Management of Kabuki Syndrome

A Clinical Guideline

Kabuki Syndrome Guideline Development Group
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Introduction...

... to Kabuki Syndrome (KS)

Kabuki Syndrome is a rare multiple anomaly syndrome with an estimated incidence of around 1 in 32,000. It was first described in 1981 by Drs Niikawa and Kuroki, working independently in Japan. The name was selected because of the facial resemblance to the makeup used in traditional Japanese Kabuki theatre. The spectrum of medical problems seen in Kabuki syndrome is diverse but all patients have similar facial features with long palpebral fissures, everted lower eyelids and arched eyebrows. A variable degree of learning disability is usually present. The cause of Kabuki remains unknown but is most likely genetic.

... to the Kabuki Syndrome Guideline Development Project

The guidelines have been developed using a robust methodology based on the one utilised by the Scottish Intercollegiate Guidelines Network (SIGN). The method has been adapted to suit rare conditions where the evidence base is limited, and where expert consensus plays a greater role. The members of the guideline development group are listed on page 23.

... to the Kabuki Syndrome Clinical Management Guidelines

What are the aims of the guidelines?
The guidelines aim to provide clear and wherever possible, evidence-based recommendations for the management of patients with Kabuki Syndrome.

Who are they aimed at?
As KS is rare, it is unlikely that many of the healthcare professionals usually responsible for managing and co-ordinating the care of people with the condition will have had much prior experience of the syndrome. As KS is a multisystem disorder, people with KS may require various diagnostic and screening tests, assessments, referrals and multidisciplinary interventions at different stages of their lives. These guidelines lay out these requirements in a clear format that is easily accessible to anybody involved in the care of an individual with KS. Though much of the information is relevant to all with KS, we have in the main used information relevant to a European audience. Though these guidelines have been prepared principally for professionals, they will also be of interest to the parents of Kabuki syndrome children. If you are reading these guidelines as a parent we would emphasise that your child may not be affected by all the complications mentioned herein as every child is an individual. We would recommend that you discuss any terminology or information which may concern you with your child’s doctor.

How are they organised?
Page 4 contains information on the diagnosis of Kabuki syndrome. Thereafter, the guidelines have been organised into sections depending on the different body systems. Within each system, different age groups are considered where relevant. Key references are provided at the back of the document if more in-depth information is needed. At the end of the guideline document we list useful resources.

NB. ABNL= Abnormal
Kabuki Syndrome
~ Diagnosis and First Steps of Management ~

Diagnosis
The cause of KS is unknown, so there is no diagnostic test available.
A secure clinical diagnosis is therefore of paramount importance.
The following diagnostic criteria, derived from those suggested by Adam et al. (2005) should be applied:

In neonates
A clinical diagnosis is extremely difficult to make in neonates.
It may be suggested by the occurrence of prenatal nuchal oedema or the presence of specific malformations which may be associated with KS, but the dysmorphic facial features are often not apparent at this age.
If in doubt it is better to review the infant at a later date before attaching a definite diagnostic label of KS.

In children

<table>
<thead>
<tr>
<th>• Characteristic face:</th>
<th>Long palpebral fissures with eversion of the lateral portion of the lower eyelid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Broad, arched eyebrows with lateral sparseness</td>
</tr>
<tr>
<td></td>
<td>Short columella with depressed nasal tip</td>
</tr>
<tr>
<td></td>
<td>Large, prominent or cupped ears</td>
</tr>
</tbody>
</table>

| • Post-natal growth retardation |
| • Developmental delay or learning disability |
| • Accessory diagnostic criteria: | Hypodontia |
| | Fingertip pads |

In adults
The features of KS change over time and the phenotype is different in adults. Particularly noteworthy are:

- The development of truncal obesity.
- The eyebrows no longer appear interrupted.
- The feet become more striking with overlapping of the toes, the hallux appears long and the fourth and fifth toes appear relatively short.

