Language Delay Revealing a Kabuki Syndrome: Case Report and Literature Review

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Abstract

Kabuki Syndrome (Kabuki make-up syndrome: KMS), first described in Japan in 1981, is a rare syndrome of unknown cause, characterized by the combination of morphological facial variations, mental retardation (intellectual disability) and various malformations. We report a case of Kabuki syndrome revealed by a language delay.

Keywords: Kabuki syndrome; Clinical manifestations; Language delay; Malformations

Introduction

Kabuki Syndrome (Kabuki make-up syndrome: KMS), first described in Japan in 1981, simultaneously by Kuroki et al. [1] and by Niikawa et al. [2]. First called Niikawa-Kuroki syndrome, it will be later renamed the Kabuki make-up syndrome, because of facial features suggestive masks and Kabuki makeup in the Japanese ancient theater. Its incidence is estimated at one in 32 000 birth in Japan. It's a rare syndrome of unknown cause characterized by the combination of morphological facial variations, growth retardation, skeletal abnormalities, mental retardation (intellectual disability) and abnormal dermatoglyphics. To these signs, are variably added other possible defects and a wide range of pathologies, hardly sparing any organ. We report a case of Kabuki syndrome: a boy of 9 years and 6 months, who visited the Child Psychiatry Department for consultation in Avicenne Military Hospital for language delay. The objective of our study is to report the case of a rare syndrome and often unrecognized and to describe its different clinical manifestations and laboratory as well as the most reported forms of revelation through a literature review.

Case Presentation

A 9 years and 6 months old child, with a male phenotypic sex, comes from a consanguineous marriage (the parents are first cousin), who visited the Child Psychiatry Department for consultation in Avicenne Military Hospital for language delay. He didn't have a medical family history, but he had a personnel history as a neonatal distress and neonatal hypotonia with a refusal of feedings and crises of crying. The child psychiatric interview revealed a delay in psychomotor acquisitions: the child could not walk until the age of 4 years and the speech and language therapy assessment showed a very limited stock of words with a failure in understanding instructions (language of a 4 year old child). The cognitive tests showed a moderate intellectual disability. Genetic counseling suspected Kabuki Syndrome and the Genetic karyotyping to metaphase stage was normal, with a normal karyotype 46, XY chromosomes.

The results of the performed investigation searched for all body systems congenital malformation revealed an inter ventricular communication and atrial septal of 4 mm in echocardiography. The ENT examination showed a cleft palate with a frenulum treated surgically, hearing loss of 30% at the audiogram. Abdominal ultrasound didn't reveal any urological malformations. The ophthalmic tests were normal, including strabismus or nystagmus. The brain MRI showed a kink outside an enlargement of the right temporal horn. The child had no history of seizures and EEG was normal. The immunological balance, seeking an autoimmune pathology, was negative. Currently the patient has a multidisciplinary management (child psychiatry, speech therapy and psychomotor rehabilitation and adapted schooling).

Discussion

The diagnosis of Kabuki make-up syndrome (KMS) is based on five cardinal clinical signs: facial dysmorphism, growth retardation, skeletal abnormalities, mental retardation and abnormal dermatoglyphics. To these signs, are variably added other possible defects and a wide range of pathologies, hardly sparing any organ. The characteristic craniofacial dysmorphism is present in 100% of the cases and gives the patient a highly evocative appearance with elongated palpebral fissures with eversion of the lateral part of the lower 1/3 of the eyelid, large arched eyebrows with sparse outer 1/3 or notch, short columella with flattened nasal tip; large prominent ears and horn; a cleft lip or palate or arched palate. The brain MR showed a kink outside an enlargement of the right temporal horn. The child had no history of seizures and EEG was normal. The immunological balance, seeking an autoimmune pathology, was negative. Currently the patient has a multidisciplinary management (child psychiatry, speech therapy and psychomotor rehabilitation and adapted schooling).

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growth retardation is usually postnatal [4]. He settled in the first year of life and increases with age, compounded by early feeding difficulties. Musculoskeletal abnormalities present in 88% of cases [4], are varied, they include brachydactyly type 5, brachymesophalangy, clinodactyly of the 5th finger, scoliosis, joints hyperluxity and dislocation. The microcephaly is inconstant. Dermatoglyphic abnormalities are typically reported with persistent fetal velar pads, they are part of the cardinal signs. Mental retardation is variable, generally moderate [5-7]. Psychomotor acquisitions are delayed due to very frequent sensory deficits, especially hearing [3,4,6] and hypotonia [3,4]. A hearing loss is common in 30–40% of the cases, sensorineural origin or secondary to chronic otitis media due to the craniofacial malformation or due to a susceptibility to infections.

