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INVESTIGATING KABUKI SYNDROME: CLINICAL AND GENETIC PROFILES REVEALED IN A CASE SERIES STUDY

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ABSTRACT

The Kabuki syndrome (KS) represents a rare congenital condition characterized by a distinctive amalgamation of craniofacial anomalies, developmental irregularities, and intellectual impairments. This investigative pursuit aims to conduct an exhaustive exploration of KS via a detailed case series analysis, with a specific focus on elucidating its clinical manifestations and probing its genetic foundations. A cohort comprising nine KS patients was meticulously identified through a retrospective review of medical records spanning from 1996 to 2022. These patients underwent a comprehensive array of clinical assessments, radiological examinations, neuropsychological evaluations, and targeted genetic analyses, particularly centered on the KMT2D and KDM6A genes. The median age of diagnosis, approximately 4.7 years, demonstrated a male-to-female ratio of 6:3. Prominently evident among the clinical features were distinctive facial dysmorphisms, including arched eyebrows and elongated eyelashes, alongside ear anomalies, fingertip pads, nasolabial irregularities, and oral malformations. Ophthalmological and otological manifestations were notably discernible, along with a spectrum of cardiovascular, gastrointestinal, and endocrine abnormalities. The prevalence of neuropsychological disorders underscored the complex nature of cognitive and behavioral challenges experienced by KS patients. Consistent with our clinical observations, genetic analyses affirmed the involvement of variants in the KMT2D and KDM6A genes in the pathogenesis of KS. In conclusion, this investigation unequivocally underscores the paramount significance of accurate diagnosis, the adoption of a multidisciplinary care paradigm, and the implementation of tailored interventions for individuals afflicted by KS. Additionally, it highlights the imperative for sustained research endeavors aimed at unraveling the genetic intricacies and molecular mechanisms underpinning this enigmatic syndrome.

1. Introduction

Kabuki syndrome (KS), recognized by its OMIM identifiers #147920 and #300867, is a rare congenital syndrome first described in Japan by Niikawa et al. (1) and Kuroki et al. (2) in 1981. This complex condition is characterized by a combination of multiple congenital anomalies alongside intellectual disability. While the precise global prevalence remains uncertain, an estimated incidence of 1 in 32,000 has been reported in Japan (3).

The prominent phenotypic features include distinctive facial dysmorphisms such as elongated palpebral fissures, eversion of the lateral third of the lower eyelid, arched and broad eyebrows, a shortened columella with a depressed nasal tip, and notable ear abnormalities like enlarged, prominent, or cupped ears. Additional defining characteristics encompass postnatal growth restriction, persistence of fetal fingertip pads, skeletal anomalies such as brachydactyly type V, brachymesophalangy, and spinal irregularities, often accompanied by mild-to-moderate intellectual disability (4,5).

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Among the varied clinical presentations, notable manifestations include ophthalmologic anomalies like ptosis, strabismus, and blue sclerae (6,7), along with auditory impairments (8). Craniofacial and dental abnormalities, including cleft lip and/or palate, hypodontia, and widely spaced teeth, are also observed. Cardiovascular complications may manifest as septal defects, bicuspid aortic valve, mitral valve anomalies, and hypertrophic cardiomyopathy (9). Renal and endocrinologic anomalies contribute to kidney position and ascent abnormalities and are associated with short stature, obesity, and isolated premature thelarche in females (10). Immune dysfunction is evident through recurrent infections, hypogammaglobulinemia, and IgA deficiency (11), while neurologic features include hypotonia and seizures (12).

The genetic basis of Kabuki syndrome involves variants in the KMT2D and KDM6A genes (13). Ng et al. first highlighted the role of heterozygous mutations in KMT2D in 2010. The KMT2D gene (located at 12q13.12) is a lysine (K)-specific methyltransferase 2 family member crucial for regulating gene expression during embryogenesis and development. Additionally, some patients exhibit mutations or deletions in KDM6A (Xp11.3, OMIM *300128), a component of the same transcription complex as KMT2D. While most pathogenic variants arise from de novo mutations, autosomal dominant inheritance has also been documented (14-16).

Niikawa et al. (1, 2) initially outlined five primary hallmark characteristics of Kabuki syndrome: postnatal growth deficiency, distinct facial dysmorphisms, skeletal irregularities, persistent fingertip pads, and intellectual disability. Subsequently, an international consortium of experts established consensus diagnostic criteria for Kabuki syndrome in 2018 (4).

