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Longitudinal Cognitive and Behavioral Presentation of Adult Female with Kabuki Syndrome

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Patient: Female, 27
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Objective: Rare disease
Background:





Kabuki syndrome (KS) is a rare disease with an estimated prevalence of approximately 1: 32 000. While the clinical presentation of KS is heterogeneous, manifestations may include: characteristic facial features, postnatal growth retardation, and skeletal abnormalities. With regards to the cognitive profile, most individuals with KS have an Intellectual Disability, but the magnitude of the impairment ranges from mild to severe, and verbal abilities are generally stronger than nonverbal abilities (i.e., visual spatial and visual perception abilities). Given the low incidence of KS, there is limited literature illustrating the longitudinal development of individuals with the condition. This report presents the cognitive and behavioral trajectory of an individual with KS.

Case Report: The patient in this case report was a 27-year-old female with KS. Her cognitive profile had remained in the average range over time, but consistent with the limited KS literature, her verbal abilities were significantly higher than her nonverbal abilities. Specifically, our patient demonstrated significant deficits in visual motor and visual perceptual skills. With regards to her core language skills, her expressive skills were average, yet her receptive skills were below average. Throughout the majority of her schooling, her academic achievement skills were mildly delayed. Notably, her performance on cognitive and academic assessments remained stable over time. During young adulthood, she developed significant internalizing symptoms, particularly depressive symptoms.

Conclusions: This is the first case report to illustrate the presentation of an individual with KS from toddlerhood through young adulthood. The patient's clinical presentation across time was relatively consistent with the KS literature to date; notable patterns of language, motor, cognitive and behavioral deficits illustrate the considerable heterogeneity that exists within the syndrome. This case report, particularly, illustrates the persistence of the cognitive profile over time and also the co-occurring psychiatric symptoms that might emerge.

MeSH Keywords: Case Reports • Cognition • Rare Diseases

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Background

Kabuki syndrome (KS) is a rare disease occurring with an estimated prevalence of approximately 1: 32 000. Kuroki et al. [1] and Niikawa et al. [2] initially identified the syndrome as Niikawa Kuroki Syndrome in the early 1980s; however, because the characteristic facial features resembled the actors of Japanese Kabuki theatre, the syndrome was also called Kabuki make-up syndrome. In the late 1990s, Kawame et al. [3] recommended removing the term “make-up” and relabeled the syndrome Kabuki syndrome.

KS is a poorly understood syndrome and is highly heterogeneous in its clinical presentation [4–8]. To date, there are no consensus diagnostic criteria for KS. The major clinical manifestations of KS include: 1) characteristic facial features such as elongated palpebral fissures with eversion of the lateral third of the lower eyelid, broad and arched eyebrows, a short columella, and large, cupped ears; 2) intellectual disability; 3) postnatal growth retardation; 4) skeletal and dermatoglyphic anomalies, including spine column abnormalities such as scoliosis, brachydactyly V, brachymesophalangy, and clinodactyly of fifth digits, as well as a persistence of fingertip pads [5,6].

Similar to the complexities and heterogeneity of the clinical presentation of individuals with KS, the specific genetic underpinnings of the syndrome are also multifaceted [9]. Presently, the diagnosis of KS is determined by clinical findings, but causal mutations in the lysine specific methyltransferase gene, 2D (KMT2D), located on chromosome 12q13.12 and lysine specific demethylase gene, 6A (KDM6A), on chromosome Xp11.3 are estimated to account for approximately 60% of patients and 5% of patients, respectively [10]. KS with a confirmed pathogenic variant in KMT2D is referred to as subtype 1, and with KDM6A, subtype 2. Mutations in KMT2D that can cause KS can either occur *de novo* or can be inherited in an autosomal-dominant manner [11]. Mutations in KDM6A are either X-linked or *de novo* mutations [12].

