Limiting Cognitive Impairment in Genetic Disorders : Kabuki Syndrome – A Case Report

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Abstract

Kabuki Syndrome (KS) is a rare genetic disorder presenting in children with unique facial features, health issues, and developmental delays that are often mistaken for other syndromic diagnoses. Children with KS, in addition, develop short stature and growth delays later in life. Being a multisystem disorder, all findings may not be present at birth and may evolve, making it difficult for clinicians to diagnose clinically during the initial days of life. Growth retardation happens in the childhood for a child born with normal weight at birth. They go on to develop intellectual disability also later in life. It is known that delays in the language domain contribute to intellectual deficiency. Literature detailing the features of this disorder, especially in the socio-emotional and the language domain, and approaches to the same are deficient. The progress achieved, especially in the cognitive and language domain, is not sufficiently documented, probably due to the paucity of reported cases. In this article, we present a case description and language-based approach to development for limiting possible intellectual disability in a child with KS. A brief review of KS is also provided, highlighting its signs and symptoms.

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- Kabuki syndrome
- Cognitive impairment
- Polydactyl
- Everted nares
- REELS

Introduction

Kabuki Syndrome (KS) is a rare genetic disorder in children with unique facial features, health issues, and developmental delays that are often mistaken for other syndromic diagnoses. In addition, KS children develop short stature and growth delays [1]. It is a rare genetic disorder presenting in children, with unique facial features, health issues, and developmental delays that are often mistaken for other syndromic diagnoses. In addition, children with KS develop short stature and growth delays later in life. Being a multisystem disorder, not all findings may be present at birth and may evolve, making it difficult for clinicians to diagnose clinically during the initial days of life. Growth retardation occurs in childhood in children born with normal weight at birth. They continue to develop intellectual disabilities later in life. Delays in language are known to contribute to intellectual deficiency. Literature detailing the features of this disorder, especially in the socio-emotional and language domains, and approaches to the same are lacking. The possible progress that can be achieved, especially in the cognitive and language domains, has not been sufficiently documented, probably due to the paucity of reported cases. In this article, we present a case description and a language-based developmental approach to limit the possibility of intellectual disability in chil-

dren with KS. A brief review of KS has also been provided, highlighting its signs and symptoms.

Case Presentation

A 3.5-year-old girl was referred for speech and language evaluation following parental complaints of speech delay with a genetically proven diagnosis of KS. She had abnormal facies with wide eyes, bushy arched eyebrows, long eyelashes, depressed nasal bridge, broad nasal tip, cleft palate, large protruding ears, eversion of the lower lateral eyelids, sparse hair in the lateral one-third of the eyebrows, and Class I malocclusion. Many may also have a hairy body, and one-third may have polydactyly, as seen in Figure 1A-1D.