NB. At any age, cytogenetic anomalies should be ruled out, using microarray analysis if possible, before a diagnosis of KS can be made.
Differential diagnoses should also be considered.

<table>
<thead>
<tr>
<th>Differential diagnoses:</th>
</tr>
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<tbody>
<tr>
<td>Turner syndrome</td>
</tr>
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</table>

First Steps of Management...
All families should be offered referral to a genetics service at diagnosis, and a key person who will coordinate the management and care of their child should be identified.
## Recommendations for the management of Kabuki Syndrome

### ~ Feeding & Gastrointestinal and Visceral defects ~

#### Infancy and Childhood

**Feeding difficulties:** are almost always present in KS. These are exacerbated by hypotonia, gastro-oesophageal reflux, velopharyngeal dysfunction and poor oral motor function.

Refer for management by specialised feeding team if possible.

As infants tube feeding may be required.

Consider gastrostomy in cases of severe feeding difficulties.

**Gastro-oesophageal reflux**

Treat by positioning in an upright position, thickening feeds and administering anti-reflux medication.

Exclude infection.

**Chronic diarrhoea:** reported with increased frequency in KS

Check for malabsorption and refer to paediatric gastroenterologist if present.

Exclude coeliac disease which may occur with increased frequency in KS.

**Constipation:** likely to be due to bowel or abdominal wall hypotonia, and/or reduced mobility.

Treat with standard laxatives.

An ultrasound scan of the renal tract should be carried out in all patients following diagnosis.

**Visceral malformations:** a number of malformations are seen with increased frequency in KS:

- Congenital diaphragmatic hernia
- Renal tract malformations
- Ano-rectal malformations
- Biliary atresia

Consider the possibility of bronchial tract anomalies or diaphragmatic defect (eventration) in the case of recurrent lower respiratory tract infections.

Consider the possibility of extra-hepatic biliary atresia if there is prolonged jaundice, and consider referral to a paediatric gastroenterologist.
### Recommendations for the management of Kabuki Syndrome

**~ Speech, Communication & Cleft ~**

#### Infancy and Childhood

<table>
<thead>
<tr>
<th><strong>Delayed speech and language acquisition:</strong> seen in virtually all KS patients.</th>
<th>All patients should be referred to a speech and language therapist (SLT) as part of a multidisciplinary assessment. Speech problems may become more obvious with age so SLT should be ongoing until adolescence.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Impaired understanding</strong></td>
<td>SLT can advise on strategies such as using single syllable words and pictures to aid understanding.</td>
</tr>
</tbody>
</table>

#### All Ages

<table>
<thead>
<tr>
<th><strong>Cleft palate:</strong> one third of patients have overt clefts. Submucous cleft palate (SCMP) and velo-pharyngeal incompetence (VPI) are also found with increased frequency leading to nasal speech.</th>
<th>All patients should be referred to their local cleft team for assessment of SMCP and VPI. The palate in Kabuki syndrome can be shorter than usual and VPI following cleft surgery is more common.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lip pits:</strong> seen in a small proportion of patients with KS.</td>
<td>The cleft surgeon should be made aware of the diagnosis of KS and tailor surgical treatment accordingly. They may not require treatment if small but referral should be made to plastic surgeon for consideration of surgical removal if causing problems such as persistent mucous production.</td>
</tr>
</tbody>
</table>

**ABNL**
# Recommendations for the management of Kabuki Syndrome

## Development & Behaviour

### Infancy and Childhood

- **Developmental Delay**
  - Developmental surveillance from the time of diagnosis following assessment by the local multidisciplinary child development team.
  - Ongoing review of special educational needs.

- **Autism:** there are reports of a few Kabuki children with autistic features.
  - Provide families with advice as to how to access local support systems for learning disability.
  - Enquire about these and refer on to the local Child and Adolescent Mental Health Team (CAMHS) if there are significant concerns.