In this study, we conducted a comprehensive evaluation of patients with Kabuki syndrome using medical records from Policlinico Rodolico Hospital. Our approach involved a detailed analysis of clinical, genetic, and diagnostic data to fully characterize individuals affected by Kabuki syndrome within this medical setting. This thorough investigation allowed us to compare our findings with existing scientific literature, aiming to identify consistencies, variations, and unique patterns in the clinical presentation, genetic etiology, and associated factors of Kabuki syndrome.

2. Material and methods

To achieve a comprehensive understanding of Kabuki syndrome within our patient cohort, we conducted a retrospective analysis utilizing the medical index patient database of Policlinico Rodolico Hospital. The dataset includes records of patients diagnosed with Kabuki syndrome between 1996 and 2022, with clinical oversight provided by a specialized Pediatric Unit. Ethical standards were strictly adhered to, with written informed consent obtained from the parents of all participating individuals.

In this retrospective analysis, we documented various facets of data related to craniofacial dysmorphisms, neurodevelopmental patterns, and systemic involvements. The study protocol involved systematic categorization and thorough scrutiny of anomalies within each domain.

Our study cohort comprised nine patients, including six males and three females, each undergoing comprehensive evaluations to understand their health profiles. Evaluations included auxological assessments, neurological evaluations, ophthalmological examinations, ear-nose-throat (ENT) analyses, and rheumatologic appraisals.

Laboratory investigations covered thyroid profiling, screening for autoimmune thyroiditis-related autoantibodies, celiac disease screening, and serum immunoglobulin level quantification.

Radiological investigations included spine X-rays, magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), computed tomography (CT) scans, echocardiocolor-Doppler studies, and abdominal ultrasound examinations.

Neurocognitive development was assessed using the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) and age-weighted IQ calculations, supplemented by Peabody tests and Leiter-R assessment scales.

Molecular analysis involved DNA extraction from peripheral blood lymphocytes, focusing on mutation analysis of the KMT2D (MLL2) and KDM6A genes. Amplification and sequencing were performed using the Illumina Miseq platform, with variants validated through Sanger sequencing in the proband.

The research data supporting our study outcomes are available upon request to the corresponding authors, respecting privacy and ethical considerations that preclude public access to the dataset.

3. Results

Among Upon reviewing the cohort of 9 patients enrolled in this investigation, comprising 6 males and 3 females, the subsequent findings have been ascertained. The median age of Kabuki syndrome (KS) diagnosis within our patient group was approximately 4.7 years. Subsequently, genetic analyses targeting the KMT2D and KDM6A genes, known for their association with Kabuki syndrome, were conducted among our patient cohort. Among these individuals, 5 patients displayed heterozygous mutations in the KMT2D gene, while two patients exhibited homozygosity for KMT2D and KDM6A genes respectively.

Due to the complex nature of the syndrome's manifestations and their diverse implications, the outcomes of our case study will be categorized based on phenotypic and clinical-instrumental dimensions. The primary clinical characteristics of the patients are concisely summarized in Tables 1, 2, and 3 for comprehensive elucidation.

Phenotypic Profile and Observations Upon meticulous examination of phenotypic attributes, it is evident that all patients under investigation exhibit distinctive characteristics synonymous with Kabuki syndrome (KS). These include elongated palpebral fissures with lateral third eversion, which were universally present (100%). Furthermore, arched eyebrows displaying sparse or notched lateral thirds (100%), abundant and lengthy eyelashes (100%), hypertelorism (78%), and ptosis (22%) were noted. Notably, 89% of patients displayed large and cupped ears, 78% showed a flat or trapezoid philtrum, and a nasal configuration characterized by a depressed nasal tip and hypoplastic columella was observed in 78% of cases. Additionally, micrognathia was apparent in 67% of subjects, along with fingertip pads, which were universally evident (100%).

In one case within the study group, a patient initially presented with a phenotype resembling Noonan syndrome but progressively developed more distinct Kabuki syndrome features with age. In all cases, a notable rotation of the ear axis was evident. Brachydactyly and/or clinodactyly of the fifth digit were observed in 33% of cases, while an overlapping second toe over the third toe was documented in 11% of subjects.

Furthermore, 75% of individuals exhibited oral cavity anomalies, including a high-arched palate (44%), malocclusion (11%), early eruption of incisors (11%), and pointed incisors with diastema (11%). A comprehensive summary of the collected data is presented in Table 1.

Clinical and Instrumental Findings Ophthalmological assessments revealed ocular abnormalities in 55% of the evaluated patients. These ocular anomalies included ptosis (2/5), keratoconus, decreased visual acuity due to vascular anomalies, anomalies of the ocular fundus with papillary pigmentation, strabismus, and coloboma concomitant with microcornea.