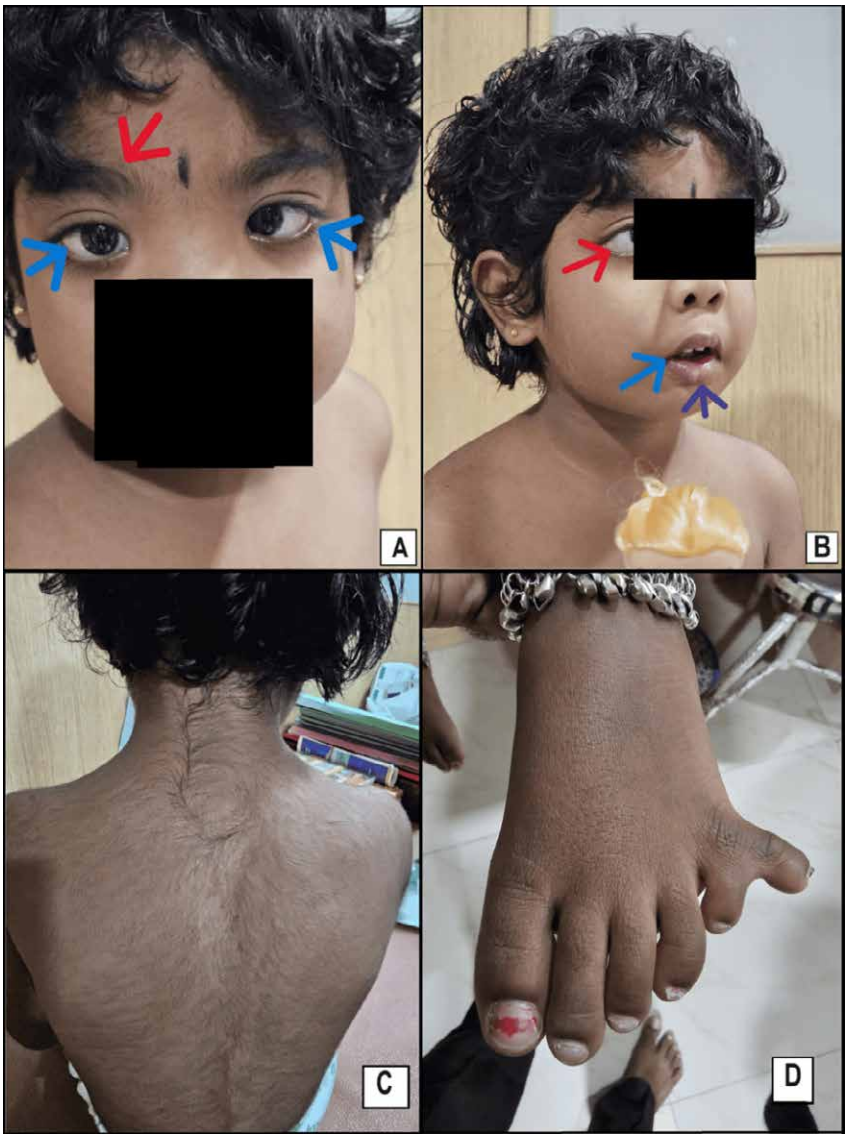

Figure 1: Dysmorphisms in Kabuki syndrome

(A) Long eyelashes with bushy arched eyebrows, depressed nose, and sparse hair on the lateral side of the eyebrow. (B) Wide eyes with everted eyelashes on the lateral side of the lower eyelids, lower lip pit, class one malocclusion, (C) hairy trunk, and (D) polydactyly. Red arrows- show the bushy eyebrows and lack of hair in the outer one-third of the eyebrows. Blue arrows- show the eversion of lateral one-third of eyelids, wide palpebral fissure, and long eyelashes. The purple arrow in Figure 1B shows the pit in the lower lip.

She weighed 10 kg (less than the third centile), and her height was 85 cm (less than the third centile), short of her age. She had a developmental delay with mild delays in gross and fine motor domains,

as she sat at 11 months, walked at 19 months, could only scribble, spill when she fed herself, and was unable to tell a single word, although she could understand and follow commands. She did not mingle with peers and was deficient in her preverbal skills. She was born with a birth weight of 2.9 Kg, developed difficulty in feeding during the postnatal period, and was on nasogastric feeding for a few days. During the initial years, the patient was hypotonic and developed recurrent chest infections. She underwent grommet insertion for recurrent middle ear infection. Her speech delay was initially attributed to middle ear pathology, which led to a delay in workup. Although she had an initial motor delay, she recovered well, and at presentation, she only had significant speech, language, and socio-emotional delays. Her full blood count was normal; the absence seizure diagnosed with the electroencephalogram (EEG) was treated medically; MRI was normal; and the echocardiogram(ECHO) showed an ostium secundum type of atrial septal defect and a small patent ductus arteriosus. Multisystem involvement and developmental delay led to suspicion of a genetic disorder, and whole exome sequencing was performed, which was reported as a KMT2D mutation. Wechsler's Preschool and Primary School (WPPS-IV) assessment showed that the Full-Scale Intelligence Quotient (FSIQ) score was within the low average range for average verbal comprehension, below average visual processing, low average working memory, fluid reasoning, and speed of processing. The child had limitations in intelligence, as expected, which is bound to increase with age, considering the language and fine-motor limitations. Her formal speech assessment showed that the child communicated mainly through the gestural mode. She followed a two-step command. A few misarticulation (dental, fricative, and sibilant) errors were noted, which were attributed to dental malocclusion (class I malocclusion). Simplification of clusters was also observed in addition to prosody and articulation errors, which became pronounced following speech therapy since the spontaneous verbal utterances increased in length and complexity, negatively impacting intelligibility. Abnormal oral resonance was also observed owing to the high-arched palate and oral motor hypotonia. The Communication Deal Developmental Checklist (CDDC) was administered, and its oro-motor assessment subscale showed oro-motor deficiency. The Auditory Brainstem Response test (ABR test) showed the 5th wave at 31.1/s repetition rate using click stimuli and rarefaction polarity until 50 dBnHL for the right ear and 45 dBnHL for the left ear. This indicated mild hearing loss in the right ear, and minimal hearing loss in the left ear. These findings could not explain the initial significant language and speech delays she exhibited. Immittance audiometry showed a B-type tympanogram bilaterally, with an ear canal volume of 0.4 cm3, and an acoustic reflex test showed the absence of ipsilateral reflex (left ear, no reflex). An otolaryngology consultation was performed, corrective measures were taken, and the child was given speech therapy along with developmental therapy for the affected domains.

The child attended therapy sessions and formal school. The speech therapist worked on low and high vowels with visual feedback, syllable repetition, articulatory placements, auditory feedback, and oro-motor interventions aimed at the muscles involved in cheek and tongue movements. Once the child began experimenting with sounds, the phonological and developmental errors that crept in were managed successfully. A plastic surgery review of the corrected cleft palate was performed because of the velopharyngeal insufficiency. Mild hypernasality and audible nasal turbulence due to the presence of obligatory velopharyngeal insufficiency were corrected by reducing the loudness, which in turn was thought to contribute to the velopharyngeal insufficiency. Developmental therapists, who work on multiple domains simultaneously by selecting targeted activities based on the level of development of each domain, work in tandem with the speech therapist to produce better expression of speech and language by the child. The CDDC noted improvement in the developmental domains of gross motor (34 months), fine motor (30 months), activities of daily living (34 months), receptive language (30 months), expressive (22 months), cognition (30 months), social (32 months), and emotional (32 months). The WPPS-IV showed a significant improvement in intelligence following the intervention. The Receptive Emergent Expressive Language Scale 4 (REELS-4) score improved receptive and expressive language as in *Table 1*.