To date, the research on the cognitive profiles of individuals with KS has largely been limited to the use of global measures of general intellectual functioning (i.e., broad intelligence tests), as opposed to more granular or precise measures of neuropsychological function. Therefore, understanding of the nuances in the cognitive profile in individuals with KS is limited. Additionally, the available literature utilizes cross-sectional data or a review of (often limited) records. Nonetheless, the work to date does suggest that the heterogeneity of the condition extends beyond the clinical and genetic presentation to the cognitive presentation as well. Most individuals with KS have an Intellectual Disability, but the magnitude of the impairment ranges from mild to severe [4,7,8]. Vaux and colleagues [4], for example, reported on a sample of 7 patients with KS. Full Scale

IQ (FSIQ) scores, using a variety of available assessments scales, ranged from 32 to 89, with an average score of 62 (population means of the assessment measures are 100 with a standard deviation (SD) of 15). Caciolo et al. [8] recently found that in a sample of 17 individuals with KS, using a range of IQ assessments, 7 individuals (41%) obtained a score greater than 2 SD below the mean, 4 individuals (24%) received a score between 1 and 2 SD below the mean, and 6 individuals (35%) obtained a score in the average range. Lehman and colleagues [7] also reported a similar range in a larger sample (n=31). Mean Full Scale IQ, using the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV), was 57, with a range of 40 to 103 (again, the population mean of the assessment measure is 100 with a SD of 15). Furthermore, individuals with KS often have stronger performance in verbal abilities (Verbal IQ) than in non-verbal abilities (Performance IQ) [7,13]; however, this can vary based on the specific type of mutation in the KMT2D gene. For example, Lehman and colleagues [7] reported that Full Scale IQ and Verbal Comprehension Index (VCI) scores were 10 points lower in a sample of 21 KS patients with a truncating mutation, compared to individuals with other types of mutations.

The few reports available that utilized more detailed cognitive assessment batteries have illustrated specific deficits in visuo-spatial and visuoconstructional abilities, spatial memory and spatial reasoning, with relative strengths in verbal reasoning skills [14]. Individuals with KS also have marked impairments in motor skills [13]. Recently, Caciolo et al. [8] reported the visual motor integration skills in a sample of 17 individuals with KS. They found that regarding visual motor integration, more than half of the participants (57%) obtained a score $\leq 5^{\text{th}}$ percentile both in visual-motor integration and in the visual perception subtest. In the motor control subtest, the percentage of individuals with a score $\leq 5^{\text{th}}$ percentile was 71%. With regards to the behavioral presentation, individuals with KS are highly socially motivated and engaging, but they can have impairments in sustained attention and inhibition [8,13]. Using the Child Behavior Checklist (CBCL; 15), Caciolo et al. [8] found some individual variation in their sample, but as a whole, scores were within the normal limits for internalizing and externalizing problems.

The language profile of individuals with KS is varied, consistent with the multisystem nature of the disorder. For example, in a sample of 16 individuals, Morgan et al. [16] reported that dysarthria was common, and oromotor function was also generally impaired. Both receptive and expressive language skills were reduced in many of the individuals, but there was not a specific profile of language deficits. Similarly, in a review of records of patients with KS, Vaux and colleagues [4] reported that in the 7 patients with language testing, receptive and expressive language skills were impaired, as a whole. However, the range of scores was wide, from significant impairment to

below average. Most recently, Caciolo and colleagues [8] reported that in the sample of 17 individuals with KS, receptive language was impaired, as assessed by a picture vocabulary test [17].

Likely given the low incidence of KS, to our knowledge, there has not been any work longitudinally in individuals with the disorder; there have not been any papers that have illustrated the developmental trajectory of individuals with KS, particularly into adulthood. Given increasing awareness of KS and the advancement of genetic testing, more individuals with KS will likely be identified and begin aging into adulthood. As a result, this case report is of significant value to clinicians working with individuals with KS, and to clinicians working in other rare diseases that have a cognitive component. The paper comprehensively illustrates the cognitive and behavioral profile, over time, of a young adult with KS, and will therefore provide useful information towards the possible trajectory of individuals with KS.

Case Report

Our patient was a 27-year-old white female who was diagnosed with KS at 8 years of age. The initial diagnosis was made based on clinical presentation, and it was confirmed based on genetic testing at 22 years of age (*de novo* substitution mutation in KMT2D).

Early history

Our patient was born full-term, with no concerns prenatally or immediately following her birth. She was born with a cleft of the soft and hard palate that was surgically repaired at about 1 year of age. Medical history was also notable for reflux and difficulties with feeding (e.g., frequent choking, selective eating), chronic otitis media, strabismus, and umbilical hernia. Her parents became concerned about her development in the first year of life, as she was not meeting developmental motor milestones by the expected ages. For example, she did not walk independently until about 18 months of age. Language development was within normal limits (first words at 12 months of age and phrase speech at about 18 months of age). Both hearing and vision were within normal limits based on parental report and review of available general practitioner medical examination records.