- **Behaviour:** Poor attention span has been reported by parents of children with KS.
  - Individual assessment of behaviour problems necessary.
  - Interventions will be tailored and specific.
  - Behavioural management advice and support to family as required.

### Adolescence and Adulthood

- **Developmental Delay**
  - Do not underestimate capabilities. Many people with KS can learn basic literacy skills, for example.
  - Speech and language input remains important in adolescents as language skills often don’t mature at the normal rate.

- **Behaviour**
  - Behavioural management advice and support to family as required.
  - Access to social skills training, and programmes to teach basic self help, employment and independent living skills as needed.
# Recommendations for the management of Kabuki Syndrome

## Cardiovascular

<table>
<thead>
<tr>
<th>All Ages</th>
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<tbody>
<tr>
<td><strong>Cardiac defects:</strong> in 40-50% of KS patients. Many are left-sided obstructive lesions with aortic coarctation. Atrial septal defect (ASD) and ventricular septal defect (VSD) are the most common malformations seen. Aortic dilatation has been seen in association with aortic lesions.</td>
</tr>
<tr>
<td><strong>Arrhythmia:</strong> has been reported in one patient.</td>
</tr>
<tr>
<td><strong>Blood pressure</strong></td>
</tr>
<tr>
<td>Echocardiogram should be carried out on all patients at the time of diagnosis. Particular attention should be paid to detection of left-sided obstructive lesions and the presence of aortic arch dilatation. All patients with structural cardiac anomalies should be referred to the care of a cardiologist. For those patients who need further investigation e.g. catheterisation or angioplasty, the potential increased risk of aortic aneurysm should be considered. Patients with aortic anomalies should have annual monitoring for aortic dilatation because they are at increased risk of dissection. Electrocardiogram (ECG) is not necessary routinely, but should be carried out if arrhythmia is suspected. Measure annually in all patients.</td>
</tr>
</tbody>
</table>
# Recommendations for the management of Kabuki Syndrome

## Neurology & Seizures

### Infancy and Childhood

<table>
<thead>
<tr>
<th>Hypotonia</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>present in virtually all infants with Kabuki syndrome.</td>
<td>Refer for physiotherapy assessment after diagnosis.</td>
</tr>
<tr>
<td></td>
<td>Review physiotherapy support at regular intervals.</td>
</tr>
<tr>
<td></td>
<td>Avoid invasive diagnostic tests to establish other causes e.g. muscle biopsy.</td>
</tr>
</tbody>
</table>

### All Ages

<table>
<thead>
<tr>
<th>Seizures</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>occur in 15-25% of KS patients.</td>
<td>Epilepsy is frequently described in KS, so a low threshold for investigation and early neurology referral is recommended.</td>
</tr>
<tr>
<td></td>
<td>Refer for MRI scan if seizures occur.</td>
</tr>
<tr>
<td></td>
<td>Treatment of is seizures as per the general population, following usual guidelines.</td>
</tr>
<tr>
<td></td>
<td>Check particularly for hypoglycaemia as a precipitating cause.</td>
</tr>
<tr>
<td>Structural central nervous system (CNS) malformations: a variety of different structural malformations have been reported but none are found consistently in KS.</td>
<td>MRI does not need to be carried out routinely, but should be carried out in cases with severe microcephaly, macrocephaly, seizures or neurological signs suggesting intracranial pathology.</td>
</tr>
</tbody>
</table>
# Recommendations for the management of Kabuki Syndrome

## Endocrine & Growth, Puberty & Sexual health

### Infancy and Childhood

**Neonatal hypoglycaemia:** noted with increased frequency but often manifests before the diagnosis of KS is made. Hypoglycaemia may also be present in older children.

**Growth impairment:** Growth hormone deficiency has been reported in some patients.

**Blood sugar should be checked if there is onset of seizures or suggestive symptoms.**

**Monitor height and weight.** At present no KS-specific growth charts are available. Refer to endocrine/growth clinic if height and/or weight < 2nd centile, or if rate of growth has decreased significantly. Check GH if height <3rd centile, treatment with GH may be considered. If treated with GH monitor for scoliosis.

