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Kabuki Syndrome (Kabuki Make – Up Syndrome, Niikawa Kuroki Syndrome)

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Abstract:

Kabuki syndrome is a congenital disorder of genetic origin with multiple malformation syndrome characterized by distinctive facial features, heart defects, intellectual disability, postnatal growth deficiency and behavior abnormalities. It is suspected to be a single gene , Autosomal Dominant disorder (1). (2),(3)

We present the clinical features, developmental evaluation and the genetic findings of a childwith Kabuki syndrome

Keywords: Kabuki Syndrome , Dysmorphism, Delayed Milestones

Introduction

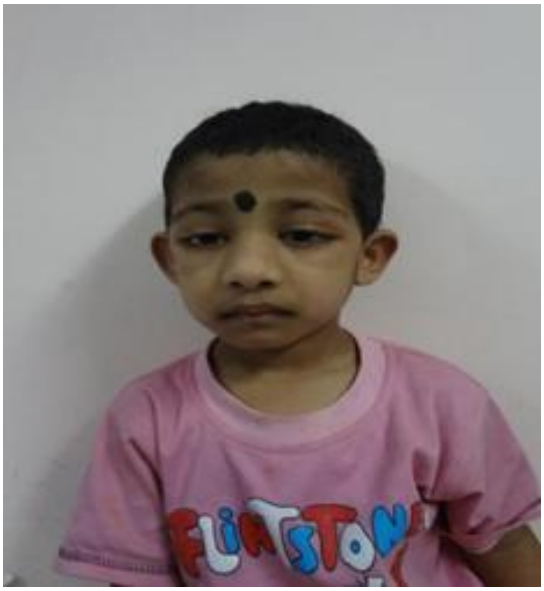
Kabuki Syndrome is a rare genetic disorder, first described by Niikawa and Kuroki in Japan. It isnamed after the characteristic facial features - long palpebral fissures with eversion of lower lateral eyelid, broad arched eyebrows with lateral sparseness which resembles the make up of Kabuki actor, a traditional Japanese theatre form (2).(4)

The prevalence of Kabuki syndrome is 1 in 32,000 in Japan, and the incidence outside Japan ispresumably the same as in Japanese population.

The five cardinal manifestations of Kabuki syndrome are 1) characteristic facial features (100%) 2)Skeletal abnormalities (92%) 3) dermatoglyphic abnormalities (93%) 4) mild to moderate intellectual disabilities (92%) and 5) postnatal growth deficiency(83%). The two known genes involved in Kabuki syndrome are KMT2D, and KDM6A and are located on chromosome 12 and X-chromosome with cytogenic location (12q13.12,Xp11.3) respectively. The leading current hypothesis is that KS is a single gene, Autosomal Dominant disorder, with majority of them representing new mutations(2).

We would discuss the clinical features and developmental progress of a child with Kabukisyndrome.

Case report:



3 year 6 month old male child from Orissa , 1st born to non-consanguinous parents presented with developmental delay in attaining developmental milestones since early infancy. The mother's antenatal period was uneventful and he was delivered by Emergency Caesarean section, indication being fetal distress. He was admitted in the NICU for respiratory distress. In neonatal period he had recurrent hypoglycemia requiring 15% dextrose infusion and Inj. Hydrocortisone following which sugars normalized. He was also treated with and antibiotics for probable sepsis.

His development has been delayed since early infancy

Gross Motor

He attained head control-at 8 months -, was sitting without support at 12 months and walked after2 years

Fine motor: Palmar grasp was present at 1 year and was scribbling at 2 years.

Language: He was babbling unmeaningfully and was communicating with gestures.

Social : He was interacting well with parents, however stranger awareness was present.

Currently he walks independently, is able to speak a few words with meaning, able to hold pen with mature tripod grasp and scribble. He has started indicating his toilet needs. The parents have noticed some abnormal behaviors like inconsistent response when called, poor eye contact, absence of pointing, hypersensitivity to certain loud sounds and avoidance of sticky food. His vision and hearing are normal.

Past history: He had one episode of fever provoked seizure at one year of age. Developmentallyhe is ambulant.