In our case, the diagnosis was based on the facial anomalies characteristic of KMS, abnormal dermatoglyphs, cleft palate, growth retardation, mental retardation, and associated heart defects.

Associated malformations are potentially numerous and varied. They concern: the heart in 50% of the cases [8]. This is most often of septal defects, coarctation of the aorta are found in 25% of cases, it may also include mitral stenosis, aortic or pulmonary, tetralogy of Fallot or abnormal pulmonary venous return [9,10]. The diaphragmatic hernia [4,11,12] is present in 3–8% of cases. Renal abnormalities: renal hypoplasia or renal dysplasia or urinary tract dysplasia, dual system with ureteral duplicated, with or without ureterocele, megaureter are also described [3,4,13]. The association of extraplateal biliary atresia has been reported sporadically, as a possible neonatal sclerosing cholangitis or congenital hepatic fibrosis [3,4,14,15]. Several publications mention the significant frequency of anorectal anomalies (imperforation or fistula) [16,17]. The central nervous system is not spared. Many anomalies have been described (microcephaly, arachnoid cysts, hydrocephalus with stenosis of the aqueduct, posterior cranial fossa abnormalities, polymicrogyria) [18,19]. The presence of epilepsy is often reported and concerns 10 to 40% of patients. Immune dysfunctions are also common. Most often, these are various autoimmune manifestations: [20,21] hematologic (thrombocytopenia, anemia, neutropenia), celiac disease, insulin dependent diabetes, vitiligo, and, rarely, autoimmune dysthyroidism. Deficits of humoral immunity with hypo gamma globulin are also reported in this context [22] favoring recurrent infections. Endocrine disorders are multiple, deficiency in growth hormone [23] is frequent, and it is to seek when we have short stature smaller than -3DS and recurrent hypoglycemia [24]. The occurrence of early puberty [25,26] is found in 25–43% of cases. Thyroid disorders (hypo- or hyperthyroidism) and the LH deficiency are possible but uncommon.

The causes of the syndrome remain unknown for now. Multiple intrafamily observations [27] suggest a genetic origin and a dominant inheritance with variable expressivity. However most of the reported cases are sporadic. The identified chromosomal abnormalities are numerous. They can be gonosomal (mosaic 45X-47XXX, X ring) [28,29], multiple autosomal (trisomy 10p, deletion or duplication in 2q37 [30,31]). The multiple rearrangements of 8p22-8p23,1 duplication region, triplication, paracentric inversion are frequently reported in the literature [32,33], but comparative genomic hybridization techniques have not only confirmed this [34] approach. Recently, the possible role of gene C20orf133, located 20p12-1 region deleted in a patient, was mentioned. [35] Other regions of the genome are potentially involved [36], but the authors insist on the genetic heterogeneity of the syndrome.

The mode of revelation of this syndrome is very variable, it may be hypotonia, feeding difficulties, recurrent infections, growth retardation or obesity. Language delay in the KMS has been reported by several authors, and it is linked in some cases with deafness; other authors suggest a neurological origin of the delay, while in several cases the delay is associated with the presence of a cleft lip and palate, neonatal hypotonia or mental retardation. [37]. It’s necessary to complete the clinical approach with an assessment, which will include, at first, karyotyping, heart and abdominal ultrasound, an ENT examination, AEP and scan of the temporal bones, ophthalmologic examination and skeletal X-rays. Depending on the patient’s age and clinical guidelines, other explorations will be considered (psychomotor assessment and psychometric assessment tests, Dynamic Dosing GH front of a short stature, looking for an autoimmune pathology and exploration humoral immunity; odonto stomatological balance sheet). Using a pediatric geneticist and a center of competence is needed when it is possible, since it allows the confirmation of the diagnosis, identification of the cases identified and the appropriate implementation of new molecular biology techniques. The management of its anomalies is mainly symptomatic.

Conclusion

Kabuki syndrome is not related only to Asian populations and it is probably still frequently unknown. [3] The diagnosis is based mainly on the clinical picture. The mode of KMS revelations are highly variable as well as the associated malformations. The outcome of these patients can be better understood through the multiplication of identified and tracked cases. The management adapted to each case is needed to improve the course and prognosis of these patients.

References


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