Otological manifestations were identified in 22% of cases, characterized by recurrent bilateral purulent otitis leading to chronic otitis and mild conductive hearing loss, as confirmed by audiometric and impedance measurements.

Cardiovascular evaluations highlighted the presence of cardiac anomalies in 44% of patients. Valvular dysplasias affecting the tricuspid, pulmonary, mitral, and aortic valves were the most commonly encountered abnormalities, often resulting in valve insufficiency. Additionally, atrial septal defects contributing to left-to-right shunts, right atrial dilation, and ventricular septal defects were observed.

Vascular imaging studies, including angio-CT and angio-MRI, revealed vascular anomalies in 22% of cases. Specifically, one patient exhibited internal carotid and Willis circle anomalies, while another presented with a single umbilical artery. Notably, both cases were accompanied by concurrent cardiac anomalies.

Genitourinary exploration via abdominal ultrasound detected anomalies in 66% of cases, including cryptorchidism (2/6), renal agenesis (1/6), fused kidney with three renal arteries (1/6), bifid urethra (1/6), and pyelectasis (1/6).

Gastroenterological anomalies manifested in 33% of patients, characterized by anterior anus, umbilical hernia, and moderate esophagitis with cardias incompetence.

Skeletal and osteoarticular abnormalities were identified in 89% of cases, including joint laxity (7/8), flat foot (2/8), congenital hip dysplasia (2/8), severe osteoporosis with a Z score < -4.5 (1/8), ankle valgus (1/8), pectus excavatum, vertebral anomalies leading to loss of physiological lordosis, and a dysmorphic coccyx.

Neurological evaluations revealed clinical and instrumental abnormalities (89%). Clinical assessments revealed hypotonia in five patients, with one patient experiencing multiple episodes of lower limb motor neuropathy and autonomic neuropathy resulting in sphincter control loss. Brain MRI examinations indicated anomalies in seven out of nine patients, revealing a dilated fourth ventricle (43%), symmetric ventricular dilation, cerebellar vermis hypoplasia, dysmorphic corpus callosum, and left-sided temporal-polar cysts.

Intellectual disability, defined as an intellectual quotient (IQ) < 70, was documented in 78% of cases through specialized assessments. Mild (IQ 50-69) and moderate (IQ 35-49) intellectual disabilities were observed in 43% and 14% of cases, respectively. In the remaining patients, cognitive deficits were clinically observed without formal documentation. Furthermore, one out of nine patients exhibited aggressive behavior.

Auxological evaluations revealed postnatal growth deficiency in 67% of patients, resulting in a harmonious low stature with heights falling below -2 standard deviations (SD) in 44% of cases. Endocrinological and metabolic investigations revealed obesity in 67% of cases, isolated premature thelarche in 11% of cases, hypothyroidism in 22% of cases, and growth hormone deficiency in 11% of cases.

Immunological analyses identified alterations in lymphocyte subclasses indicative of autoimmune lymphoproliferative syndrome (ALPS), combined IgG, IgM, and IgA deficiency compatible with common variable immunodeficiency (CVID), and a polymorphic presentation characterized by polyserositis, valve insufficiency, peripheral neuropathy, and malar rash reminiscent of a lupus-like immunological disorder, which unfortunately contributed to the demise of the affected patient. Additionally, several patients (5/9) experienced recurrent infectious episodes, predominantly affecting the respiratory tract, with MRI results revealing persistent mastoid region hyperintensity due to chronic inflammatory processes.

Oncological disorders were documented in 22% of cases, including stage IV neuroblastoma (1/2) and hepatoblastoma (1/2).

Lastly, a single patient presented with a pulmonary anomaly characterized by right lung hypoplasia with lobar aplasia.

