Characteristics of children with Kabuki syndrome and hyperinsulinemic hypoglycemia

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Background

Kabuki syndrome (KS) is a rare multiple congenital malformation and intellectual disability syndrome. KS is caused by pathogenic variants in the genes *KMT2D* or *KDM6A*. In 0.3-4 % of patients, KS is reported to be associated with hyperinsulinemic hypoglycemia. The objective of this study was to characterize the clinical, biochemical and molecular data of children with KS and hyperinsulinemic hypoglycemia. Data of 6 female children with KS and hyperinsulinemic hypoglycemia from three centres in Germany and Denmark were retrospectively analysed.

Tab. 1 Clinical and metabolic features	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age at last visit	4 years	7 years	13 years	1 year	14 years	14 months
Gender	female	female	female	female	female	female
Presentation of hypoglycemia	DOL1	DOL1	DOL1	DOL1	DOL1	DOL1
Plasma Glucose	0.78 mmol/l (14 mg/dl)	1.17 mmol/l (21 mg/dl)	0.61 mmol/l (11 mg/dl)	1.67 mmol/l (30 mg/dl)	0.67 mmol/l (12 mg/dl)	1.0 mmol/l (18 mg/dl)
Insulin in hypoglycemia at diagnosis	15.9 mU/l	15.3 mU/l	16.56 mU/l	17.0 mU/l	Elevated insulin. No specific data.	Insulin 2.2 mU/l
Initial glucose requirements	n.d.	8 mg/kg/min	23 mg/kg/min	n.d.	11.3 mg/kg/min	n.d.
CHI medication	Diazoxide 10 mg/kg/d, gradually tapered to 6 mg/kg/d at 3 years	Diazoxide 10-12.5 mg/kg/d, gradually tapered to 6.5 mg/kg/d	Diazoxide <3.5 mg/kg/d until the age of 9 years	Diazoxide 5 mg/kg/d	Diazoxide 5 mg/kg/d	Diazoxide 5 mg/kg/d
Feeding regime/ nutritional support	Nasogastric tube feeding within the first months of life	Nasogastric tube feeding within the first months of life; Maltodextrin & Glycosade before bedtime (30 g/13 g)	Tube feeding until 8 years of age; carbohydrate enriched meals	Breastfeeding	Breastmilk pumped and regular breastfeeding	Nasogastric tube feeding within the first months of life
Fasting tolerance	3 months: 3 h 22 months: 10 h (all under Diazoxide)	8 months: 3.5 h 7.5 years: 10.5 h (all under Diazoxide)	7 years: 13 h (under Diazoxide); 9 years: 18 h (without treatment)	n.d.	2½ months: 3 h (under Diazoxide); no fasting tolerance tests since then	10 months: 6 h (under Diazoxide)
Age of KS diagnosis	10 months	7 years	9 years	1 year	14 years	9 months
Genotype	Heterozygous de novo pathogenic variant in KDM6A c.278_279insTT (p.Asp94Leufs*7)	Heterozygous pathogenic variant in KMT2D c.9964C>T p. (Gln3322*), no segregation testing performed	Heterozygous de novo pathogenic variant in KDM6A c.3680G>A (p.Trp1227*), skewed x-inactivation	Heterozygous de novo pathogenic variant in KDM6A c.1139delG (p.Arg380Lysfs)	Heterozygous de novo pathogenic variant in KDM6A c.16339-2A>G (exome trio scan)	Heterozygous pathogenic variant in KMT2D c.9997C >T (p.Gln333Ter)
Facial/Eye/Oral	Elongated palpebral fissures; coarse facial features; high palate; low set prominent ears; depressed nasal bridge; low hairline; strabismus	Elongated palpebral fissures; arched eyebrows; long eyelashes; deep voice; prominent ears; strabismus	Elongated palpebral fissures; arched eyebrows; long eyelashes; low set, prominent ears; broad philtrum	Elongated palpebral fissures; elongated eye distance; arched eyebrows; marginal epicanthus; prominent ears; depressed nasal bridge	Flat face; elongated eye distance; up-slanting eye fissures; smooth philtrum; congenital glaucoma; nystagmus; hypodontia; hypoplastic maxilla	Elongated palpebral fissures; arched eyebrows; long eyelashes
Skeletal	Short stature (-2.21 SDS)	Normal stature (-1.75 SDS)	Short stature (-2.5 SDS)	Normal stature (0.12 SDS); hip instability	Short stature (-2.0 SDS)	Short stature (-3.9 SDS)
Neurological	Pathological EEG with sporadic spike-wave, no clinical seizures; developmental delay	Recurrent afebrile seizures since ~6 years of age, anticonvulsive treatment	Muscle hypotonia; microcephaly; 3 febrile seizures; developmental delay; anxiety disorder	Developmental delay; hyperactivity	Mental retardation; delayed fine motoric function	Muscle hypotonia; developmental delay
Cardiovascular	PDA (spontaneous closure); left ventricular hypertrophy (only neonatal); PFO	VSD; PDA; pulmonary artery banding, surgical PDA- and VSD-closure	Hypertrophy of the ventricular septum (only neonatal); PFO (spontaneous closure)	Hypertrophy of ventricular septum; minor aortic valve insufficiency	-	Aortic isthmus stenosis
Gastrointestinal	Gastroesophageal reflux; feeding difficulties	Feeding difficulties; recurrent vomiting	Feeding difficulties; gastroesophageal reflux; recurrent vomiting	Recurrent vomiting	-	Feeding difficulties; recurrent vomiting
Urogenital	-	-	Duplicated kidney	-	-	-

DOL = Day of life; KDM6A encodes lysine-specific demethylase 6A ; KMT2D encodes lysine-specific methyltransferase 2D; SDS = Standard deviation score; PDA = Patent ductus arteriosus; PFO = Patent foramen ovale; VSD = Ventricular septal defect; EEG = Electroencephalography

Discussion/Conclusion

In our study, all children presented with hyperinsulinemic hypoglycemia on the first day of life. Treatment with Diazoxide achieved normoglycemia. Nasogastric tube feeding was required in the majority of patients, but primarily because of insufficient feeding and not as part of the hypoglycemia treatment. It took months to years to diagnose KS. Thus, this entity should be carefully considered in children with hyperinsulinemic hypoglycemia especially in the presence of other extrapancreatic/syndromic features, even if these are subtle in young infants. Surprisingly, compared to a recent metaanalysis showing *KMT2D* variants in 399 of 449 patients, 4 out of 6 of our patients had a variant in *KDM6A*. This might indicate that hyperinsulinemic hypoglycemia occurs more likely in *KDM6A*-associated KS, and *KDM6A* loss-of-function variants predispose more specifically to beta cell dysfunction compared to *KMT2D* loss-of-function.

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