Kabuki syndrome: diagnostic and treatment considerations

Bethany D Kasdon Psy D
Candidate for Licensure

Judith E Fox PhD
Associate Professor, Director, International Disaster Psychology
Graduate School of Professional Psychology, University of Denver, USA

ABSTRACT
Kabuki syndrome (KS) is a rare genetic disorder first diagnosed in 1981. Unknown by most primary care physicians and clinicians in the mental health fields, children with KS present with unique facial characteristics, mental retardation, health problems and socio-emotional delays that are often mistaken for other diagnostic problems. Literature detailing the psychological and psychosocial features of this disorder is scant, and psychotherapeutic approaches have not been described. In this article, we present a case description and treatment of a child with KS and her family. A brief review of KS is then provided, highlighting its signs and symptoms. Factors related to differential diagnoses are identified to aid primary care and mental health clinicians in better understanding this unique syndrome. Interventions with similar populations are discussed from which a psychological approach to KS is suggested. Finally, implications for primary care physicians are described and suggestions for further research indicated.

Keywords: differential diagnosis, Kabuki syndrome, psychosocial treatment

Introduction
This article details the clinical presentation of children with Kabuki syndrome (KS) and psychological treatment considerations. A case example is first presented to illustrate the psychological issues associated with this disorder, including developmental disability, chronic physical illness and socio-emotional problems. An intervention approach aimed at assisting both this child and family is described. While no psychotherapeutic approach to KS has appeared in the literature, interventions often applied to related disorders may inform one. The treatment literature dealing with developmental disability, chronic physical illness and socio-emotional problems are particularly useful in this regard and are described.

The genetic basis for KS and its discovery are then presented with detailed information regarding the specifics of its clinical presentation. Information regarding differential diagnoses is examined to aid primary care and mental health providers in detection and referral for mental healthcare for those presenting with this rare condition. Interventions applied to related disorders are presented to assist mental health professionals in flexibly addressing the psychological manifestations of KS. The implications of this information for primary care physicians is then discussed and suggestions for future research are offered to determine best practices in the diagnosis and treatment of KS.
Case of KS: clinical presentation

Case overview

‘Sarah’ is a 5-year-old Caucasian female who was originally referred to a mental health clinic for a cognitive and developmental evaluation. The results of the evaluation indicated that Sarah had an IQ score of 77 and was functioning, developmentally, at 2 years of age. During the testing process, however, some behavioural concerns also became apparent and a referral for psychological treatment was made. During the course of psychotherapy, a geneticist determined that Sarah met the requirements for a Kabuki diagnosis. This diagnostic classification included: characteristic facial features, short stature, developmental delay, cognitive impairment, social inappropriateness and expressive language delay. Additional medical testing indicated that Sarah had several of the medical conditions also associated with KS, including absence seizures, heart and kidney concerns. Sarah’s mother, Megan, had several concerns that illustrate the concomitant presentation of socio-emotional, developmental delay and family stress factors that accompanied this child’s and family’s experience of this chronic, genetically based illness that required addressing in psychotherapy.

Socio-emotional factors

Sarah evidenced social skill deficits as well as problems in self-soothing and emotional regulation. Work on social skills in therapy included role plays to develop skills in conversation, listening, emotional expression and friendship-making. Sarah also practised these skills in therapy through the use of structured games to learn rules, frustration tolerance and turn taking. During the course of therapy, Sarah’s mother was advised to enrol Sarah in preschool, camps and dance classes to provide further practice in and exposure to social relationships.

Problems in self-soothing were approached by providing Sarah with a ‘toolkit’ to assist her in utilising tactile means of soothing and reducing stress. This included fabric pieces of different texture, koosh and stress balls. These were placed in a small bag that Sarah could take with her. She was encouraged to use these both in session and during the week when feeling frustrated and having difficulties regulating her behaviour.

Developmental delay

Sarah’s ‘meltdowns’ were hard to control, and seemed to stem from both a cognitive limitation and a difficulty with change or the unexpected. The ‘1–2–3 Magic’ system was taught to both Sarah and her mother, as a discipline technique. This technique was effective as it gave Sarah three chances to change her behaviour, and was concrete enough for her to understand the rules. In addition to teaching Sarah’s mother techniques for discipline, she was coached to identify and increase areas where Sarah could exhibit more control in her life as well as in ways she could prepare Sarah for changes or transitions. Sarah’s mother was also encouraged to provide Sarah with a lot of specific positive reinforcement, rather than focusing on her negative behaviour.