### Adolescence and Adulthood

**Obesity:** often develops from time of puberty.

**Monitor weight through into adulthood.** Advise on healthy diet and exercise.

**Puberty:** boys and girls with KS go through a normal puberty. Some reports suggest that puberty may be slightly later than normal in boys. Premature thelarche is frequent in KS.

**Pubertal development should be monitored with referral to endocrinologist if concerns arise.** Extensive endocrinological work-up not necessary.

**Management of menstruation**

**Combined Oral Contraceptive:** contraception should be considered if situation arises and if women are considered vulnerable.

**Allow girls to progress normally through puberty before considering any treatment.** Consider use of combined oral contraceptive (COC) or Depo-Provera to suppress/lighten periods. In the UK COC is used most often. Using one of these methods also provides effective contraception, which may influence the decision to treat in some cases.

**Surgical management such as endometrial ablation or hysterectomy is not normally recommended.** Normal contraindications apply.
## Recommendations for the management of Kabuki Syndrome

### Orthopaedics

| All Ages |
|------------------|--------------------------------------------------|
| **Joint laxity:** seen in virtually all patients. | Refer for physiotherapy assessment. |
| **Hip dislocation:** occurs with increased incidence secondary to joint laxity. May develop even if neonatal hip check is normal. | Refer for occupational therapy (OT) if affects fine motor skills. |
| **Scoliosis:** may occur secondary to hypotonia and to vertebral malformations. | Monitor hips until walking. |
| **Patellar dislocation:** frequent in late childhood/adolescence, particularly if there is co-existing obesity. | Refer to orthopaedic team if dislocation suspected. |
| **Cervical spine instability:** specific problems with the cervical spine have not been reported in KS, however care should be taken in view of joint laxity. | Check the spine clinically on an annual basis. |
| **Flat feet:** common in KS. | X-ray if there is clinical suspicion of scoliosis. |
| | Refer to orthopaedic surgeon if scoliosis is confirmed. |
| | Enquire re: symptoms and check position of patella on an annual basis. |
| | Refer to an orthopaedic surgeon if there are signs or symptoms of patellar dislocation. |
| | In individuals with marked joint laxity avoid activities such as trampolining. Avoid use of bouncy chairs in infants. |
| | Make anaesthetist aware of possible cervical instability if anaesthetics are needed. |
| | Refer to physiotherapist for advice, and possible referral to orthotics. |
# Recommendations for the management of Kabuki Syndrome

## Immunology & Skin

### All Ages

**Immunity:** check levels of T cells, T cell subsets and immunoglobulins at diagnosis.

If abnormal refer to paediatric immunologist for advice regarding any necessary immunisations.

Normal immunisation schedule may be followed if levels are normal. Refer to an immunologist if there are recurrent infections.

**Respiratory tract infections:**

Lower respiratory tract infections may have other causes apart from impaired immunity. These include aspiration pneumonia and anatomical variation of the bronchial tree.

Check full blood count (FBC) and thyroid function every two to three years.

Enquire about presence of purpura or symptoms of anaemia.

The presence of vitiligo may also indicate autoimmune disease.

Refer to immunologist if autoimmune disease develops.

**Autoimmune disease:** there is an increased risk of autoimmune disease, particularly:
- Idiopathic thrombocytopenic purpura
- Autoimmune haemolytic anaemia
- Vitiligo (benign condition, most likely with an autoimmune basis).

**Hirsutism:** Excessive hair growth has been reported in around one fifth of patients.

**Pilomatrixoma:** small subcutaneous nodules, usually found on the scalp.

**Small/dystrophic nails:** Commonly reported by parents. Similar to those seen in other conditions with in-utero lymphoedema.