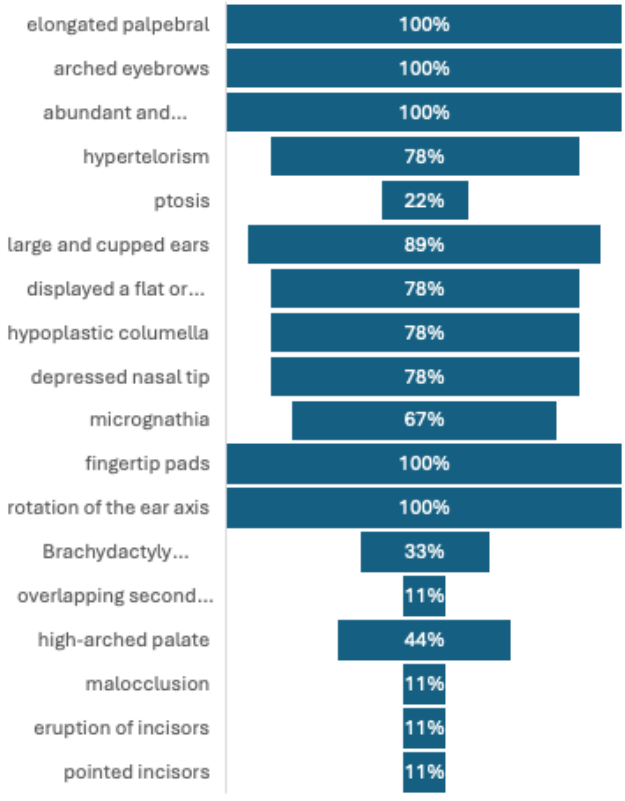

Figure 1. Kabuki Syndrome phenotypes in our cohort

4. Discussion

Kabuki syndrome, also referred to as Kabuki make-up syndrome or Niikawa-Kuroki syndrome, is an uncommon congenital genetic condition characterized by a distinct combination of unique craniofacial dysmorphisms, developmental irregularities affecting multiple organ systems, and varying levels of cognitive impairment (1, 2). This investigation aims to provide a comprehensive elucidation of the clinical and genetic aspects of Kabuki syndrome (KS) based on a cohort of nine patients.

The cohort presented in this study comprises nine individuals who were referred by their primary pediatricians due to the identification of facial dysmorphisms and/or systemic manifestations suggestive of syndromic disorders. Therefore, phenotypic attributes assume significant importance as diagnostic criteria for Niikawa-Kuroki syndrome.

Among our series of cases, all patients exhibited the characteristic facial dysmorphisms associated with Kabuki syndrome (KS), including elongated palpebral fissures with lateral third eversion of the lower eyelid, arched and broad eyebrows with sparse lateral third or notches, short columella with a depressed nasal tip, and large or cupped ears. However, one patient initially presented with atypical clinical features, including neck pterygium, short stature, low-set ears, and pectus excavatum, which initially raised suspicions of Noonan syndrome. Subsequent genetic testing, however, ruled out this diagnosis. To date, no documented association exists between Kabuki syndrome and neck pterygium, although a unique connection between the syndrome and a form of congenital lymphatic dysplasia has been reported in a singular case (17). The authors of that study emphasize the importance of vigilance regarding any indications of lymphatic involvement in Kabuki syndrome patients, as it may signify an underreported aspect of the syndrome.

Notably, the phenotype of the aforementioned patient evolved over time, with the emergence of cutaneous venous reticulations and visual impairment, initially suggesting Wyburn-Mason syndrome. However, fundus examination excluded the characteristic arteriovenous malformations associated with Wyburn-Mason syndrome. Eye-related features, such as slanted palpebral fissures, arched eyebrows, and ear anomalies, became more pronounced by the age of eight, prompting suspicion of KS, which was subsequently confirmed through the identification of a KMT2D gene mutation.

This case presentation highlights the pivotal role of differential diagnosis in cases where the complete spectrum of typical KS manifestations is not immediately evident. Therefore, ongoing clinical assessments, the search for specific structural anomalies, and the exclusion of conditions capable of mimicking or obscuring the Kabuki phenotype are essential.

The incidence of fingertip pads, observed in 100% of our cases, exceeds the percentages reported in existing literature reviews (93% and 85%) (1, 13). As for oral cavity anomalies, six of our patients exhibited anomalies such as a high-arched palate and dental irregularities, particularly affecting tooth shape and size. Several studies have affirmed the role of KMT2D and KDM6A in tooth development (8, 18-19). The occurrence of brachydactyly and clinodactyly of the V finger was relatively low (33%) compared to the 92%-100% reported in other studies (3, 13).

The prevalence of cardiac anomalies is estimated to be within the range of 40% to 50% among reported cases in the literature (5). Yoon et al., in their work, have suggested an increased incidence of left-sided heart anomalies such as aortic stenosis, mitral stenosis, or left ventricular hypoplasia, often in the absence of right-sided heart anomalies (9). In our clinical observations, we predominantly identified anomalies affecting the right-sided cardiac valves, specifically tricuspid dysplasia and pulmonary valve dysplasia. Intriguingly, we documented anomalies involving the mitral and aortic valves in a single patient who concurrently presented with a Lupus-like syndrome, raising the possibility of Libman-Sacks endocarditis.

Importantly, we consistently observed the presence of atrial and ventricular septal defects, findings consistent with a multitude of prior studies (8, 13, 20).