Family stress: chronic illness

Not only did Sarah and her family cope with the stress of her condition, her brother’s medical illness and witnessing the invasive medical procedures he regularly received taxed Sarah’s coping abilities and presented significant stress for the family. Sarah exhibited significant separation anxiety, vocalised fear about death and had emotional ‘meltdowns’ at doctor appointments. Significant time was spent in therapy with a medical play toolkit with which Sarah played out serious medical procedures. After several sessions of repetitive medical play without positive resolution (indicative of potential trauma), the therapist suggested a more positive ending to the medical procedure. As therapeutic rapport strengthened over several sessions, Sarah was increasingly willing to take suggestions about resiliently focused resolutions to these play scenarios.

Role plays with dolls were also an important element of the psychotherapeutic work related to enhancing Sarah’s coping with chronic illness. During these role plays, Sarah was able to express her fear about her family’s health and her anger and sadness about the impact chronic illnesses have had on their lives. The role plays also provided the therapist the opportunity to suggest coping and breathing techniques for the ‘dolls’ and articulate positive self-statements and reframes to aid in handling difficult situations.

Parent consultation also included coaching in how to speak with both Sarah and her brother in age-appropriate ways about illness and death, and how to increase needed autonomy and independence despite her understandable anxiety regarding their well-being. Additionally, Megan was provided with children’s books on grief and loss that she could read to the children between sessions.
Termination

Termination with Sarah was gradual, when significant gains were made in all three major areas. Sarah’s disruptive behaviour had significantly diminished, and she no longer exhibited symptoms of separation anxiety. Sarah was attending doctor’s appointments and behaving appropriately, and attending school regularly with good reports from teachers and staff. Prior to termination, Sarah won a friendship award at school.

What do we know about Kabuki syndrome?

Genetics

In 1969, Norio Niikawa MD, a geneticist in Japan was treating a child patient presenting with unique facial characteristics, mental retardation and various health problems. Never having seen this constellation of symptoms before, Dr Niikawa wondered if he was faced with an undiagnosed condition, a disorder with a genetic basis. Over the next several years, this physician treated several other patients with the same symptoms in his outpatient genetics clinic, furthering support for a disorder never before diagnosed.4

In 1979, Dr Niikawa presented his findings and hypothesis at the first Japan Dysmorphology Conference. A fellow physician at this conference (Dr Kuroki) recognised the symptoms, and realised that he had also seen several paediatric patients with this presentation; he presented two of his own cases at the second annual conference the following year. In 1981, the two doctors separately submitted articles on this new diagnosis to the Journal of Pediatrics.4

Dr Niikawa coined the term ‘Kabuki syndrome’ (also known as Kabuki make-up syndrome or Niikawa–Kuroki syndrome) as a reference to traditional Japanese theatre. Many of the children presenting with this diagnosis had unusual, elongated lower eyelids, and this feature is reminiscent of the theatrical make-up worn by actors in Kabuki theatre.5,6

Along with the discovery of the KS diagnosis, was the belief that this was a disorder specific to Japanese individuals. KS was identified in 1 of every 32,000 births, making it a relatively rare genetic condition.4 Since the 1980s, however, children from various ethnicities have been diagnosed with KS including Northern European, Brazilian, Filipino, Vietnamese, Arab, East Indian, Chinese, Mexican, African, Australian and New Zealand.7 Currently, over 350 cases of KS have been explored within genetic and paediatric literature worldwide. Because the condition is generally not diagnosed, these numbers are believed to be an underestimate of actual KS cases.4

KS is strongly believed to be genetic, and research identifying the specific genetic marker is progressing. Researchers have recently found a potential linkage to mutations in a gene called MLL2, although further investigation is underway.7 Information gathered on diagnosed cases indicates that the ratio of male to female patients is approximately equal (1.16 to 1, respectively).2 In 14 published cases, a diagnosis of KS was present in multiple family members; in many cases, however, transmission of the syndrome is unknown. Further, in the examination of two cases of identical twins, only one set of twins both had the diagnosis. This suggests that the genetic mutation may occur after the fertilised egg divides.4

Research on birth order and paternal age associated with KS has not provided any indications related to its source. Children from every birth order position have been diagnosed with the condition, and the mean age of fathers with diagnosed children is 33.3.7,8

Clinical presentation of Kabuki syndrome

The constellation of aesthetic, physical, cognitive and social characteristics unique to KS is important to recognise. Below, different symptoms of KS are outlined, along with the percentage of their occurrence in documented cases of this disorder.

