Personalized pediatrics – an example of a monogenic condition

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Specific approach to children with a rare genetic condition

- Rare disease = a different approach or the one as in other children without the condition? (2016: 350 KS cases)
- Difficulties in establishing and optimal treatment if it is specific to KS – small cohorts!!!
- Small comparative analyses
- There may be isolates abnormalities, not necessarily reflecting the disease of the whole organism and not necessitating tretament (e.g. *thelarche*)
- **In very rare conditions it is rather the physician who listens to it's patients, not the other way round!!!**

Axial signs in genetic conditions

- Should concern different areas of development
- Are important when comes to the standards of care (one should focus on them)
- Example of KS:

1. developmental delay or intellectual disability,
2. infantile period hypotonia,
3. characteristic dysmorphism.

Dysmorphic features

- Long palpebral fissures with eventration of lateral third of lower palpebrae
- Arched and wide eyebrows
- Low-hanging columella(lower part of nasal septum)
- Flat nasal tip
- Large and prominent or cup-shaped earlobes
- Persistent fetal pads

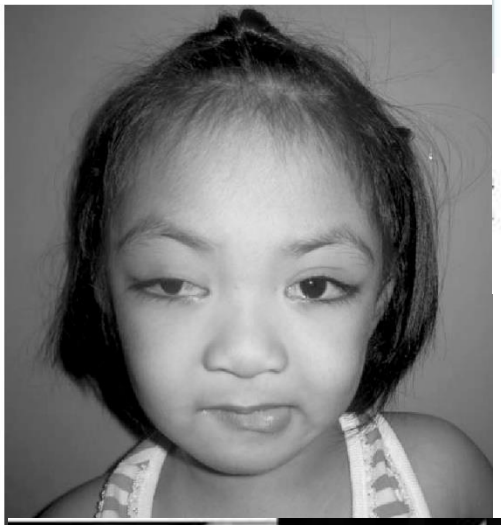

FIG. 9. Low hanging columella. Please note in the left panel

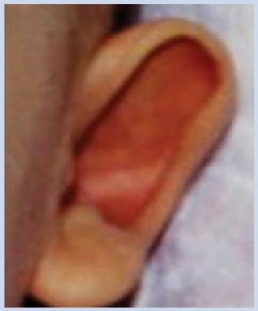

FIG. 22. Cupped ear.

FIG. 34. *Long palpebral fissures*, and *Lateral ectropion* are obvious in this boy.

Diagnostic criteria (facilitate diagnosis?)

1. **Definitive criteria:**

a) **Developmental delay and/or intellectual disability,**

b) **Infantile hypotonia,**

c) **At least one of those listed below:**

- **Presence of the path or likely path variant in *KTM2D* or *KDM6A***
- **Typical dysmorphism as above**

Molecular diagnostics of KS

***KMT2D* and *KDM6A* ,step-by-step' analysis:**

1. **Sequencing of the whole *KMT2D* gene (Sanger)**
2. **Deletion/duplication analysis of *KMT2D* (aCGH, MLPA)**
3. **Sequencing of the whole *KDM6A* (Sanger)**
4. **Deletion/duplication analysis of *KDM6A* (aCGH, MLPA)**

Multigene panel including both genes

Whole-exome sequencing (WES)

Hypoglycemia

- **Hyperinsulinism = hypoglycemia (when congenital hypoglycemia from congenital hyperinsulinism: there MUST be oral administration of high-sugar beverages or, when severe hypoglycemia, intravenous glucose or glucagon subcutaneously, intramuscularly or intravenously) (1% hyperinsulinism = KS)**
- Or diazoxide and octreotide
- Effective therapy = on drugs for up to 14-15 hours without meals (overnight)
- Treatment of mild hypoglycemia: fast-absorbing carbohydrates, preferably in liquid or gel form in the amount of 10-20g, e.g. glucose, or other simple sugars - 200-250 ml of fruit juice or coca-cola, glucose gel or dextrose tablets. After 15 minutes of taking carbohydrates, glycemic control is recommended.
- Hypoinsulinism - growth disorders and hypotension?
- Check your blood sugar if you develop seizures or a pre-epileptic condition
- **Problem of the unconscious person with KS (glycemia? Epilepsy?)**

Growth hormone (GH)

- **Monitor height and weight (and head circumference) on centile charts! Specialist physician if height and/or weight <3 centile, or if growth rate has dropped significantly (by two or more lines on a chart)**
- Postpartum growth disorders in KS: M 162cm, K 145cm
- 18 pre-pubertal (bone age!) children with KS (Maastricht) after stimulation tests - some with GH deficiency and some with normal GH production
- Response to GH: growth after a year: +> 0.5SD (non-GH deficit vs. GH deficit + 0.62SD vs. + 1SD)
- "Tallest" have the lowest height gain
- GH in the process of acceptance as a way to treat short stature of the Netherlands
- **GH has an effect on growth AND on body build**
- **In the case of treatment with GH, monitor for scoliosis and glycemia!**

