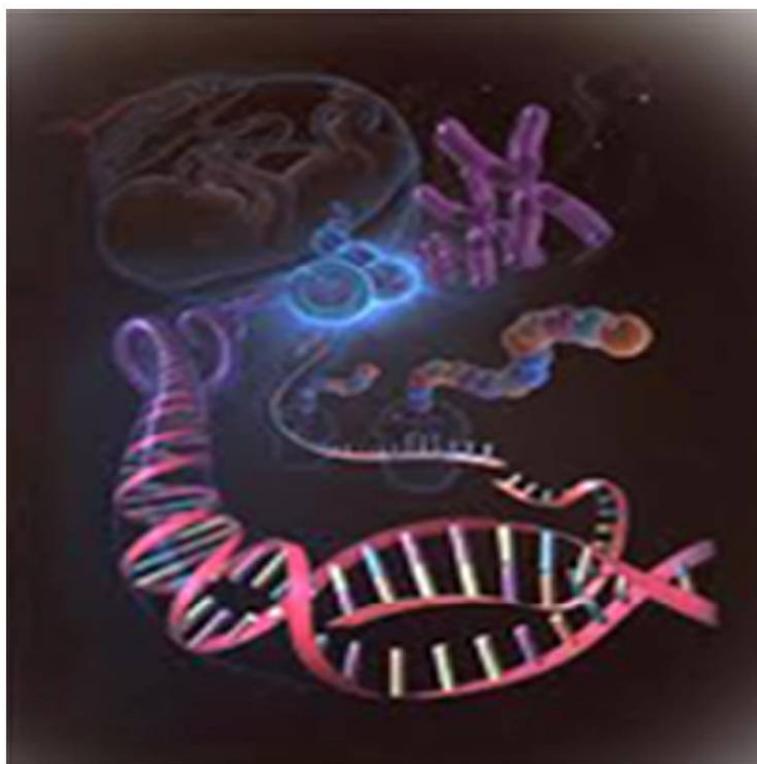




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Research Paper

CLINICAL HETEROGENEITY OF KABUKI SYNDROME: STUDY OF MOROCCAN PATIENTS

N Serbati¹, S Nassereddine², H Dehbi², S Nadifi^{2*}

*Corresponding Author: **S Nadifi**, ✉ Labgenmed2@yahoo.fr

Kabuki syndrome (KS, Niikawa-Kuroki syndrome, MIM:147920) is a rare multiple congenital anomaly/mental retardation syndrome described simultaneously by Niikawa *et al.*, 1988 and Kuroki *et al.*, 1981. The estimated frequency of this syndrome is about 1/32 000 in Japan. KS is characterized by postnatal growth retardation, distinctive facial features, dermatoglyphic anomalies, skeletal dysplasia, and mental retardation. The molecular basis has been recently elucidated. In our report, we present three patients with different clinical features. The first is 17 years old, with a rare congenital heart defect, a perception deafness, neurogenic bladder, facial dysmorphism, joint hyperlaxity and fetal pads. The second patient presents mental retardation, dysmorphic features and seizures. In the third case, there was a mild mental retardation with joint hyperlaxity, facial features and fetal pads. Through the study of these three cases we confirmed that the phenotypic heterogeneity of the kabuki syndrome which makes it under diagnosed.

Keywords: Kabuki-Niikawa Syndrome, Clinical heterogeneity, Moroccan patients, Genetics, MLL2 gene

INTRODUCTION

Kabuki syndrome (Kabuki make-up syndrome or Niikawa-Kuroki syndrome) was first described in Japan in 1980 (Niikawa N and Matsuura N, 1981; and Kuroki Y *et al.*, 1981), is a rare disorder of unknown cause, characterized by multiple congenital malformations associated with mental retardation, postnatal growth delay and facial dysmorphism.

The name of Kabuki make-up refers to the resemblance of the facial features with the characteristic make-up used by actors of Kabuki, one of the traditional performing arts in Japan.