Test	Pre-intervention Findings	Post intervention findings
WPPS		
FSIQ	low average; SS=89; PR= 23.	SS=99, PR= 47, CI: 93-105
verbal comprehension	average range (SS= 92; PR= 30)	average range (SS= 92, PR= 30)
visual processing	below average range (SS= 80; PR= 9)	low average range (SS= 85, PR= 16)
working memory	low average range (SS= 85; PR=16)	low average range (SS= 87, PR= 19)
fluid reasoning	low average range (SS= 88; PR= 21)	average range (SS= 94, PR= 34)
speed of processing	low average range (SS= 87; PR=19)	average range (SS= 94, PR= 34)
REELS-4		
RLA	18-20 months	28-32 months
ELA	11-12 months	16-18 months

Table 1: Improvement in Intelligence and Language abilities following interventions

WPPS-4-Wechsler Preschool and Primary Scale of Intelligence Fourth Edition; SS- standard score; PR- percentile; REELS-Receptive Expressive Emergent Language-4th edition; RLA_ Receptive language age; ELA- Expressive language age

Discussion

The phenotypic features of the index child, including everted outer eyelids, a high-arched palate, and frontal bossing, align with those documented in previous Kabuki syndrome (KS) case series [1]. Approximately one-third of patients have been reported to exhibit cleft lip and palate, while a high-arched palate is observed in nearly two-thirds of cases. KS remains an underdiagnosed condition among patients with cleft lip and palate [2]. In addition to typical cleft palates, preauricular tags and Tessier type 7 lateral clefts have been infrequently reported in KS [3]. In such instances, the use of a 3D-printed obturator device has been attempted to facilitate early direct breastfeeding, thereby promoting better weight gain and subsequent surgical cleft repair [4]. A notable delay in expressive language, as observed in this child, is a common characteristic of KS, as highlighted in previous studies that reported delayed speech and language acquisition [5,6]. Interventions addressing hypernasality and turbulence due to velopharyngeal insufficiency have improved speech intelligibility. However, these issues were ameliorated through loudness modification, which justifies such interventions. If postnasal turbulence remains untreated, it may lead to the development of posterior nasal fricatives, potentially resulting in reduced hearing, as noted in earlier research [7]. Children with KS often exhibit mild cognitive delays [8]. However, the child in this study demonstrated significantly lower intelligence, likely attributable to deficiencies in language acquisition. Hearing interventions, combined with speech therapy, developmental therapy, and correction of velopharyngeal turbulence, may have contributed to improved speech clarity and intelligence. This underscores the necessity of assessing each factor contributing to developmental delays individually and targeting interventions accordingly. Furthermore, the WPPS-IV assessment indicated that improvements in visuospatial skills were less pronounced compared to other domains. This finding aligns with recent research attributing such deficits to challenges in visual construction due to visual perceptual processing and visuospatial skills [9]. In the absence of effective treatments for this genetic disorder, management strategies focus on correcting manifestations and enhancing functional skills and quality of life for affected children [6]. Following three months of intervention, the previously nonverbal child began to imitate, vocalize, and follow two-step commands. The REELS-4 assessment six months later recorded a receptive language age of 28-32 months and an expressive language age of 16-18 months. This underscores the importance of managing these syndromic children in an integrated manner rather than addressing issues in isolation. Correcting hearing deficits, addressing speech

and language challenges associated with cleft palate, and addressing the inherent language delay of the syndrome, alongside activities that enhance fluid reasoning, verbal comprehension, working memory, and processing speed in a developmentally appropriate, domain-specific manner, can improve socioemotional and speech domains as well as the intelligence of these children, even in the presence of genetic compromise.

Endocrinology evaluation though initially unremarkable, should be done on follow up as they may develop endocrine abnormalities resulting in short stature as well as immune deficits, increased susceptibility to infection, and auto immune disorders mandating a immunology consultation.

Conclusions

In rare syndromic children with developmental delays, the number needed to treat, produce, and document any significant progress is often limited. Hence, the true potential for the development of such children is rarely recorded. This is true in KS, where intelligence is mildly affected. Addressing the hearing issues with the management of cleft palate, with post-surgical training and multi-domain targeted developmental therapy, helps the child to improve not only in speech and language but also in intelligence. Therefore, a detailed assessment of each domain of development and speech mechanism is needed, and efforts should be made to get maximum output from these children. Surgical correction of the cleft lip or palate produces cosmetic differences, but follow-up actions aimed at optimizing the skill acquisition produce a significant difference in functional ability. Improvement in intelligence and socioemotional domains is possible in genetic conditions like KS if training on skill attainment is well managed.

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