Seizures/epilepsy

- 15-25% in KS (?)
- **Are they preceded by hypoglycemia ??**
- KABUK1 (36%): a group of 14 pts with KS (2-20 years) with the onset of seizures 9-12 years (the earliest description in KS is 2 years)
- **Seizures most often respond to the treatment with monotherapy**: carbamazepine (Tegretol, Neurotop, Finlepsin) most commonly used; valproic acid (Convulex, Depakina)
- Polytherapy and newer preparations (good response to levetiracetam predicted in some pts with KS)
- Ketogenic diet: in murine KS models, it improves cognitive function and may increase resistance to obesity caused by high-fat diet

Seizures/epilepsy [Seizure, 2011]

Table 1
Demographic and electroclinical data of patients with KS.

Patient/sex	Age at seizure onset (yrs)	Seizure semiology	Interictal EEG	Brain MRI	Therapy	Age at follow-up (yrs)	EEG outcome	Seizure outcome
1/M	5.5	PS	Right temporo-occipital spikes	Callosal hypoplasia	VPA	11.2	Normalized	Controlled
2/F	3.0	PS	Bilateral temporo-occipital spike–wave complexes	Adenohypophysis hypoplasia	CBZ	12.4	Normalized	Controlled
3/F	3.2	PS + SG	Bilateral fronto-temporal sharp waves	Normal	VPA	8.3	Normalized	Controlled
4/M	5.3	PS	Right fronto-temporal spike–wave complexes	Enlargement of lateral ventricles	VPA	10.6	Still paroxysmal	Controlled[a]
5/F	3.4	PS	Left temporo-occipital spike–wave complexes	Normal	VPA	9.1	Normalized	Controlled[a]
6/M	4.3	PS	Bilateral temporo-occipital spike–wave complexes	Normal	VPA	9.7	Normalized	Controlled
7/F	6.4	PS	Bilateral temporo-occipital spike–wave complexes	Normal	VPA	11.8	Normalized	Controlled
8/M	4.0 mo	ES → PS	Hypsarrhythmia → bilatera temporo-occipital polyspikes	Normal	Multiple AEDs	9.2	Still paroxysmal	Not controlled[b]
9/M	3.7	PS	Left temporo-occipital spike–wave complexes	Normal	Multiple AEDs	9.0	Normalized	Controlled[a]
10/M	5.0	PS	Right temporo-occipital sharp waves	Normal	Multiple AEDs	11.8	Still paroxysmal	Not controlled[a]

M: male, F: female, Yrs: years, Mo: months, PS: partial seizure, SG: secondary generalization, ES: epileptic spasms, EEG: electroencephalogram, MRI: magnetic resonance imaging, VPA: valproic acid, CBZ: carbamazepine, and AED: antiepileptic drug.

[a] Still on therapy.

[b] Death for status epilepticus at AED withdrawn.

Tumors???

