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Distinctive Dysmorphism: Clinical Imaging Perspectives in Kabuki Syndrome

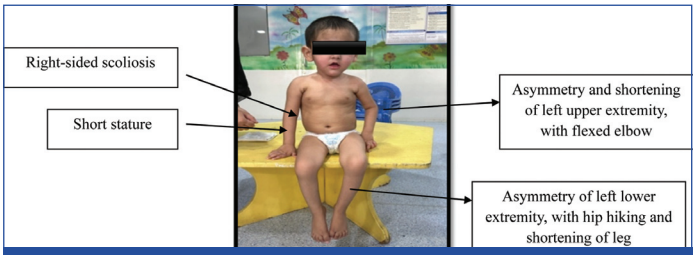
NAMRATA SANT[1], TANAYA RAJESH JADHAV[2], PRASHANSA KASAT[3], CHITWAN AGRAWAL[4]

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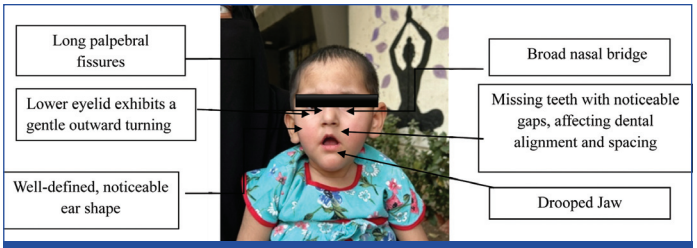
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Kabuki Syndrome (KS), also known as Niikawa-Kuroki syndrome or Kabuki make-up syndrome, is a cluster of congenital abnormalities and mental impairment [1]. It was initially identified concurrently by two Japanese groups, Niikawa N et al., and Kuroki Y et al., [2,3]. The estimated prevalence is approximately 1 in 32,000 live births [3]. The disorder affects males and females. It is rare syndrome characterised by five cardinal features such as distinctive facial dysmorphism including eversion of lower lateral eyelids, arched eyebrows with lateral thinning, depressed nasal tip, prominent ears in 100% of cases; skeletal anomalies comprising spinal deformities, brachydactyly V in 92%; dermatoglyphic abnormalities such as fingertip pads, absent triradii c/d, increased ulnar/hypothenar loops in 93%; mild to moderate intellectual disability in 92%; and postnatal growth deficiency in 83%. Additional findings include visceral anomalies, feeding difficulties, hypotonia, hearing issues, cardiovascular abnormalities and recurrent infections [4].

A two year and five-month-old female, the first child born out of consanguineous marriage to a G1P1L1A0D0 mother, with no co-morbidities, delivered preterm at 32 weeks via cesarean section due to oligohydramnios. With a birth weight of 1.8 kg and a critically low APGAR score of 2/10, she required a five-day NICU admission for respiratory distress, feeding difficulties, hypoglycaemia which was treated with Intravenous infusion of 10% glucose, feeding, and fluid replacement normalised the blood glucose levels. Later patient developed pathological neonatal jaundice oxygen support and phototherapy. By 1.5 years of age, due to global developmental delay, i.e., not able to sit without support, persistent feeding refusal, presence of primitive reflexes, hypotonia associated with proximal muscle weakness, patient underwent investigations; such as: (a) brain MRI, which was structurally normal; (b) EEG identified localised monomorphic delta activity (slowing) in the right temporo-occipital region without active epileptiform discharges; (c) Brainstem Auditory Evoked Responses (BAER) revealed bilateral hearing loss ranging from severe to profound; (d) total serum bilirubin (7.1 mg%), Direct bilirubin (1.4 mg%) and Indirect bilirubin (5.7 mg%) plasma lactate (4.1 mmol/L), and C-reactive protein (39.9 mg/L) were found elevated in laboratory tests. Musculoskeletal features are shown in [Table/Fig-1] and facial dysmorphism features are shown in [Table/Fig-2]. Patient also underwent various genetic testing: (a) whole-exome sequencing for neuromuscular disorders: Single Nucleotide Variant (SNV) and Copy Number Variant (CNV) which showed no detection of any variant; (b) mitochondrial genome sequencing showed negative report; (c) whole exome sequencing, which revealed two heterozygous Variants of Uncertain Significance (VUS) in the PPP3CA and KDM6A genes. This confirmed a pathogenic X-linked variant in the KDM6A gene (Ser34Arg, Exon 1), establishing the diagnosis of Kabuki Syndrome (KS) 2 [Table/Fig-3]. Further, patient was started on Intragastric Feed via Nasogastric tube, i.v. antibiotics like amikacin and piperacillin/tazobactam for five days and nutritional supplements like multivitamins, vitamin D3, and levocarnitine for 30 days.



[Table/Fig-1]: Musculoskeletal features showing short stature, right-sided scoliosis, and asymmetry of the left upper and lower extremity.