Qualitative behavioral presentation and parental concerns

Her parents reported that during her childhood, their primary concerns were frequent infections as well as motor delays. She was described as hypotonic, and she had significant difficulty with balance and running. Her walking gait was unsteady and appeared uncoordinated. Additionally, her fine motor skills

were quite impaired, so any task involving graphomotor skills (i.e., handwriting) was difficult for her. Furthermore, her articulation was poor; unfamiliar individuals had a hard time understanding her speech. She also presented with anxiety as a toddler and preschool-aged child. She was anxious separating from familiar adults, particularly her parents. Despite these delays and difficulties, she was compliant and cooperative with adult directions. She flexibly adapted to new situations and changing circumstances. She was also highly socially motivated. She enjoyed interacting and playing with others, and as she developed, she enjoyed engaging in social conversation about a range of topics, with both peers and adults.

Cognitive and behavioral assessments

The following was taken from a review of available records. Please note that most assessments were repeated over time (e.g., Wechsler Scales); however, for visual motor assessments, the construct was assessed over time using different scales (e.g., Beery Buktenica Test of Visual Motor Integration (one administration) and Test of Visual Motor Skills (4 successive administrations). Given that both are published, standardized scales and well regarded in the field, for this purpose (a clinical case report of cognitive and behavioral functioning), we compared results across these 2 measures, as is consistent with the approach used by others (e.g., [4,8]).

Our patient's development was first formally assessed at 13 months of age. She received the Bayley Scales of Infant Development. Her overall development fell in the Below Average range (Mental Development Index Standard Score of 80). She again received the Bayley Scales 1 year later, and her Mental Development Index score remained stable.

Between 4 and 17 years of age, she was administered a series of Wechsler Intelligence Tests in order to assess her cognitive abilities (Table 1). Her overall abilities consistently remained in the Below Average range, but she evidenced a notable cognitive profile; her verbal abilities were significantly stronger than her nonverbal abilities, which is consistent with prior findings in KS [13] and particularly with individuals with a substitution mutation such as was found to be her case [7]. We were able to analyze her cognitive abilities further beginning at age 12 years with the transition to the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV) when verbal and nonverbal abilities are divided into 2 index scores each. With this model, the patient's verbal reasoning abilities (Verbal Comprehension) were generally in the average to just below average range, and her verbal working memory abilities were average. Her nonverbal reasoning (Perceptual Reasoning) abilities were in the borderline impaired range, except for 1 administration at 12 years of age, when they measured in the average range. Her speed of processing ranged from below average to impaired.

Table 1. Cognitive (intelligence) assessments.

Age (years: months)	Assessment	Verbal IQ*	Performance/ nonverbal IQ*	Full scale IQ*
4: 5	Wechsler Preschool and Primary Scale of Intelligence	92	71	80
5: 9	Wechsler Preschool and Primary Scale of Intelligence	106	70	86
8: 3	Wechsler Intelligence Scale for Children-III	100	79	89
10: 10	Wechsler Intelligence Scale for Children-III	100	79	89
11: 8	Wechsler Intelligence Scale for Children-III	94	62	76
12: 7	Wechsler Intelligence Scale for Children-IV	VCI 106 WMI 91	PRI 106 PSI 85	99
14: 7	Wechsler Intelligence Scale for Children-IV	VCI 95 WMI 88	PRI 77 PSI 65	77
17: 5	Wechsler Adult Intelligence Scale	VCI 83 WMI 92	PRI 75 PSI 74	76

* Standard Scores, $M=100$, $SD=15$ for the published intelligence assessments. VCI – Verbal Comprehension Index; WMI – Working Memory Index; PRI – Perceptual Reasoning Index; PSI – Processing Speed Index.

Table 2. Academic achievement testing: Wechsler individual achievement test (WIAT).