TABLE 1 Primary pediatric tumors associated with Kabuki syndrome

Study	Sex and age at tumor diagnosis	*KMT2D* variant (NM_003482.3)	Clinical and radiological features	Tumor type	Tumor location	Treatment	Tumor relapse	Outcome
Ijichi (1996)	M, 3 y	-	FD, ID	Burkitt lymphoma (EBV +)	Abdomen	CT	No	Complete remission
Scherer (2003)	F, 2 y	-	FD, ID, CHD, hypotonia, seizures, recurrent ear and respiratory infections, brachymesophalangia, hip dysplasia, left kidney duplication, hypothyroidism, GHD, hearing impairment	Pre-B ALL	-	CT	No	Complete remission
Merks (2005)	F, -	-	-	Neuroblastoma	-	-	-	-
Shahdadpuri (2008)	F, 21 mo	-	FD, DD, horseshoe kidney, CHD	Low-grade fibromyxoid sarcoma	Chest	Surgery	No	Complete remission
Tumino (2010)	M, 6 y	-	FD, ID, growth delay, microcephaly, hypotonia, hyperlaxity, congenital hypothyroidism	Hepatoblastoma	Right hepatic lobe	CT, surgery	No	Complete remission
	F, 6 mo	-	CHD, congenital hypothyroidism, hyperlaxity, growth delay	Neuroblastoma	Adrenal and right hepatic lobe	Wait-and-see approach	No	Complete remission
Casanova (2011)	F, 16 y	-	FD, ID, ectopic left kidney, tooth agenesis, hip dysplasia, hypoplastic CC	Synovial sarcoma	Right lung	CT + surgery + RT	Yes	Died few months after the end of RT
Karagianni (2015)	F, 10.5 y	c.7307_7308insT, p.Ser2438Ilefs*11	FD, ID, hypotonia, CHD, ectopic pelvic kidneys, ventriculomegaly, vescicoureteral reflux, growth delay, recurrent ear and respiratory infections	Giant cell fibroblastoma	Right laterocervical	Surgery	Yes, treated with second surgery	Complete remission
Bernier (2016)	F, 30 mo	Not specified	FD, unspecified syndromic features	Pilomatricoma	Left cheek	Surgery	No	Complete remission
	F, 8 y	Not specified	FD, unspecified syndromic features	Pilomatricoma	Nuchal and behind right ear	Surgery	No	Complete remission
	M, 8 y	Not specified	FD, unspecified syndromic features	Pilomatricoma	Back	Surgery	No	Complete remission
de Billy (2018)	M, 5y	c.511-1G > A	FD, ID, horseshoe kidneys, CHD, sensorineural hearing loss	Burkitt lymphoma (somatic t[8;14])	Rhinopharyngeal	CT	No	Complete remission
Teranishi (2018)	F, 3y	c.13285C > T, p.Q4429*	FD, ID, hypoplastic left heart, Dandy-Walker syndrome, hypothyroidism, duplicated ureter, bilateral hearing impairment	Wilms tumor	Right kidney	Surgery + CT	No	Complete remission

Abbreviations: ALL, acute lymphoblastic leukemia; CC, corpus callosum; CHD, congenital heart defect; CT, chemotherapy; DD, developmental delay; EBV, Epstein-Barr virus; F, female; FD, facial dysmorphism; GHD, growth hormone deficiency; ID, intellectual disability; M, male; mo, months; RT, radiation therapy; y, years.

Pilomatrixoma – benign tumor

- Malherbe's calcifying epithelial tumor
- Usually in the 1st-2nd decade of life: asymptomatic slow-growing nodule originating from the hair
- Head & neck area - 2/3 of nodules
- Only a lump excision with a margin (2100 cases) is enough!

Nutritional problems and treatment

- **Nasogastric tube or gastrostomy (basically only PEG): the tube has an effect on motility, increases salivation and the risk of inflammation so a more convenient PEG (but with PEG one should be very careful in infants and/or children with body weight <5-10kg)**
- Treatment of gastroesophageal reflux, allowing a person to sit upright, increasing the "mass" of foods, and possibly providing anti-reflux medication. Macrogoles - can be used chronically (better to administer with electrolytes!): Dicopeg, Dulco, Forlax
- Exclude celiac disease (gluten intolerance), a condition that occurs more often in KS (gastroscopy!)

Nutritional problems and treatment

- Constipation: probably caused by hypotension of the intestine and/or the abdominal wall and/or due to reduced mobility
- Diet high in fiber, laxative and probably treatment with standard laxatives
- High risk of obesity in adolescence and young adults - a varied diet, physical activity

- http://www.ptzkd.org/new/wp-content/uploads/2017/05/Zalecenia-leczenia-zywieniowego-u-dzieci-z-przewleklymi-chorobami-ukladu-nerwowego-120217.pdf

The assessment of energy needs (compared to growth age) can be made using formulas for basic (resting) energy expenditure, expressed in kcal / day [35]: W = body weight in kg; H = body length (height) in cm.
Boys: <3 years: 0.167 x W + 15.174 x H - 617.63-10 years: 19.59 x W + 1.303 x H + 414.910-18 years: 16.25 x W + 1.372 x H + 515.518-30 years: 15.057 x W - 0.1 x H + 705.8 Girls: <3 years old: 16.252 x W + 10.232 x H - 413.53-10 years old: 16.969 x W + 1.618 x H + 371.210-18 years old: 8.365 x W + 4.65 x H + 200.018-30 years old: 13.623 x W + 2.83x H + 98.2
Example: A girl 4 years and 11 months (59 months): body weight 19 kg, body length 102.4 cm. The growth age is 46 months (3 years and 10 months).
Calculation of resting energy expenditure, compared to growth age: 16.969 x W + 1.618 x H + 371.2 = 16.969 x 19 + 1.618 x 102.4 + 371.2 = 859.3 kcal6
To determine your total daily energy needs, follow these guidelines:
1. In the case of obese patients, the supply should correspond to the basic energy expenditure.
2. In the case of intensively rehabilitated patients, the basic energy expenditure should be multiplied by a factor of 1.2 - 1.4.
3. In the event of unsatisfactory weight gain during the first 4 to 6 weeks of treatment, the ratio should be set at 1.5.
4. In patients with reduced physical activity, energy supply should correspond to the result of basic energy expenditure multiplied by a factor of 1.25.