Physical abnormalities

Unique and distinct facial features are necessary for the KS diagnosis. Children with KS are often described as having broad, large foreheads. Sparse arched eyebrows are also common of children with this diagnosis, along with a turning out of the lower lateral eyelid.4 Heavy and thick eyelashes, far set eyes and a flattened nose have also been observed. The upper lip is thin and an arched or cleft palate is not uncommon. The area between the nose and mouth is often large or tented without an upper lip pit. Large ears, ear malformations, persistent fetal fingertip pads and shortened fifth digits are also characteristic physical symptoms.6,9,10
Medical conditions

While the presentation of each medical condition associated with KS varies considerably, a high percentage of children diagnosed with this syndrome do have medical complications. Fifty-five per cent of children with KS experience delayed growth and remain small in size throughout life. Skeletal problems are diagnosed in ~92% of Kabuki cases including scoliosis and hip dysplasia, which may also be associated with the child’s small stature.5,6,11 Forty-two per cent of children diagnosed with KS have cardiovascular defects. These include ventricular septum defects, atrial septum defects, narrowing of the aorta and arrhythmia.4 Renal problems and frequent urinary tract infections are not uncommon in KS presentation (28%) and 0–40% of paediatric cases suffer from localised seizures.12,13

Cognitive factors

Mental retardation or cognitive delays are a common feature of KS. Eighty-four to ninety-two per cent of diagnosed patients have an Intelligence Quotient (IQ) of 80 or less.4,14 Expressive and receptive language difficulties are also a common presentation in KS patients, affecting ~33% of individuals. Speech development is often delayed and expression often sounds slurred or incoherent. Errors in speech and syntax are also present. One hypothesis about the language delays in children with this diagnosis is that recurrent ear infections (~63%) result in hearing loss. The hearing loss at an early age would impair these children’s language acquisition. Hearing loss would also help explain the receptive language difficulties often apparent in KS children.15

Socio-emotional factors

A less common but noteworthy disorder associated with KS is autism spectrum disorders. Several patients within the literature that have been diagnosed with KS have a dual diagnosis of autistic disorder. Many more, however, display behaviour common to children or adults who have autism, including social inappropriateness, impaired interpersonal relationships, communication difficulties, few specific interests and repetitive behaviour. Children with a KS diagnosis are also described as manifesting anxiety, inattentiveness and emotional disturbance.7,11,16

Longevity

KS is a relatively new diagnosis. Children first diagnosed in the 1980s would be in their 40s today, although little long-term follow-up has been performed. It is currently believed that children with this diagnosis are likely to live into adulthood. Heart problems and the potential for infection or renal failure, however, make the prognosis for an average life span uncertain.4,7

Differential diagnosis

Pervasive developmental disorders

As children with KS often present with symptoms similar to those of autism or a comorbid diagnosis of autism, differentiating between the two diagnoses is warranted. Children with autism are likely to present with verbal, cognitive and developmental delays. Like KS, children with autism may also be diagnosed with an epilepsy or seizure disorder, and struggle to connect with other children. Similar to symptoms of autism, Asperger’s and pervasive developmental disorder (PDD), children with KS often exhibit inappropriate social behaviour, engage in repetitive actions and experience difficulty transitioning from one task to another.17

Several distinctions between PDDs and KS are worth noting. PDDs do not require a distinct physical presentation for diagnosis, and children with a PDD diagnosis do not experience the medical complications common in children with KS. The social disturbance in children with autism is often more significantly impaired than in children with KS, and children with autism are more likely to experience sensory integration issues and a comorbid diagnosis of pica. Further, while KS is almost equal in male to female diagnosis (1.16 to 1 respectively), the diagnosis in Asperger’s (2.3 to 1) and autism (4 to 1) is significantly higher in male children.4,17–19