Age (years: months)	10: 10	11: 8	12: 8	14: 4	15: 4
	WIAT*	WIAT*	WIAT-II*	WIAT-II*	WIAT-II*
Mathematical reasoning	47	39		10	30
Numerical operation	7	6		34	16
Pseudoword decoding				7	14
Reading comprehension	30	27		50	47
Spelling	27	19		23	21
Word reading				5	3
Mathematics composite	21	18	8		
Oral language composite			12		
Written language composite			18		
Writing composite		25			
Written expression	50	66			
Basic reading	7	10			
Reading composite	9	9	6		

* Scores reported in percentile ranks. All available data is reported. At some time points, only portions of the assessments were administered. Only percentile ranks were reported, and since percentile ranks are less specific than standard scores, the conversion to standard scores is not possible.

Based on clinician report, her poor non-verbal abilities were likely magnified by a deficiency in motor skills (motor output was required for many of the non-verbal tasks administered).

Academic achievement testing was conducted annually from when the patient was 10 to 15 years of age using the Wechsler

Individual Achievement Test. In general, her academic achievement fell in the low average to average range (Table 2). Her performance was generally stronger in mathematics than reading. While her Mathematical Reasoning skills, in relation to her peers, decreased over time, her reading comprehension percentile improved, in relation to her peers. There is no

Table 3. Language assessment: Clinical evaluation of language fundamentals (CELF).

Age (years: months)		Receptive language		Expressive language		Total language	
		SS*	%	SS*	%	SS*	%
9: 10	CELF 3	80	9 th	112	79 th	95	37 th
11: 8	CELF 3		14 th		75 th		39 th
17: 5	CELF 4			99	47 th		

* Standard Scores, $M=100$, $SD=15$. All available data is reported. At age 11: 8, only percentile ranks were reported, and since percentile ranks are less specific than standard scores, the conversion to standard scores is not possible. At age 17: 5, only the Expressive Language domain was administered.

Table 4. Visual-motor testing.

Age (years: months)	Assessment	Standard Score*	Percentile
5: 9	Developmental Test of Visual-Motor Integration 4 th edition	75	5 th
12: 5	Test of Visual Motor Skills	67	1 st
14: 4	Test of Visual Motor Skills	73	4 th
15: 5	Test of Visual Motor Skills – Revised	74	4 th
16: 5	Test of Visual Motor Skills – Revised	75	5 th

* $M=100$, $SD=15$.

Table 5. Visual-perceptual testing.

Age (years: months)	Assessment	Standard Score*	Percentile
12: 5	Test of Visual Perceptual Skills (Non-motor) – Revised	55	1 st
14: 4	Test of Visual Perceptual Skills (Non-motor) – Revised	56	1 st
15: 5	Test of Visual Perceptual Skills (Non-motor) – Revised	81	10 th

* $M=100$, $SD=15$.

known literature regarding academic achievement skills in KS with which to compare her skills. However, it is noteworthy that her achievement testing revealed an inconsistent pattern of achievement over time, which is in contrast to her cognitive testing that showed a stable pattern over time.

Our patient's speech and language development were also inconsistent, displaying a striking pattern of strengths and weaknesses. She had significant difficulties with articulation, as demonstrated by her score in the 4th percentile on the Goldman-Fristoe-2 Test of Articulation. This is consistent with the literature on KS [4,16,18], and her difficulties were likely furthered by her cleft palate. Her performance on the Clinical Evaluation of Language Fundamentals (CELF) suggested solidly average core language scores over time, although her expressive language

abilities were significantly stronger than her receptive language abilities (Table 3). Our patient also expressed difficulty with pragmatic aspects of language, such as defining semantic word relationships and making inferences. The literature suggests that variability in language skills is common among individuals with KS, although the specific strengths and weaknesses are not well characterized [4,16].

The patient's visual motor skills remained quite weak throughout her development. Her visual motor skills were first tested at age 5 years. At the time of that evaluation, she scored between the 1st and 5th percentile on the Bender Gestalt Test and Developmental Test of Visual-Motor Integration-4th Edition. Testing revealed a deficiency in visual-motor integration and fine-motor dexterity. Visual motor skills testing in subsequent

years revealed a persistent pattern of difficulties in this area (Table 4). Her visual-motor integration deficits were consistent with the profile of other individuals with KS [8,13].