This syndrome was wrongly thought to be specific to Japanese population where the occurrence was estimated at 1/32000 (Niikawa. N *et al.*, 1988). But, in the last few years, several series of non-Japanese patients with KS have been reported by European groups.

¹ Laboratory of medical genetics, Medical school of Casablanca, Morocco.

² Laboratory of medical genetics, Medical school of Casablanca, Morocco.

The sex ratio in KS is almost equal and no increased rate of consanguinity is found (Lerone M *et al.*, 1997), but it is associated with advanced paternal age (Armstrong L *et al.*, 2005). Overall, the sporadic occurrence suggests a de novo origin of autosomal dominant mutations (Niikawa N, 1988; Courtens W, 2000; and Silengo M, 1996).

Several people with KS features have been found to carry abnormalities of chromosomes, including the sex chromosomes and various autosomes (Maas, Van de Putte, Melotte *et al.*, 2007). One patient had a pericentric inversion of the Y (Maas, Van de Putte, Melotte, *et al.*, 2007).

Recently, several mutations in MLL2 gene have been linked to KS syndrome (Ng *et al.*, 2010).

Kabuki syndrome has a wide phenotypic spectrum that can make the diagnostic very difficult for clinicians and the most striking aspects of KS are the unique facial features, which usually prompt the clinician to consider this diagnosis (Adam M P *et al.*, 2004).

We present three new cases of KS in Moroccan population to underlie the occurrence of this disorder in non-Japanese and to illustrate the clinical variability that can make this syndrome still be under diagnosed.

Case Reports

Case 1

We report the case of 17 years-old girl admitted in the medical genetics department for multiple malformations syndrome. The patient was born to non consanguineous healthy parents, in non-medical conditions with history of neonatal pain.

From birth, she was followed for symptoms of congenital heart disease. Echocardiography with Doppler and the assessment of hemodynamic functions has confirmed the

diagnosis of Double-chambered right ventricle. The clinical evolution was marked by a neurogenic bladder with renal infections. At the age of 1 year old, the patient has undergone cleft lip and palate surgery. She also had psychomotor developmental delay (sitting and walking delay) and postnatal growth retardation (Height: 132 cm, weight: 29kg, head circumference: 50 cm). There was no similar case in the family.

The period of infancy was marked by recurrent otitis that causes bilateral hearing loss.

She had facial dysmorphism with high arched eyebrows sparse laterally, long palpebral fissures with everted lower eyelids, long eyelashes accompanying microcephaly. Her nose was broad with depressed tip, and ears were prominent and protruding. She had Scar of a cleft lip and palate surgery and pits on the lower lip. She had a generalized hypotonia. On oral examination she had high arched palate and dental malposition with crowded teeth. The patient had also persistent fetal finger pads, square fingers and clinodactyly of 4th and 5th fingers. In the feet, the patient had brachyphalangy and overlapping toes.

The patient presents tonico-clonic Seizures. She, also, had lumbar scoliosis and joint hyperlaxity.

Case 2

A 12 years-old boy was referred to human genetics division to be evaluated for seizures and mental retardation. He was born to a normal pregnancy by vaginal delivery with neonatal pain. His birth weight was 3500g. His parents were healthy first degree cousins. There was no familial history of seizures or mentally retarded persons.

At the age of 2 years-old, the patient had a tonic-clonic seizure and the electroencephalography confirmed the diagnosis but no specific type was defined. A CT brain revealed discrete atrophy of the left temporal lobe associated with discrete enlarged ventricles. The status epilepticus was well controlled by an appropriate treatment (Urbanyl and Depakine). The patient had also global developmental delay in motor skill acquisitions, speech and a moderate mental retardation.

He had joint hypermobility, muscular hypotonia and persistent fetal pads.