It is noteworthy that several of our patients receive specialized care at cardiology centers, ensuring the expert management of their cardiac aberrations and the preservation of optimal cardiac functionality.

Neurosensory deafness was not identified within our examined patient cohort. Conductive hearing loss was documented in a single patient, attributed to recurrent episodes of acute suppurative otitis media resulting in chronic otitis due to the child's immunological disorders. However, available literature reports suggest a higher prevalence of otological complications, with reported frequencies ranging from 30% to 82% (8, 13).

Among our patients, ocular anomalies were evident in 62.5% of cases, encompassing conditions such as coloboma, strabismus, ptosis, and keratoconus. Numerous literature sources describe ocular anomalies (40%-60%), often including additional features such as blue sclera, hypermetropia, and corneal staphyloma (6-7, 21-22). Notably, no existing reports associate KS with keratoconus.

In terms of genitourinary anomalies, reported in 20%-40% of cases according to literature (6, 23), such anomalies were observed in 66% of our patients. The most frequent anomalies included horseshoe kidney, hypospadias, and cryptorchidism, aligning with our study's findings. An instance of unilateral renal agenesis was noted in one patient, a rarity infrequently associated with KS (24). Moreover, our study revealed a patient with supernumerary renal arteries, a unique anomaly not previously reported in association with KS.

A distinctive and uncommon anomaly identified in our study was right lung hypoplasia accompanied by upper lobe aplasia. Pulmonary anomalies are infrequent among Kabuki patients, and the limited documented cases predominantly involve bronchial architectural irregularities like bronchial pruning (25) and bronchial isomerism (26).

In examining orthopedic concerns within our cohort, the notable prevalence of joint laxity and skeletal anomalies (89%) aligns with findings reported in various studies (approximately 80%) (20, 27-29). Noteworthy frequencies of flat foot and ankle valgus were observed, both stemming from multifactorial origins. Given the concurrent presence of obesity in patients with ankle valgus, a potential correlation between weight gain and outward ankle deviation arises, particularly in the context of joint laxity, evident in all our valgus patients. Another complication of joint laxity, developmental hip dysplasia, was detected in two patients and successfully addressed through bracing. This underscores the significance of early intervention to potentially correct issues before they become irreversible.

Additionally, severe osteoporosis was observed in one patient, a condition previously unreported in any Kabuki case. Nevertheless, we do not regard this alteration as a direct outcome of KS, considering that the patient also manifested a Lupus-like syndrome. Osteoporosis is a prevalent comorbidity in Lupus, primarily attributed to the extended administration of corticosteroids, medications recognized for their association with osteoporosis as a complication.

Prevalent gastrointestinal alterations encompassed anorectal anomalies and gastroesophageal reflux (20, 30), both found in 33% of our patient group. Furthermore, the identification of three accessory spleens is a novel finding, absent in existing literature cases. Due to the lack of statistical comparison with other studies and the potential causal and parafysiologic nature of accessory spleens in the general population, an association between this anomaly and the syndrome cannot be definitively established or ruled out.

In the realm of neurological anomalies, a high frequency (89%) was noted in our experience. Hypotonia dominated, consistent with numerous reviews reporting prevalences spanning 51% to 98% (6, 13). Additional anomalies within our cohort, such as isolated dilation of the fourth ventricle and lateral ventricle, lack precedent in other KS cases. Nevertheless, a case of ventriculomegaly and non-neoplastic aqueductal stenosis has been documented (31).

Furthermore, left temporal-polar lobe cysts were identified alongside symmetric lateral ventricle dilation. Existing literature only reports two instances of Kabuki patients with temporal lobe cysts (32, 33), making this the third reported association of its kind.

Moreover, cerebellar vermis hypoplasia surfaced in our study, unaccompanied by additional structural anomalies on MRI examination. Currently, this presentation without concomitant manifestations such as posterior fossa cysts and hydrocephalus remains undescribed; however, a case involving cerebellar vermis hypoplasia, alongside posterior fossa cysts and hydrocephalus characteristic of Dandy-Walker malformation, has been reported, albeit with rare association to KS (34).

Consistent with established literature data (4, 35-36), cognitive impairment was evident in 78% of cases, while the remaining patients displayed cognitive-linguistic deficits during clinical evaluation, although not formally documented.

Postnatal growth deficiency, identified in 67% of cases within our study, may be linked to hypotonia affecting infant feeding or growth hormone deficiency. Our findings align with existing literature, reporting short stature prevalence ranging from 60% to 85% (3, 13).