Additionally, our patient's visual perceptual skills were tested at multiple intervals throughout her later school-aged period, specifically at age 12, 14, and 15 years. Similar to her performance on visual-motor skills testing, she scored below average on the Test of Visual Perceptual Skills (non-motor) – Revised across time, although there was a notable improvement in later adolescence, between age 14 and 15 years (Table 5), again consistent with available literature [8].

Social/emotional presentation

Our patient's teachers and clinicians described her as delightful and eager to please. She worked diligently on tasks with a high tolerance for frustration. She was well-liked by peers, highly socially motivated, and enjoyed interacting with others. However, her overall social development was immature for her age; she presented as a much younger child in terms of her interests and style of interacting. During her childhood, she had many friends, although they were typically chronologically younger than she was. Her mother described that as a toddler and preschool-aged child, her daughter was anxious upon separation from her parents. Her mother attributed this to her medical needs and poor articulation at that time, which made it difficult for others to understand her speech. Once she entered formal schooling, her anxiety diminished. She was described as a very happy, easy going, and charismatic child and adolescent.

Following completion of high school, our patient developed more pronounced internalizing symptoms, particularly symptoms of depression as well as increased anxiety. She became quite socially isolated and withdrawn. She seemed to take less pleasure in activities and needed more encouragement to engage with others. She had no expressed interest in romantic relationships. She developed pronounced general worries about her wellbeing, but no specific fears. She enjoyed spending time with one older adult outside of her family, but otherwise, she spent much of her time alone. Given her deficits, at the time of this writing, she was not able to secure employment, despite her efforts and interest in holding a job.

Discussion

Although the literature on KS is in its earliest stages, it is clear the disorder is quite complex. There is significant heterogeneity between individuals at both the genetic and phenotypic levels, to the extent that there are no consensus clinical diagnostic criteria.

As a case example, our patient had a highly varied cognitive profile; her verbal abilities were generally intact, with the exception of articulation, yet her visual perception and visual spatial skills were poor. Additionally, her gross and fine motor skills were quite weak. Importantly, this pattern remained consistent over time. Despite this varied cognitive profile and clear areas of cognitive vulnerabilities, as a child, our patient was socially motivated, affable, and compliant.

Although our patient was content and eager to engage with others as a younger child, as she transitioned into her later adolescence and young adulthood, more significant mood symptoms emerged. These symptoms might be related to KS, but more likely, the mood symptoms were associated with the transition to adulthood itself. For many individuals with mild-moderate intellectual disabilities, the transition to adulthood is quite challenging. Accessing health care can become difficult, as individuals switch from pediatric to general medical providers, and formal schooling ends, leading to a decrease in supports and peer contact. Adult services tend to be more fragmented with higher variability in both quality and availability [19,20]. Our patient's situation was consistent with this pattern; she no longer received any special education services or vocational support and quickly lost her peer group as she finished high school. Yet, given her disability, she was not able to hold full-time employment. It was likely this isolation, reduced structure, and feelings of uncertainty about her future, led to symptoms of anxiety and depression.

Importantly, this is the first case report that presented an individual with KS over time, from young childhood into adulthood, outlining the cognitive and behavioral profile across development, not just as a cross-sectional view. The report also critically highlights the needs of young adults with rare diseases and intellectual impairments into adulthood, when often access to service, support, and even appropriate peer groups diminish dramatically, potentially contributing to comorbid psychiatric symptoms.

Although this report is impactful given it is the first report to describe an individual with KS across the lifespan, the scope of this presentation focused on the individual's cognitive and behavioral presentation. Individuals with KS also have comorbid medical conditions and complications, particularly in young childhood. Further work should expand on multiple aspects of individuals with KS from an interdisciplinary perspective.

Conclusions

This case report presented here is novel and impactful, most notably because of the depth and longitudinal nature of the cognitive data. From our comprehensive literature review, the current case report is the first to illustrate the presentation

of an individual with KS from toddlerhood through young adulthood. KS is a rare disorder, and as described, both the clinical and genetic presentations of KS are quite heterogeneous. As such, this case presentation of detailed longitudinal data has the potential to increase awareness of the disorder. Additionally, it broadens our understanding of the developmental trajectory of KS, which is significant, as that will offer families and providers a clearer understanding of prognosis

and the ability to better anticipate needs of individuals with KS as they age, which can in turn, lead to stronger and more appropriate service provision.

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