During nutritional treatment, periodic monitoring of weight change and body length is necessary. In the event of excessive or insufficient weight gain in 3-6 month periods, the nutritional recommendations must be reviewed. The first follow-up visit should take place after 4-6 weeks of treatment, so that the recommendations can be verified.
In relation to the above-mentioned case, total energy needs at the beginning of the treatment can be determined in accordance with section 2: 859.3 kcal x 1.2 = 1031 kcal (which means a supply of 54 kcal / kg body weight). In the event of treatment failure and maintaining the same body weight after 4 weeks, the supply should be increased to 1289 kcal (after applying a factor of 1.5), in accordance with point 3 (i.e. 68 kcal / kg of current body weight)

Ophthalmology

- Night-time lagophthalmos: creams, *eyelid taping*, soft lenses, botulinum toxin inj
- Surgery: golden plate
- However most children with KS: not very significant eyesight problems

Developmental delay/ID

- Always rule out hearing loss as the cause of cognitive problems: glue ear due to frequent recurrent ear infections (conductive hearing loss) (is there palatal insufficiency or submucosal cleft? or is hearing loss sensorineural one? - ENT)
- **PALATAL INSUFFICIENCY CAN LEAD TO NUTRITIONAL PROBLEMS, EAR INFECTIONS AND SPEECH EXPRESSION PROBLEMS!**
- Such hearing loss causes speech perception disorders
- Overall, average IQ = 35-69 (doubtful utility)
- Van Dongen: 29 pts with KS (5-48 years) vs control population vs 15 pts with other genetic syndromes

Developmental delay/ID

- Generally: weaker skills in all cognition spheres as compared to control group without a genetic syndrome
- More adequate is the comparison with the groups with other genetic conditions:

1. Specific deficits of visual memory and spatial coordination
2. No differences: planning and cognition in social sphere
3. Relative verbal strength

Table I Medical characteristics of participants with Kabuki syndrome

Domain	*n*	Specification
Ocular problems	17	Minor problems successfully compensated by glasses or disturbed stereoscopic vision/strabism
	4	Severe problems: total loss of sight in one eye for all four participants and for three of them additionally a loss of 50% in the other eye[1], loss of 85% and tube vision in the other eye[1], and nystagmus[2]
Hearing problems	3	Single sided deafness
	7	Minor hearing problems were present without a need for hearing aids
	9	Hearing problems that were successfully compensated by hearing aids
	7	Hearing problems that were not sufficiently compensated by hearing aids. Hearing was however still sufficient for cognitive assessment
Brain imaging reports	-	Reports present for three participants; these did not show any structural anomalies, besides microcephaly in one participant
Possible neural damage as a result of brain trauma	3	Oxygen shortage during birth [1], cerebrovascular accident [2], oxygen shortage as a result of low blood sugar [2]
Brain functioning	1	History of epileptic seizures, currently in remission with the use of Depakine
Psychopharmacotherapy	3	Antipsychotics (aripiprazol, risperidon and Dipiperon)
Sleep medication	5	Melatonin
Hormone treatment	9	-

Physical rehabilitation and psychological support

- Ways of physical rehab are not different from those of other children with hypotonia and motor delay
- More adequate are auditory than visual stimuli due to weaknesses in visual sphere!
- Specific weakness concerns precise hand movements, therefore workshops indicated

Behavioral therapies

- Applied Behavior Analysis – positive augmentation of beneficial behaviors and elimination of risky behaviors
- Positive augmentation through rewarding positive behaviors

Hypotonia / gross motor dysfunction

- Dutch register: only one individual with KS, that is wheel-chair bound after numerous surgeries
- Part of KS (majority of children) is joint hypermobility = patellar instability, od large joints, which with age RATHER(?) has tendency to disappear
- **During intubation prior to large invasive procedures there may be a hypermobility that may lead to cervical spine instability! Anesthesiologist must place the child in a secure position before intubation**

Hypotonia / gross motor dysfunction

Am J Med Genet A. 2019 Feb;179(2):219-223. doi: 10.1002/ajmg.a.60696. Epub 2018 Dec 17.

Hypermobility in individuals with Kabuki syndrome: The effect of growth hormone treatment.

Schott DA[1,2], Stumpel CTRM[3], Klaassens M[1].