On examination

Child was alert, but restless with fleeting eye contact. There were multiple dysmorphic features like everted lower palpebral fissures, low protruding ears, broad nose with bulbous tip, down slanting eyes, long eyelashes with retrognathia.

Anthropometry: Weight 13.7kg, height 96.5cm, Head circumference 47.5cm (<3SD)Vitals were stable. There were no neurocutaneous markers

Systemic examination

Cardiovascular system- First and second heart sounds were normal Respiratory system- Breath sounds were heard equally on both sides Abdomen-soft, no organomegaly

Central nervous system: Muscle bulk, tone and reflexes were normal. There were no cranialnerve deficits. No cerebellar signs. Examination of his skull and spine were normal.

He underwent a detailed assessment by the Developmental Pediatrics Team:

Assessment by the Psychologist

The child was observed for his development in areas of attention, behavior, play pattern andearly learning skills.

Social skills: He was comfortable in a social environment. He maintained eye contact briefly and had goodsocial reciprocity with his parents.

Attention: He was motivated to do activities with parental guidance. Activities had to be changed frequentlyand modified tasks pertaining to his interest had to be provided to sustain his attention.

Play skills: He needs to be guided during play and he expressed interest for play activities appropriately. Behavior:

He was mildly restless but could be engaged with stimulating activitiesLearning:

Attention: He was motivated to do activities with parental guidance. Activities had to be changed frequentlyand modified tasks pertaining to his interest had to be provided to sustain his attention.

Play skills: He needs to be guided during play and he expressed interest for play activities appropriately. Behavior:

He was mildly restless but could be engaged with stimulating activitiesLearning:

Occupational Therapy Assessment

Gross motor: He can run well. He can kick a ball. He could walk up and downstairs withoutsupport.

Fine motor: He prefers right more than the left hand. He had a pincer grasp and controlled release into the container. He can open and close pen cap. He unscrews bottle lids. He can threadbeads in a lace. He can scribbles using digital pronate grasp.

Activities of daily living: He can eat snacks by himself. He needs assistance in all activities of daily living.

He has some simple constructive and manipulative skills,

Formal Developmental Assessment

On the **GRIFFITH'S MENTAL DEVELOPMENT SCALES** his current developmental profile was as follows:

LOCOMOTOR subscale: his performance corresponded to 20.8 months.

PERSONAL SOCIAL subscale: his performance corresponded to 24 months. This subscalemeasures the child's adaptive, play and daily living skills.

HEARING AND LANGUAGE subscale: His performance corresponded to 15.4 months. Thissubscale measures the child's receptive and expressive achievements collectively.

EYE-HAND CO-ORDINATION subscale: His performance corresponded to 19.5 months. Thissubscale measures the child's co-ordination for visuo-motor activities and coordination

PERFORMANCE subscale: His performance corresponded to 22.1 months. This subscale measures the child's speed of performing visuo-spatial and perceptual tasks within a stipulatedtime frame.

Based on the observations by the multi-disciplinary team a detailed home program with activitiesto enhance attention, comprehension, communication and social skills training was suggested to the parents.

Investigations

Complete blood counts, Liver function tests, Creatinine, Thyroid function Tests, Vitamin Dlevels, Serum B12 and Folic acid levels were all within normal limits.

Ultrasonography of the Abdomen and pelvis: Normal ECHO: Normal

Genetic Test Results:

Clinical exome analysis revealed a heterozygous variant c.15641G & gt; A, in exon 48 of KMT2D gene [TranscriptID(ENST00000301067) which was consistent with Kabuki syndrome .

Genomic coordinate chr12:49420108C & gt ;T; GR Ch 37 / hg19 build] leading to change in aminoacid [p. R5214H] causing

Kabuki syndrome.(OMIM#147920). This variant has not been reported previously in ExAC database and 1000G project. Further, in silico analysis predicted this variant to be disease causing.