No specific treatment required but the nails should be kept short and trimmed.
Recommendations for the management of Kabuki Syndrome

~ Vision & Hearing ~

Infancy and Childhood

**Hearing loss:** has been documented in 40-45% of children with KS. In the majority this is a conductive loss due to chronic otitis media but the risk of sensorineural hearing loss is increased and this possibility should also be explored as it is likely to be under-diagnosed. In many patients the hearing loss is mixed.

- Assess hearing at time of diagnosis, and annually throughout infancy and childhood, and adolescence if necessary.
- All children with hearing impairment should have audiology follow-up.
- If there is a sensori-neural component to the hearing loss an MRI scan of the petrous temporal bone should be arranged as Mondini dysplasia of the inner ear may be present.
- Vestibular assessment is recommended in patients with vestibular symptoms, sensori-neural hearing loss or inner ear abnormalities.
- Treatment of hearing loss is by:
  a) amplification
  b) speech and language therapy
  c) cochlear implantation
  d) surgery for ossicular malformation
  e) in cases of Mondini dysplasia with periymphatic fistula surgery is indicated to prevent the development of menigitis.
- Children with recurrent otitis media should have their hearing tested.
- Consider grommets or T-tubes for conductive hearing loss due to chronic otitis media.
- All children should have a formal ophthalmological assessment at the time of diagnosis.
- If abnormalities are detected they should be followed up by the ophthalmology team.
- Manage using standard treatment.
- Refer children with recurrent or severe infections or where there is obvious lacrimal duct atresia or stenosis to the ophthalmology or oculoplastics team for further management.
- Consult ophthalmologist. Drops may be needed to protect cornea.
# Recommendations for the management of Kabuki Syndrome

## Dental

| All Ages |
|-------------------|-----------------|
| **Missing, fused or unusual-shaped teeth:** common in KS. Caries do not occur with greater frequency in KS. | **ABNL** |
| | Most patients do not need any special management. |
| | Ensure good dental hygiene. |

| Childhood |
|-------------------|-----------------|
| **Dental hygiene and management** | **ABNL** |
| | Enrol patient in an individualised preventative oral healthcare programme from an early age. |
| | Routine follow up and regular dental examinations by a family dentist or local community dental services are essential. |
| | Missing teeth/malocclusion/other dental anomalies: refer to a consultant in paediatric dentistry for multidisciplinary management. |
| | Parents report that using an electric toothbrush is easier and gives better results than manual brushing. |
| | Refer to a paediatric dentist for an assessment at the age of 8 years once secondary dentition present. |
# Recommendations for the management of Kabuki Syndrome

## Anaesthesia

### All Ages

**Anaesthesia in patients with KS**: many children with Kabuki syndrome undergo surgery as some stage. There are very few reports of significant complications occurring with anaesthesia in KS but several points need to be taken into consideration.

- The anaesthetist should be made aware of the diagnosis of Kabuki syndrome and its associated medical problems including structural malformations, learning disability and hypotonia.
- Screen for congenital heart disease before surgery.
- Be aware of the possibility of difficult intubation because of structural anomalies (narrowing) of the airways, and manage accordingly.
- Care should be taken with positioning of the cervical spine because of associated joint laxity.
- Anaesthesia for cleft palate repair should be undertaken by an anaesthetist with specific experience working within a recognised cleft centre.
Bibliography

General papers & Guidelines

Anaesthesia

Behaviour & Development
Bibliography

**Birth defects**

**Cancer**

**Cardiac**

**Dental**
Bibliography

Diagnosis

Endocrine, Growth & Obesity

Immunology & Skin

Neurology & Seizures
Bibliography

Neurology & Seizures continued...

Orthopaedics

Speech, Communication & Cleft

Vision and Hearing
Bibliography

Vision and Hearing continued...

Information for Parents

Sources of Information and Support

Support for parents and other family members is cited in the literature as being an important provision for families affected by KS. The groups listed below are useful sources of support and information.