He also had facial dysmorphism with long face, high arched eyebrows sparse laterally, long palpebral fissures with everted lower eyelids, long eyelashes accompanying microcephaly. His ears were large, prominent and posteriorly rotated. He had trapezoid philtrum with prominent wide upper central incisors. The karyotype analysis was normal (46,XY). He was diagnosed as Kabuki syndrome due to clinical findings.

Case 3

A 6 years-old boy was referred to our department for mental retardation, speech delay and facial dysmorphism. He was born to non consanguineous healthy parents by cesarean delivery. The period of infancy was marked by feeding difficulties but no growth delay was diagnosed. The patient had facial features including prominent forehead, high arched eyebrows sparse laterally, long palpebral fissures with everted lower eyelids, long eyelashes and hypertelorism with discrete synophris. The ears were large and low-set.

In oral examination: he had high arched palate and small spaced teeth. The patient had also

persistence of fetal pads, clinodactyly of 5th fingers and joint hyperlaxity (Figure 1). The EEG revealed a slow rhythm without epileptic abnormalities. No cardiac abnormalities were found in cardiac ultrasound. The karyotype was normal 46, XY.

DISCUSSION

Prevalence

The prevalence of KS in Japan has been estimated to be 1/32000. In Australian and New-Zealand (White *et al*, 2004) estimated the minimal birth prevalence of KS to be 1/86000 but they felt that this may actually be an underestimate of the prevalence of KS because of under-recognition.

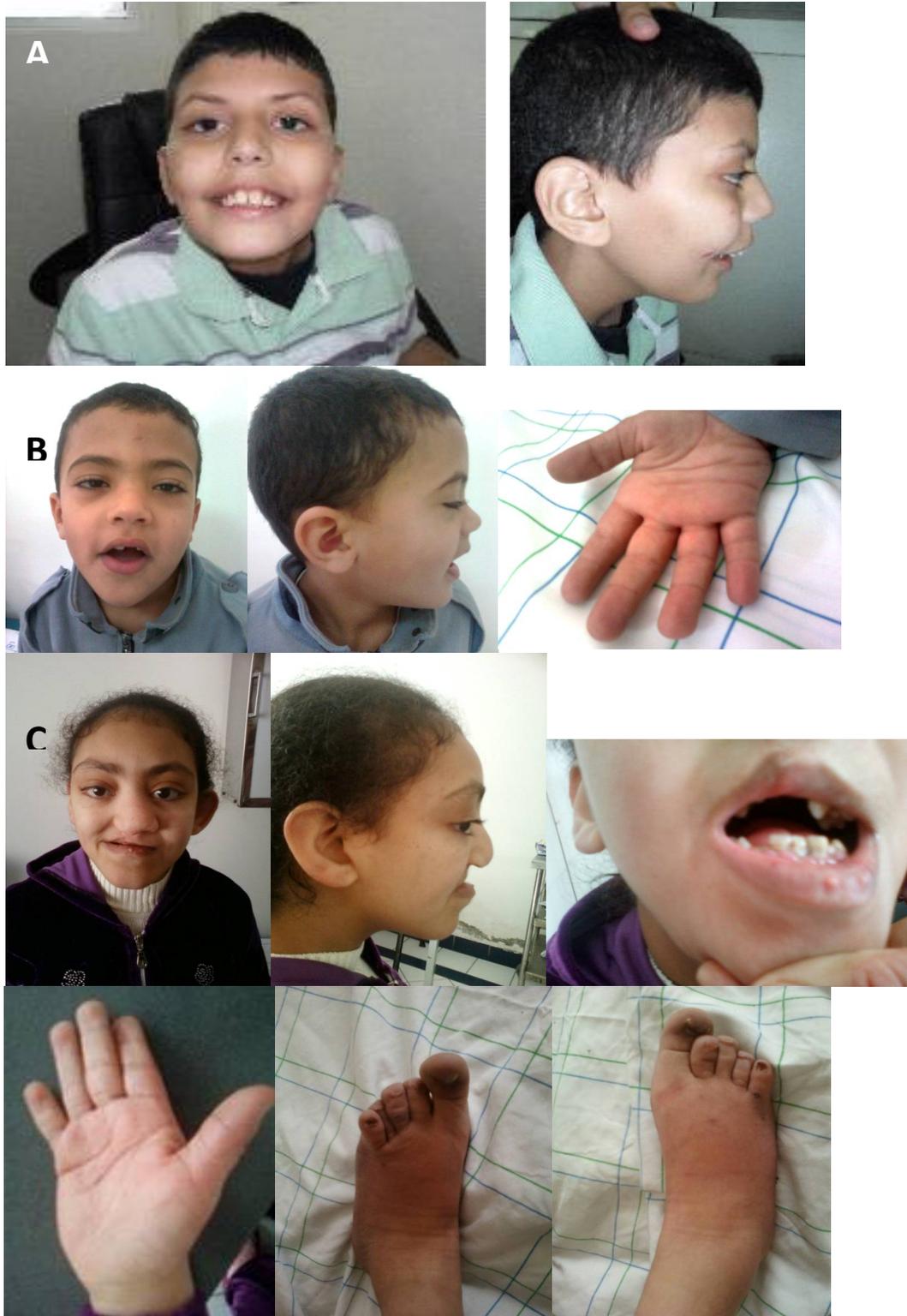
In Morocco, the prevalence is not determined. This can be explained by failure of patients with Kabuki (Niikawa–Kuroki) syndrome to be referred to the genetic service and failure of clinicians to diagnose the condition. Adam *et al*. (2004) presumes that the prevalence in other races will approximate that seen in the Japanese population.