Concerning endocrine and metabolic manifestations, obesity emerged as the most prevalent (67%). The paradoxical hallmark of post-age-5 obesity, despite initial feeding difficulties, is likely due to polyphagia. This alteration's frequency (approximately 57%) is substantiated by several studies, supporting its pathogenic hypothesis (10, 37).

In contrast, isolated premature thelarche was exhibited in only one case, despite its higher prevalence as an endocrinological anomaly. A study by Banka et al. identified this alteration in 41% of patients with KMT2D gene mutations (38).

Furthermore, we documented growth hormone deficiency (GHD) in one patient, subsequently treated with replacement therapy. A 2013 study by Ito et al. reported hypothalamo-pituitary axis complications in just 9 cases across literature; among these, GHD, the most common, was present in 6 (39). Despite its rarity, it's noteworthy that GH testing was only conducted in one patient; hence, potential GHD in the remaining short-statured patients cannot be ruled out.

Lastly, hypothyroidism was observed in 2 patients, both receiving Levothyroxine therapy. However, this manifestation is not commonly reported in scientific literature (40).

Immunological evaluations of our patients indicated a 78% complication rate, predominantly manifesting as heightened susceptibility to infections, particularly respiratory. In two patients, MRI showed mastoid hyperintensity suggestive of inflammation, even without symptoms. Additionally, immunodeficiency disorders such as Autoimmune Lymphoproliferative Syndrome (ALPS) and Common Variable Immunodeficiency (CVID) were diagnosed. Among these, only CVID has been documented in association with the syndrome (41). Although ALPS has not yet been reported in Kabuki patients, it falls within the realm of common autoimmune complications. Instances of autoimmune hemolytic anemia, autoimmune idiopathic purpura, vitiligo, and autoimmune thyroiditis have been reported (42).

Furthermore, a unique and exceptional autoimmune disorder was observed in our study: a Lupus-like syndrome. This led to conditions like polysierositis, sensory and motor neuropathies, severe autoimmune pancytopenia, and eventual fatality. While a link between Kabuki syndrome and systemic lupus erythematosus (SLE) or Lupus-like syndrome hasn't been documented in literature, certain SLE-associated antibodies, such as anti-phospholipid antibodies, have been found in a Kabuki patient's serum (43).

Lastly, oncological complications were identified in our study, including neuroblastoma and hepatoblastoma (44). The connection between neuroblastoma and Kabuki syndrome has been reported in two patients (45, 46). In both instances, prompt identification and removal of neoplastic masses underscore the importance of thorough evaluation and timely diagnosis for optimal patient management.

Regarding genetic evaluation analysis, only one patient exhibited overlapping nucleotide sequences with the normal reference sequence. Nonetheless, this patient manifested significant clinical and phenotypic elements of Kabuki syndrome. Such patients demonstrating clinical and phenotypic characteristics of Kabuki syndrome without mutations in the primary causative genes are termed "Kabuki-like." A recent review by Lintas and Persico on Kabuki-like patients, constituting around 30% of KS cases, reveals that mutations may be detectable in genes other than KMT2D or KDM6A. These genes (e.g., EPC1, ANKRD11, KDM1A) share functional or biological processes with the aforementioned causative genes (16).

Therefore, for suspected KS cases, it is prudent to expand genetic investigations to encompass both genes for a comprehensive pathogenetic understanding. Subsequently, in cases lacking mutations, exploration of additional potential genes becomes advisable.

5. Conclusions

Kabuki syndrome is a complex and diverse condition characterized by a wide range of clinical manifestations affecting multiple bodily systems. Our study provides a comprehensive exploration of both the clinical and genetic aspects of this syndrome. Identification of consistent phenotypic features reaffirms the distinct nature of this disorder, while highlighting significant variability in its presentation across different populations.

The findings from our research emphasize the critical importance of early diagnosis, a multidisciplinary approach to patient care, and vigilant surveillance to identify and manage potential complications. Our genetic investigations underscore the urgent need for ongoing research efforts aimed at unraveling the intricate molecular mechanisms underlying Kabuki syndrome.

In summary, our results contribute significantly to the growing body of knowledge on Kabuki syndrome, forming the foundation for more tailored strategies in patient care and management. However, further research is essential to gain a deeper understanding of the underlying pathogenetic mechanisms, develop personalized therapeutic interventions, and provide optimal support to affected individuals and their families.

Fostering collaborative partnerships among medical professionals, researchers, and patients is crucial for advancing our understanding and treatment of this complex genetic syndrome.