Fetal alcohol syndrome

Making the distinction between a diagnosis of fetal alcohol syndrome (FAS) and KS can be especially difficult, as both exhibit distinct facial features required for diagnosis. Children with both diagnoses often present with a cleft lip or palate, flattened nose, a thin upper lip and a lack of upper lip pit.9,20–22 Growth, speech and language delays and mental retardation are also common symptoms of both diagnoses.23 Like KS, children with FAS often exhibit inappropriate social behaviour and can suffer from seizures. Finally, children with both diagnoses often struggle with inattention and hyperactivity.
Unlike KS, however, children with FAS are often described as having small drooping eyelids that are often spaced far apart. An underdeveloped midface (which involves prominent eyes and an under bite) is also common in children with FAS.\(^{20,22}\) While children with FAS often struggle with social interaction (similar to KS) the nature of their interactions is described as overly friendly and lacking in discrimination. Further, unlike KS, children with FAS are more likely to be impulsive, demonstrate poor judgement and have a greater risk of drug abuse and criminal behaviour as adults. FAS is also more likely to be diagnosed at higher rates in minority or low socio-economic status populations. Finally, an important distinction between these diagnoses is that while KS appears to result from a genetic mutation, FAS is a result of a prenatal teratogen. In distinguishing between these diagnoses, a thorough examination of the mother’s drug and alcohol history is crucial.\(^{20,24,25}\)

## Down syndrome

It is important to differentiate between Down syndrome (DS) and KS as similarities between the two are abundant. Like KS, DS is a genetic diagnosis. Children with DS often present with distinct facial features, mental retardation, health concerns and socially inappropriate behaviour.

The physical presentation in DS is, however, distinct from KS. Children with DS are described as having a small skull, large forehead and a small, flattened nose. The eyes are often almond-shaped and spaced far apart on the face, while the ears are often underdeveloped. Another prominent feature described in DS (and distinct from KS) is an underdeveloped top jaw and normal bottom jaw, creating the look of an under bite. Individuals with DS often have a protruding tongue and premature loss of teeth. Loose skin and fine hair are often also commonly described physical features of DS.\(^{26,27}\)

While children with DS also present with social difficulties, the quality of the challenges they face is different from children with KS. Children with DS are often described as child-like in nature and can be inflexible and stubborn. Additionally, children with DS are generalised as overly compliant and socially suggestible. Concerns regarding the social behaviour of children with DS focus on their lack of discrimination in social relationships, and the risk they will be manipulated or victimised by higher-functioning individuals.\(^{28}\) Finally, while children with DS are at risk of health issues, congenital heart defects are the overwhelming concern.\(^{29}\)

While several other genetic syndromes may be considered in the diagnosis of KS (Langer–Giedion syndrome, Van Der Woude syndrome, West syndrome, Fragile X syndrome and Turner syndrome) they fall outside the scope of this article. Clinicians interested in learning more about these diagnoses are encouraged to reference the existing literature for more information.\(^{29–31}\)

As mentioned previously, children with KS will present to psychotherapy with a unique combination of problems and therapeutic needs. They will look physically unique and likely be experiencing cognitive deficits. The family of a child with KS also may be dealing with the child’s diagnoses of seizures, heart and kidney problems and therefore be facing issues surrounding chronic illness. Additionally, parents of the child may be feeling frustrated and exhausted from the child’s socially inappropriate behaviour, temper tantrums and separation anxiety.

## Psychotherapeutic considerations for intervention

No literature currently exists regarding psychotherapeutic approaches to treatment of KS. Psychotherapeutic approaches that address the features of KS as they have been presented in other clinical populations, however, may inform a treatment approach. Literature on interventions with other clinical populations that manifest key similar features of socio-emotional problems, developmental delays and chronic physical illness are, therefore, considered.