Clinical Criteria

We report, in this article, three unrelated patients with different clinical presentation from paucisymptomatic to complete phenotype.

Our patients were diagnosed as Kabuki syndrome on the basis of clinical findings. Five cardinal manifestations were defined by Niikawa *et al* (1988, study of 62 patients). Its classical phenotypic features included a “peculiar face” in 100% of their patients, skeletal anomalies in 92%, dermatoglyphic abnormalities in 93%, and mild to moderate mental retardation in 92% of their patients. Other numerous clinical finding were

Figure 1: Facial Features, Fetal Pads, Lip Pits And Toes Abnormalities in Ks Patients. (A, B, C: Patients 2, 3, 1)



less frequently reported in KS including visceral abnormalities, premature breast development in females and susceptibility to frequent infections.

Kabuki syndrome is a very heterogenous disorder. As we presented in Table 1, the patients had differences in clinical features and severity of the symptoms.

The case 1 had a typical face with the five cardinal manifestations and other less frequent features like seizures, recurrent otitis, cardiovascular malformation and urinary tract abnormalities. The second patient presented the peculiar face with fetal pads, mental retardation and joint hypermobility. In this case the most important symptom was the seizures that are causing more problems for the pediatrician. The

third patient was referred to our consultation for mental retardation and facial dysmorphism.

The patient no. 1 had pits on the lower lip, known as congenital sinuses or fistulas that occur between the 40th and 50th day of embryonic life, they are frequently seen in patients with Van Der Wood syndrome (VDWS), Popliteal pterygium syndrome and occasional in branchio-oculo-facial syndrome and oral-facial-digital syndrome I (schnitzel *et al*, 1986). In Kabuki syndrome, this sign is considered as a rare manifestation of the symptoms spectrum. Such lip pits in patient with KS were reported in a Brazilian girl with KS and anorectal anomalies (kokitsu-nakata. 1999). Another case of Kabuki syndrome with lower lip pits was reported in a 5 year-old female

Table 1: Differences in Clinical Features and Severity of the Symptoms Between Our Patients

