications of renal anomalies in KS patients, comparing them with patients without such defects and considering their genetic diagnosis. Ultrasonography showed the following findings in 71 patients: a horseshoe kidney (22%), hypodysplasia (6%), renal ectopy (4%), and renal duplication (1%). Ureteral duplication and hydronephrosis were observed in 11 KS patients. Genotype-phenotype analysis showed that 76% of patients had a mutation in the *MLL2* gene.

To the best of our knowledge, only two cases of severe renal failure that required kidney transplantation have been documented to date[11,26]. It is worth noting that renal thrombosis after the first failed transplant was not directly related to the syndrome itself or vascular complications. There was no disproportion in the size of the transplanted kidney, and the donor's age and weight matched those of the recipient's. Anatomical compatibility of the organ was confirmed – single vessels were visible in the renal hilum. Current knowledge on the effect of immunosuppression on the immune system in KS patients is insufficient and requires further investigations. The patient was screened for potential coagulation disorders; laboratory findings excluded thrombophilia. Another attempt at kidney transplantation was successful and uncomplicated. Renal thrombosis appears to be a typical complication of kidney transplantation in this case – although rare, it does occur in young children. Currently, the patient remains under close specialised care, with no abnormalities in renal function follow-up.

The diagnosis of KS is based on the identification of typical phenotypic features, followed by further genetic verification.

The presented case of a KS boy who underwent kidney transplantation is the third such case reported in the literature. Patients with KS require periodic monitoring of renal function. The described children were diagnosed with a rare syndrome characterised by a complex spectrum of phenotypic features, a still poorly understood genotype and a different course of renal disease, which determined the length and quality of the patient's life.

Conflict of interest

The authors report no financial or personal relationships with other individuals or organisations that could adversely affect the content of the publication and claim ownership of this publication.

Author contributions

Original concept of study: PN-W, AP, MT, JR. Collection, recording and/or compilation of data: PN-W, AP, MT, JR. Analysis and interpretation of data: PN-W, AP, MT. Writing of manuscript: PN-W, AP, MT, JR. Critical review of manuscript: PN-W, MT, JR. Final approval of manuscript: PN-W, MT, JR.

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