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References

1. Niikawa, Norio, et al. "Kabuki make-up syndrome: a syndrome of mental retardation, unusual facies, large and protruding ears, and postnatal growth deficiency." The Journal of pediatrics 99.4 (1981): 565-569.
2. Kuroki, Yoshikazu, et al. "A new malformation syndrome of long palpebral fissures, large ears, depressed nasal tip, and skeletal anomalies associated with postnatal dwarfism and mental retardation." The Journal of pediatrics 99.4 (1981): 570-573.
3. Niikawa, Norio, et al. "Kabuki make- up (Niikawa- Kuroki) syndrome: A study of 62 patients." American journal of medical genetics 31.3 (1988): 565-589.
4. Adam, Margaret P., et al. "Kabuki syndrome: international consensus diagnostic criteria." Journal of medical genetics 56.2 (2019): 89-95.
5. Adam MP, Hudgins L, Hannibal M (1993-2021) In: Adam MP, Ardinger HH, Pagon RA et al (eds) (2011, Updated 2019) Kabuki Syndrome. GeneReviews® [Internet], Seattle (WA) Available from: https://www.ncbi.nlm.nih.gov/books/NBK62111/
6. Bögershausen, N., and B. Wollnik. "Unmasking kabuki syndrome." Clinical genetics 83.3 (2013): 201-211.
7. Chaudhry, Imtiaz A., et al. "Ocular manifestations in Kabuki syndrome: the first report from Saudi Arabia." International ophthalmology 28 (2008): 131-134.
8. Peterson-Falzone, Sally J., Mahin Golabi, and Anil K. Lalwani. "Otolaryngologic manifestations of Kabuki syndrome." International journal of pediatric otorhinolaryngology 38.3 (1997): 227-236.
9. Yoon, Ja Kyoung, et al. "The strong association of left-side heart anomalies with Kabuki syndrome." Korean journal of pediatrics 58.7 (2015): 256.
10. White, S. M., et al. "Growth, behavior, and clinical findings in 27 patients with Kabuki (Niikawa–Kuroki) syndrome." American Journal of Medical Genetics Part A 127.2 (2004): 118-127.
11. Giordano, Paola, et al. "Autoimmune haematological disorders in two Italian children with Kabuki syndrome." Italian journal of pediatrics 40.1 (2014): 1-5.
12. Kawame, Hiroshi, et al. "Phenotypic spectrum and management issues in Kabuki syndrome." The Journal of pediatrics 134.4 (1999): 480-485. 13. Cheon, Chong-Kun, and Jung Min Ko. "Kabuki syndrome: clinical and molecular characteristics." Korean journal of pediatrics 58.9 (2015): 317.
14. Ng, Sarah B., et al. "Exome sequencing identifies MLL2 mutations as a cause of Kabuki syndrome." Nature genetics 42.9 (2010): 790-793.
15. Bögershausen N, Gatinois V, Riehmer V, et al. "Mutation update for Kabuki syndrome genes KMT2D and KDM6A and further delineation of X-linked Kabuki syndrome subtype 2." Hum Mutat. 2016;37(9):847-864. 16. Lintas C, Persico AM. "Autistic phenotypes and genetic testing: state-of-the-art for the clinical geneticist." J Med Genet. 2009;46(1):1-8.
17. Morcaldi, G., et al. "Congenital lymphatic dysplasia in Kabuki syndrome: first report of an unusual association." Lymphology 43.4 (2010): 188-199.
18. Cudzilo, Dorota, and Ewa Czochrowska. "Orthodontic treatment of a Kabuki syndrome patient." The Cleft Palate-Craniofacial Journal 55.8 (2018): 1175-1180.
19. Porntaveetus, Thantrira, et al. "Expanding the oro-dental and mutational spectra of Kabuki syndrome and expression of KMT2D and KDM6A in human tooth germs." International journal of biological sciences 14.4 (2018): 381.
20. Matsumoto, Naomichi, and Norio Niikawa. "Kabuki make- up syndrome: A review." American Journal of Medical Genetics Part C: Seminars in Medical Genetics. Vol. 117. No. 1. New York: Wiley Subscription Services, Inc., A Wiley Company, 2003.
21. Chen, Yi-Hsing, et al. "Rare ocular features in a case of Kabuki syndrome (Niikawa-Kuroki syndrome)." BMC ophthalmology 14.1 (2014): 1-3.
22. Tanaka, Ryuma, et al. "Congenital corneal staphyloma as a complication of Kabuki syndrome." American Journal of Medical Genetics Part A 158.8 (2012): 2000-2002.
23. Courcet, Jean-Benoît, et al. "Clinical and molecular spectrum of renal malformations in Kabuki syndrome." The Journal of Pediatrics 163.3 (2013): 742-746.
24. Rosti, Rasim Özgür, and Hülya Kayserili. "Kabuki make-up syndrome with unilateral renal agenesis." The Turkish Journal of Pediatrics 51.3 (2009): 298.
25. Shah, Maulik, et al. "Cardiac conduction abnormalities and congenital immunodeficiency in a child with Kabuki syndrome: Case report." BMC Medical Genetics 6 (2005): 1-8.
26. Cappuccio, Gerarda, et al. "Bronchial isomerism in a Kabuki syndrome patient with a novel mutation in MLL2 gene." BMC medical genetics 15 (2014): 1-5.
27. Ramachandran, Manoj, Robert M. Kay, and David L. Skaggs. "Treatment of hip dislocation in Kabuki syndrome: a report of three hips in two patients." Journal of Pediatric Orthopaedics 27.1 (2007): 37-40.
28. Aslan N, Guler O, Kocyigit A, Gunes T. "The musculoskeletal system findings of Kabuki syndrome: a case report." J Pediatr Endocrinol Metab. 2014;27(5-6):465-468.
29. Rouffiange, Lucie, Jean-Paul Dusabe, and Pierre-Louis Docquier. "Recurrent dislocation of the patella in Kabuki make-up syndrome." Case reports in orthopedics 2012 (2012).
30. Abdel-Salam, G. M. H., et al. "Anorectal anomalies, diaphragmatic defect, cleft palate, lower lip pits, hypopigmentation and hypogammaglobulinemia A in Kabuki syndrome: a rare combination." Genetic Counseling 19.3 (2008): 309.
31. Kara, Bülent, et al. "Quadrigeminal cistern arachnoid cyst in a patient with Kabuki syndrome." Pediatric neurology 34.6 (2006): 478-480.
32. Kasuya, H., et al. "Kabuki make-up syndrome and report of a case with hydrocephalus." Child's nervous system 14.6 (1998): 230-235.
33. Chu, Da- Chang, et al. "CNS malformation in a child with Kabuki (Niikawa- Kuroki) syndrome: Report and review." American journal of medical genetics 72.2 (1997): 205-209.
34. Liu, Shuang, et al. "Kabuki syndrome: a Chinese case series and systematic review of the spectrum of mutations." BMC medical genetics 16.1 (2015): 1-10.