Author information

Abstract

Kabuki syndrome (KS) is a multiple congenital malformation syndrome which has been described across all ethnic groups. Most KS patients possess two genetic subtypes: KMT2D-associated, autosomal-dominant KS type 1 (KS1; OMIM 147920); and KDM6A-associated, X-linked-dominant KS type 2. Generalized joint hypermobility is one feature of KS, but its exact incidence and pattern is not well described in the literature. As part of our prospective study on the metabolic and growth effect of GH treatment, we assessed children from our Dutch Kabuki cohort who were eligible for growth hormone therapy. We assessed severity and pattern of joint hypermobility, both before and after 24 months of growth hormone replacement therapy. The prevalence of hypermobility was 31% in boys and 14% in girls using the Beighton score and 69% in boys and 57% in girls using the Bulbena score. This varies from the general population where girls are more affected. After 2 years of growth hormone treatment, there was a statistically significant decrease in the presence of joint hypermobility to 6% using the Bulbena score and none with respect to the Beighton score. We hypothesized that this result suggests a direct effect of growth hormone on connective tissue in patients with KS.

Other

- Majority of KS children have hypogammaglobulinemia and IgA deficit – most often not requiring treatment
- **In case of angioplasty or cardiac catheter placement there MAY BE an increased risk of aortic aneurysm**
- Lack of increased risk of malignant tumors = lack of screening

Other

- 2014: ‚Read-through' gentamicine therapy in nonsense (NMD) variants in HEK cells (about 20 children) and in 2 children with KS: partial recovery of the protein
- Such trials have been scarce and their effectiveness is doubtful

Clinical assessment	Visit frequency
Physical parameters (health status, body length and weight and OCF)	Every month at 1-2 years Every year later Individually with reflux or constipation
Skeleton and muscles (monitoring for scoliosis and hypotonia)	Every year
Eye (strabismus, astigmatism, myopia, lagophthalmos)	At least once a year
Hearing	Every year
Endocrinology (GH, glycemia, thyroid function)	Neonatal period: exclusion of hypoglycemia and then later assessments after 1 year GH when short stature Thyroid hormones: every 2-3 yrs
Immunology	In case of frequent infections
Development	On every visit

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Active, not recruiting	Exploiting Epigenome Editing in **Kabuki Syndrome**: a New Route Towards Gene Therapy for Rare Genetic Disorders	• **Kabuki Syndrome** 1	• Genetic: Intervention on primary cultured cells	• Arnaud de villeneuve Hospital Montpellier, Herault, France
2	☐	Completed	French **Kabuki Syndrome** Network. Epidemiology, Management of Patients and Research by Array-CGH	• **Kabuki Syndrome**		• Department of Genetic, Necker Hospital Paris, France
3	☐	Completed	Assessment of Memory in Children With **Kabuki** Syndrom	• **Kabuki Syndrome**	• Other: No arm intervention	• Genetic Departement, rare disease, personalized medicine Montpellier, Herault, France
4	☐	Completed Has Results	Actigraphic Analysis of Treatment Response	• Sleep Disorders, Circadian Rhythm • Insomnia • Psychomotor Agitation	• Drug: risperidone	• Child Psychopharmacology Institute Fargo, North Dakota, United States
5	☐	Recruiting	Rare Disease Patient Registry & Natural History Study - Coordination of Rare Diseases at Sanford	• Rare Disorders • Undiagnosed Disorders • Disorders of Unknown Prevalence • (and 271 more...)		• Sanford Health Sioux Falls, South Dakota, United States • Online Patient Enrollment System Sydney, Australia

Dokładna informacja

Artykuł dla ogółu społeczeństwa

Svenska (2014)

English (2014)

Profesjonaliści

> Streszczenie informacji

Greek (2012, pdf)
Suomi (2012, pdf)
Polski (2012, pdf)

> Wytyczne dotyczące znieczulenia

English (2015, pdf)

> Przegląd genetyki klinicznej

English (2019)

> Zestawienie informacji o niepełnosprawności

Français (2018, pdf)

Dodatkowy informacja

Dalsze informacje na temat tej choroby

- Klasyfikacje (8)
- Genów (4)
- Niepełnosprawność
- Oznaki i objawy kliniczne
- Publikacje w PubMed
- Inne strony internetowe (6)

Zasoby opieki zdrowotnej dla tej choroby

- Centra eksperckie (324)
- Testy diagnostyczne (64)
- Organizacje pacjentów (56)
- Sierocych leków (1)

Badania nad tą chorobą

- Projekty badawcze (35)
- Badania kliniczne (0)
- Rejestry / biobanki (26)
- Sieci (27)

Specjalistyczne usługi socjalne

- Eurordis informator