This missense variant has been reported already as disease causing variant in HGMD database [HGMD ID: CM105480]. This change is in FY-rich, N-terminal domain. Correlating all the evidences, this variant is considered as pathogenic.(5)

Gene transcript	Location	Variant	Zygosity	Disease	Inheritance	Classification
KMT2D(-) (ENST00000301067)	Exon48	C,15641G>G/A (p,Arg5214His)	Heterozygous	Kabuki syndrome- 1	Autosomal dominant	pathogenic

Genetic Counselling

After making the diagnosis based on the clinical features and the Genetic test the parents werecounseled by the Geneticist. Kabuki syndrome (KS) is inherited in an Autosomal Dominant manner and in most cases of the KMT2D related KS occurs de novo. However as the exact percentage of de-novo cases is not known prenatal diagnosis using Chorionic villus sampling was advised to the parents at 10 -11 weeks of gestation in the next pregnancy.

For this child the parents were advised about the following:

1. Frequent monitoring of height, weight, and head circumference yearly
2. Frequent developmental monitoring and developmental support. Interventions areadvised as required
3. Annual monitoring of vision is important as the child can develop ocular symptoms likecataract, lagopthalmos and retinopathy
4. Annual hearing evaluation and expectant monitoring for otitis media to detect early, and prevent conductive hearing loss.

Discussion

Various authors had reviewed the clinical features of Kabuki syndrome, the most recent being Mutsumoto and Niikawa in a large series involving 350 individuals. The table below describesthe clinical features present in Kabuki and compares with the findings in our patient(6).

S.No	System Involved	Clinical Presentation of KS	Symptoms present in ourchild
1	Dysmorphism(4)	Elongated palpebral fissures with eversion of thelateral third of the lower eyelid; Arched and broad eyebrows; Short columella with depressed nasal tip;Large, prominent, or cupped ears	Present Present Present Present
2	Growth and Fedding	Post natal growth retardation(35-81%), Feeding difficulties , GERD Failure to thrive	Present (Height was 10th percentile and microcephaly was present - 47cm)
3	Development and Behaviour	Intellectual Disability Motor Impairment, Speech Delay, Autistic Traits.	Present Present Present Present
4	Neurological	Hypotonia (25-89%),Joint laxity, Seizures (10-39%), Arnold Chiarri I Malformation.	Fever provoked seizures MRI was not done. But no clinical features present
5	Cardiovascular	Congenital Heart defects (40-50%), Coarctation of Aorta, Septal Defects.	Absent – ECHO wasnormal
6	Endocrine	Premature Thelarche (7-50%) ,Hypoglycemia, Congenital Hypothyroidism, GH deficiency,	Not applicable Neonatal hypoglycemia was present Absent GH assay was not done,
7	Ophthalmology	Blue Sclerae, Strabismus, Ptosis, Coloboma, corneal abnormalities, cataract, optic nerve hypolplasia, Duane anomaly, pigmented retinopathy, Marcus Gunn phenomenon, nocturnal lagophthalmos, corneal abrasion and scarring.	Absent
8	Ears andHearing	Dysplastic ears ,Ear pits, Chronic otitis media, conductive hearing loss(40%),Inner ear malformation ,vestibular and aqueductal enlargement, Cochlear and semicircular aplasia	Prominent ears
9	Craniofacial	Cleft lip , cleft palate, high arced palate, feeding difficulties otitis media because of this, lower lippit.	Absent
10	Dental	Hypodontia, Malocclusion	Absent
11	Gastro Intestinal Tract	Congenital diaphragmatic hernia and eventration, neonatal cholestasis, Imperforate anus	Absent – Ultrasonography was normal
12	Genitourinary	Single fused kidneys, Renalectopia, PUJ obstruction, Hydronephrosi, duplication of collecting system Hypospadiasi, cryptorchidism,micropenis hypoplastic labia. -	Absent – Ultrasonography was normal
13	Musculoskeletal	Joint hypermobility, dislocation, scoliosis, kyphosis, hemivertebrae ,butterfly vertebrae and sagital clefts.	No abnormality
14	Immunological	Hypogammaglobulinemia, low IgA, ITP, hemolyticanemia, recurrent sinopulmonary infections.	Absent – but no history of recurrent infections.

Conclusion

Kabuki syndrome, being a multisystem malformation syndrome, needs a multidisciplinary team for optimum management and prevention of complications. Genetic confirmation of diagnosis should ideally be done in all clinically suspected cases. Genetic counseling for prenatal diagnosis and molecular testing should be offered for those with positive family history or with history ofprevious siblings being affected.

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