35. Matsuoka R, Kimura R, Sese J. "Use of the Wechsler Intelligence Scale for Children-IV to detect cognitive impairment in pediatric patients with Kabuki syndrome." Mol Syndromol. 2019;9(2):115-120.
36. Morgan, Angela T., et al. "Speech and language in a genotyped cohort of individuals with Kabuki syndrome." American journal of medical genetics Part A 167.7 (2015): 1483-1492.
37. Arnaud, M., et al. "Le syndrome Kabuki: mise au point et revue de la litterature." Archives de Pediatrie 22.6 (2015): 653-660.
38. Banka, Siddharth, et al. "How genetically heterogeneous is Kabuki syndrome?: MLL2 testing in 116 patients, review and analyses of mutation and phenotypic spectrum." European Journal of Human Genetics 20.4 (2012): 381-388.
39. Ito, Naoko, et al. "Hypothalamic pituitary complications in Kabuki syndrome." Pituitary 16.2 (2013): 133-138.
40. Gürbüz, Fatih, et al. "Coexistence of Kabuki syndrome and autoimmune thyroiditis." Journal of Clinical Research in Pediatric Endocrinology 8.1 (2016).
41. Hoffman, Jodi D., et al. "Immune abnormalities are a frequent manifestation of Kabuki syndrome." American journal of medical genetics Part A 135.3 (2005): 278-281.
42. Ming, Jeffrey E., et al. "Autoimmune disorders in Kabuki syndrome." American Journal of Medical Genetics Part A 132.3 (2005): 260-262.
43. Arsov, Todor, et al. "Systemic lupus erythematosus: A new autoimmune disorder in Kabuki syndrome." European Journal of Medical Genetics 62.6 (2019): 103538.
44. Karagianni P, Sfakianaki M, Stiakaki E, et al. "Kabuki syndrome in a Greek boy with hepatoblastoma: a possible association." J Pediatr Hematol Oncol. 2016;38(2):163-165.
45. Tumino, Manuela, et al. "Kabuki syndrome and cancer in two patients." American Journal of Medical Genetics Part A 152.6 (2010): 1536-1539. 46. Merks, Johannes Hans M., Huib N. Caron, and Raoul CM Hennekam. "High incidence of malformation syndromes in a series of 1,073 children with cancer." American journal of medical genetics Part A 134.2 (2005): 132-143.