[Table/Fig-2]: Facial dysmorphism.

By the age of 2.5, the patient showed global developmental delays, achieving milestones such as rolling over at 10 months and sitting with support at 15 months, but remained unable to stand or walk independently. Her weight and height measurements were below the third percentile, indicating severe growth retardation, according to her clinical profile [5]. She also showed significant delays in speech and fine motor skills, as well as widespread hypotonia and the absence of deep tendon reflexes in the lower limbs. Physical examination revealed dysmorphic features characteristic of Kabuki Syndrome, including long palpebral fissures with lower eyelid eversion, arched eyebrows with lateral thinning, a broad nasal bridge, and a drooping jaw. Additional findings included right-sided scoliosis, limb asymmetry, and dental anomalies characterised by hypodontia and microdontia.

Several genetic syndromes should be considered in differential diagnosis of Kabuki syndrome because they share overlapping clinical features such as developmental delay, hypotonia, hearing loss, craniofacial abnormalities, skeletal defects, and feeding difficulties: (i) CHARGE syndrome, excluded by absence of coloboma, choanal atresia, and characteristic cranial nerve defects, along with negative CHD7 gene testing [6]; (ii) 22q11.2 deletion syndrome, ruled out by absence of thymic hypoplasia, hypocalcaemia, and the 22q11.2 microdeletion on chromosomal microarray analysis [7]; (iii) Branchio-oto-renal syndrome- excluded by the absence of branchial cleft anomalies, renal malformations, and because children with BOR syndrome usually have normal growth, unlike the postnatal growth deficiency seen in Kabuki syndrome [8]. (iv) Van der Woude syndrome- ruled out by the absence of the typical lower lip pits and cleft lip/palate [9].

The overall clinical picture, imaging findings, biochemical enzyme assay, and genetic testing confirmed diagnosis of Kabuki Syndrome 2,

Gene and transcript	Exon/Intron number	Variant nomenclature	Zygosity	Classification	OMIM phenotype	Inheritance
PPP3CA (NM_000944.5)	Exon 5	c.532T>A p.Cys178Ser (22X/63X)	Heterozygous	Uncertain significance	PPP3CA-related disorders	——
KDM6A (NM_001291415.2)	Exon 1	c.102C>G p.Ser34Arg (15X/32X)	Heterozygous	Uncertain significance	Kabuki syndrome 2	X-linked dominant

[Table/Fig-3]: Craniofacial phenotype of Kabuki syndrome associated with eversion, arched eyebrows, broad nasal bridge, prominent ears, and drooping jaw.

due to pathogenic X-linked mutation in KDM6A gene. The patient is receiving regular physiotherapy sessions three times per week and is currently on multivitamin supplementation along with calcimax tablets. Though these impairments are non-progressive, but recognition of these features through physical examination and imaging is essential for early diagnosis, allowing physiotherapy to begin during the period of greatest neuroplasticity, helping maximise motor development, prevent secondary complications, and improve long-term functional independence. Thus, findings are consistent with kabuki Syndrome resulting from Pathogenic X-linked mutation in KDM6A gene.

Long-term prognosis or potential complications in adolescence/ adulthood: Most individuals with Kabuki syndrome survive into adulthood; however, they remain at risk for persistent developmental delay, hearing impairment, scoliosis, joint laxity, obesity, endocrine disorders, and reduced functional independence. Early multidisciplinary management and ongoing physiotherapy are important to minimise secondary complications and maximise long-term functional outcomes.

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PARTICULARS OF CONTRIBUTORS:
1. Associate Professor, Department of Neurophysiotherapy, MGM School of Physiotherapy, Chh. Sambhajinagar, A Constituent Unit of MGMIHS, Navi Mumbai, Chh. Sambhaji Nagar, Maharashtra, India.
2. Final Year Student, Department of Physiotherapy, MGM School of Physiotherapy, Chh. Sambhajinagar, A Constituent Unit of MGMIHS, Navi Mumbai, Chh. Sambhaji Nagar, Maharashtra, India.
3. Intern, Department of Physiotherapy, MGM School of Physiotherapy, Chh. Sambhajinagar, A Constituent Unit of MGMIHS, Navi Mumbai, Chh. Sambhaji Nagar, Maharashtra, India.
4. Postgraduate Student, MPT (Neurophysiotherapy), Department of Neurophysiotherapy, MGM School of Physiotherapy, Chh. Sambhajinagar, A Constituent Unit of MGMIHS, Navi Mumbai, Chh. Sambhaji Nagar, Maharashtra, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Namrata Sant,
A1, 403, Millenium Park, E 26/27, Chikalthana, MIDC,
Chh. Sambhaji Nagar-431001, Maharashtra, India.
E-mail: namratassant@gmail.com

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