Clinical Symptoms	case1	case2	case3	Total	% literature
Age	17y-o	12 y-o	6 y-o		
Sex	F	M	M		
facial features	+	+	+	3/3	100%
cleft lip and/or palate	+	-	-	1/3	56%
fetal pads	+	+	+	3/3	79%
Growth	+	-	-	1/3	68%
development/ intelligence	+	+	+	3/3	88%
feeding difficulties	+	-	+	2/3	29%
Seizures	+	+	-	1/3	13 - 20%
Hearing loss	+	-	-	1/3	27%
ptosis	+	-	-	1/3	50%
congenital heart defects	+	-	-	1/3	40%
urinary tract anomalies	+	-	-	1/3	20%
gastrointestinal features	-	-	-	0/3	2,2-3,8%
Skeletal anomalies	+	-	-	01-mars	79%
joint hyperextensibility	+	+	+	03-mars	67%
Recurrent otitis media	+	-	-	1/3	63%
others	pits on lips	cerebral atrophy			

Taiwanese girl who had familial form of KS. Franceschini *et al* (1993) also reported lip lesions in a patient with KS.

The association between Kabuki Syndrome and congenital heart defects is well established. Since the first report of CHDs in KS by Niikawa and Kuroki in 1980, there have been several observations of many different forms of CHDs. The prevalence of heart defects in this population has been estimated to be between 28 and 80% (Digilio MC 2001, Galan-Gomez E 1995). The most common finding appears to be juxtaductal coarctation of the aorta followed by VSD and ASD (Adam MP, Hudgins L 2004).

Other less common cardio-vascular malformations were described (patent ductus arteriosus, conotruncal heart defects, anomalous pulmonary venous return etc) (Digilio MC *et al* 2001, Hughes HE, Davies SJ. 1994). In the case No.1, the patient had a double chambered right ventricle which is a novel cardiac finding associated to KS.

Genetics

About 400 cases have been reported worldwide. The vast majority of reported cases have been sporadic, but parent-to-child transmission in more than half a dozen instances suggests that Kabuki Syndrome is an autosomal dominant disorder. The relatively low number of cases, the lack of multiplex families and the phenotypic variability of Kabuki Syndrome have made the identification of the genes underlying Kabuki syndrome intractable to conventional approaches of gene discovery, despite aggressive efforts. Several studies had initially associated this condition to chromosomal rearrangement.

Recently, a gene causing KS was identified through exome sequencing, reporting mutations

in the histone methyl transferase (HMT) gene MLL2 in 66% of 53 patients with Kabuki syndrome (Ng *et al.*, 2010). MLL2 is a member of the so called mixed lineage leukemia (MLL) family of HMT proteins, of which MLL1 (previously called ALL1) has been extensively studied because of its frequent involvement in chromosomal rearrangements in acute myeloid and/or lymphatic leukemia (Meyer *et al.*, 2006).

Exome sequencing (Paulussen *et al.*, 2010) revealed a very wide spectrum of MLL2 mutations (nonsense, frameshift, splice site, and missense mutations), predicting a high frequency of absent or non-functional MLL2 protein and a genotype-phenotype correlation.

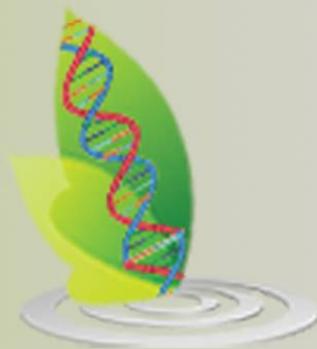
CONCLUSION

All these findings help us to underlie the great phenotypic heterogeneity in the Kabuki syndrome that should be considered by clinicians especially pediatrician. Also, the new genetic implication of MLL2 gene will encourage further functional investigations in gene expression that can help understanding the very wide spectrum in mutations and clinical features.

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Hyderabad, INDIA. Ph: +91-09441351700, 09059645577
E-mail: editorijlbpr@gmail.com or editor@ijlbpr.com
Website: www.ijlbpr.com