- **Kabuki Syndrome support groups**
  There is currently no dedicated UK-based support group for KS, however, the following groups have an international scope, and welcome enquiries from all over the world.

  - **The Kabuki Syndrome Network** ([www.kabukisyndrome.com](http://www.kabukisyndrome.com))
    The KSN is based in Canada, and is run by parents for parents. The Network aims to act as an information resource on KS, and to help families affected by KS support each other by sharing their experiences. Membership provides access to a well-used email discussion group, as well as a bulletin board and a directory of families affected by KS.

  - **Netwerk Kabuki Syndroom** ([www.kabukisyndroom.nl](http://www.kabukisyndroom.nl))
    The Dutch patient support group organises meetings for families affected by KS, publishes a newsletter and funds research into KS.

  - **Association Syndrome de Kabuki** ([http://asso.orpha.net/ASK/cgi-bin/](http://asso.orpha.net/ASK/cgi-bin/))
    The website is predominantly in French, and contains useful information on Kabuki Syndrome. The Association runs annual ‘family days’ in France, attended by experts in KS, supports research into KS, and publishes a newsletter which is circulated amongst members.

  - **Contact a Family** ([www.cafamily.org.uk](http://www.cafamily.org.uk))
    The Contact a Family website is for families who have a disabled child and whose who work with then or are interested to find out more about their needs. Contact A Family is the only UK charity providing support and advice to parents whatever the medical condition of their child, they have information on over 1,000 rare syndromes and can often put families in touch with each other.

  - **Orphanet** ([www.orpha.net](http://www.orpha.net))
    Orphanet is an online database of rare diseases and related services provided throughout Europe. It contains information on over 5,000 conditions, including Noonan Syndrome, and lists specialised clinics, diagnostic tests, patient organisations, research projects, clinical trials and patient registries relating specifically to Noonan Syndrome.

    This website contains information on how the delivery of social care is being ‘personalised’. This new approach uses individual budgets and direct payments to allow individuals more choice and control over the support they receive.
Recommendations for the management of Kabuki Syndrome  
~ Alternative therapies ~

Many families report that alternative therapies for children and adults with Kabuki syndrome have a positive effect on well-being. The vignettes below introduce just a few of the therapies that parents have found to be beneficial.

**Music therapy**
Music therapy has been used to help people with learning difficulties express their thoughts and feelings and communicate with others in a meaningful way.

**Hippotherapy**
Therapy aided by a horse, utilising the horse’s movements. Reports that posture, muscle tone, coordination, balance, sensory/motor development as well as speech and language skills can be improved by hippotherapy.

**Aromatherapy**
Many people with KS enjoy the sensory experience of touch and smell, and this approach can aid relaxation, cooperation and listening, amongst other benefits.

**Reflexology**
Reflexology (massage or application of pressure to specific parts of the feet that are believed to correspond with other parts of the body) has been described as a beneficial, non-invasive approach to therapy for people with learning difficulties.

**Brushing**
Body brushing—a technique to stimulate nerve endings—has been used to heighten reflexes and improve CNS performance in people with learning difficulties.

**NB.** Very few scientific studies have been published about these therapies, and so there is no firm evidence to prove whether they are of benefit in KS overall, but they are included here because individual families have found them to be helpful.
Acknowledgements

• The Kabuki Syndrome Guideline Development Group

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Review Area

Speech, Communication, Cleft
Endocrine, Growth & Obesity, Orthopaedics
Neurology & Seizures, Cancer, Behaviour & Development
Cardiac
Birth Defects
Anaesthesia
Immunology & Skin
Vision & Hearing

• The Kabuki Syndrome Guideline Development Team

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Caroline Harrison, University of Manchester

• DYSCERNE: A Network of Centres of Expertise in Dysmorphology (www.dyscerne.org)

• Association Syndrome de Kabuki (ASK—http://asso.orpha.net/ASK/cgi-bin/)

• Nowgen—A Centre for Genetics in Healthcare (www.nowgen.org.uk)

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