## Socio-emotional problems

Interventions for socio-emotional problems or social inappropriateness have largely focused on high-functioning children with autism and/or Asperger syndrome, because children with these diagnoses often struggle with social skills and relationships. As a result, these children experience isolation, victimisation by peers, depression, low self-esteem and school and occupational problems.\(^{32,33}\) Interventions therefore, are often aimed at helping children develop specific social skills, including: greeting others, understanding non-verbal behaviour, turn taking, sharing, maintaining conversation and judging the emotional reactions of others.\(^{32–34}\)

Much of the research on interventions for children with Asperger syndrome focuses on social skill and friendship groups. The group structure allows children to work on social skills in a fun, applicable
way, such as board games (to teach rule flexibility and turn taking), role plays (how to engage and maintain a conversation, eye contact), giving speeches and collages (emotional expression of others, non-verbal cues) and homework (generalising to other environments). Individual psychotherapy for children with Asperger’s has also been documented in the literature and includes addressing many of the same skills. The individual therapist engages in role play, fantasy and games with the child while modelling prosocial skills, emotional expression, flexibility and consistency. Research on both social skill groups and individual play therapy for Asperger syndrome strongly recommends parent involvement, especially in support groups. Support groups provide the parents with the opportunity to meet others with similar experiences, while learning to relate to their child with Asperger’s.

As described in the previous case study, this research on interventions was incorporated into the psychotherapeutic work with Sarah. Role plays and game playing allowed Sarah to develop social skills while learning to tolerate frustration and the give-and-take inherent in relationships. Work with her mother included promoting her enrolling Sarah in camps and school in order to generalise her learning in therapy to other life contexts. Parent support groups as well as individual therapy for Sarah’s mother to assist in her adjustment were recommended.

Developmental delay

Only recently has the importance of and research supporting play therapy with developmentally delayed (DD) children become apparent. Children with DD struggle with low self-esteem, social problems, anxiety and display maladaptive behaviour. Further, parents of children with DD often struggle to attach and bond, while experiencing the challenges of parenting a mentally retarded child. Play therapy can be crucial in teaching children with DD prosocial behaviour, while providing their parents the support and direction they need.

The literature on play therapy interventions with children with DD indicates that the interventions and play materials do not differ significantly from play with other populations, but that adaptations to play may be required. For instance, it is recommended that material be presented in simple components and in various media (visual, auditory, etc.), while giving the child many opportunities to practise what is learned. Rules should be presented clearly and in language the child understands, with many prompts and cues for the child to conform to the expected behaviour. The child’s positive behaviour should be identified, emphasised and reinforced as a way to encourage its recurrence, and the child should be provided with many opportunities for role play and homework in the hope of generalising the behaviours learned in play therapy to other environments.

Interventions for children with DD are often aimed at targeting social skills, frustration tolerance and aggression. Techniques such as games, role playing or even friendship groups can aid the child with DD in learning rules, turn taking, sharing and appropriate touching. Additionally, fantasy play is encouraged to aid children with DD in voicing frustration, anxiety and fear in a safe and consistent environment. Further, fantasy play provides the child with the opportunity to make developmental gains and develop a coherent sense of self. While unstructured play with the child with DD has proven to be beneficial, they may require slightly more structure and direction in play than a child without developmental delays.

The literature on working with children with DD also emphasises that the therapist should expect that gains will happen slowly. The child’s difficulties in communication, short attention span and memory difficulties can impede progress. It is recommended that therapy happen consistently and termination proceed as a gradual process. Parents are also strongly encouraged to be actively involved in the therapy process and join support groups for parents of children with DD.

The research on therapy with DD children was also considered in developing interventions with Sarah as previously described. A new discipline system was implemented in Sarah’s life (1–2–3 Magic) to create structure and consistency. Therapeutic work assisting her in understanding what was expected of her and the use of frequent positive reinforcement were crucial to behaviour change.

Family stress: chronic illness

Various problems arise for both the child and family that experience paediatric chronic illness. Parents struggle with financial concerns, navigating medical and social services and locating resources for their child. Additionally, they may have difficulty fulfilling the needs of all their children, and are likely to become overprotective and anxious about the well-being of their children. The child with a chronic illness is also more likely to experience psychological distress, due to invasive medical procedures, separation from caregivers, loss of control, fear about their own health and observing caregiver distress. As a result, chronically ill children often
experience anxiety and depression, social and adjustment difficulties, struggle with life change or transition and exhibit disruptive and aggressive behaviour. 44,46,47

As a result of the aforementioned problems, various interventions for the family with a chronically ill child have been discussed within the literature. For example, it is recommended that the play therapy environment be a safe, supportive and completely non-judgemental space for the child. As a loss of control is often a predominant issue for the chronically ill child, play interventions should be unstructured and non-directive. 47 It is recommended that medical toys and toolkits be made available to the child, without directing the child to necessarily use them. If the child so chooses, medical toys have been demonstrated to increase the child’s sense of control, allows them to create positive resolutions to medical procedures and facilitates expression of anxiety and fear with some safe distance. Medical fantasy play also provides the play therapist with the opportunity to introduce coping and self-soothing techniques to the child, in hopes of reducing stress and anxiety. 44,45

Interventions for the child with chronic illness proved crucial in psychotherapy with Sarah. Role playing with dolls allowed her to express her anxiety, anger and sadness and to have this therapeutically received in a supportive and therapeutic relationship. Once the emotion or issue was identified, coping skills, self-soothing and positive self-statements could be introduced into the play, allowing Sarah to learn new techniques for coping with her illness.

Interventions for the parents or caregivers of the chronically ill child have also been outlined in the literature. Support groups are encouraged, to allow parents to connect with other families. These groups can also help educate parents on the chronically ill child’s perspective. Additionally, filial family therapy (in which the therapist teaches the parent a form of play therapy) is strongly suggested. Filial family therapy can aid the parent in talking with the child about illness in an age-appropriate way, helping to identify areas in which the child may exercise more control, and provide an opportunity for the parent to enjoy the child without focusing on negative behaviour. 43,46,48

Implications for primary care

The case study presented in this article highlights the utility of early detection and intervention for children with KS. At 5 years old, Sarah was able to make large gains in self-soothing, emotion regulation, interpersonal relationships and coping mechanisms before her life was irreparably impacted. Additionally, Sarah’s diagnosis precipitated the development of a treatment team to provide cohesive care for both Sarah and her family. While the diagnosis of KS in primary care practices will likely be rare, it is crucial that providers become aware of this diagnosis in order to make appropriate mental health and medical referrals, and provide the patient with the most comprehensive care. Further, understanding the multifaceted and pervasive nature of the developmental, psychological and family factors associated with this genetic disorder provides an illustration that underscores the need for primary care providers to comprehensively evaluate the impact that many genetically based problems may have on child development and family functioning, encouraging children and their parents to seek the assistance of a multidisciplinary team that includes mental health providers.

Conclusion

KS is a recently identified genetic syndrome that is increasingly becoming recognised in primary care settings. Early detection is essential and the constellation of symptoms presented by KS is important to address in psychological treatment. Clinicians should be prepared to provide interventions informed by research that have addressed these types of symptoms for other childhood disorders. Further, the psychotherapist who encounters this diagnosis will also likely encounter parents whose resources and patience have been taxed. Effective therapy is likely to include finding appropriate resources and support for the parents, where little resources are available. Both the child and family also benefit from the development of a collaborative treatment team of doctors, teachers, physical, occupational and speech therapists and psychotherapists working collectively for the child and family. Most importantly, practitioners who encounter this diagnosis should expect to be flexible and creative in finding effective interventions where none currently exist.

Future research into intervention and treatment of KS is crucial in understanding how we can be most beneficial to this growing population. For example, little research is available on working with the developmentally disabled child. More specifically, how does the clinician effectively treat issues of grief, loss and separation anxiety in a child with cognitive limitations? Additionally, therapists are urged to pursue research on group therapy for KS, as
children with this diagnosis would likely benefit from the socially supportive aspects of the group dynamic. Similarly, no research is currently available on working with an adult with KS, which is crucial in understanding the long-term outcome for this diagnosis. Most important, however, is the need for other clinicians to share their experiences in treating children with this diagnosis.

This article is written to offer some information to the primary care providers and mental health professionals about KS and to increase awareness about its challenging therapeutic issues. It is the authors’ hope that this article will begin a discussion and fuel research on a diagnosis that will likely be recognised more frequently in the future, heightening the awareness of the multifaceted effects that such genetic disorders may have on the developing child and her family, emphasising the need to address these effects comprehensively and in a multidisciplinary fashion.

REFERENCES

Kabuki syndrome diagnosis and treatment


ADDRESS FOR CORRESPONDENCE
Judith E Fox, Graduate School of Professional Psychology, University of Denver, 2460 S. Vine Street, Denver CO 80208, USA. Email jufox@du.edu
Accepted June 2012