Persistent hyperinsulinism in Kabuki syndrome 2: case report and literature review

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Abstract

Kabuki syndrome is a clinically and genetically heterogeneous congenital malformation syndrome with protean clinical manifestations. This reflects the important epigenetic role in embryonic development of the two genes currently known to be associated with Kabuki syndrome *i.e., KMT2D* and *KDM6A,* which are responsible for Kabuki syndrome 1 and Kabuki syndrome 2, respectively. Hypoglycemia is thought to be a rare manifestation of Kabuki syndrome; however it may be under diagnosed. Herein we describe the case of a 5-year-old girl with Kabuki syndrome 2 in whom persistent hyperinsulinism was diagnosed at 4 years of age. We postulate an epigenetic mechanism for hyperinsulinism where specific loss *KDM6A* demethylation of the H3K27me3/me2 mark may lead to deregulated pancreatic β-cell development.

Introduction

Kabuki syndrome (KS) is a clinically and genetically heterogeneous congenital malformation syndrome first described by Niikawa and Kuroki in 1981.[1,2] Heterozygous pathogenic mutations in the *KMT2D* gene (OMIM 602113) are responsible for Kabuki syndrome 1 (KS1 OMIM 147920). The *KMT2D* gene located to chromosome 12 and encodes a lysine-specific methyltransferase.[3] Heterozygous pathogenic mutations in the *KDM6A* gene (previously known as *UTX*, OMIM 300128) are responsible for Kabuki syndrome 2 (KS2, OMIM 300867).[3-7] The *KDM6A* gene is located on the X-chromosome and encodes a histone demythalase that interacts with *KMT2D*.

KS presents with a range in prevalence from 1:32,000 in Japan to 1:86,000 in western countries.[7-9] KS is characterized by five cardinal manifestations, which include: i) a characteristic face recognized by eversion of the lower lateral eyelid, a depressed nasal tip, arched eyebrows with the lateral one third dispersed, and prominent ears; ii) skeletal anomalies including brachydactyly and scoliosis; iii) abnormal dermataglyphic presentation including fingertip pads and increased loops in the fingerprint; iv) mild to moderate cognitive impairment; v) postnatal growth deficiency despite average birth weight and height.[7-9] Other commonly reported clinical manifestations include recurrent otitis media, cleft palate, neonatal hypotonia, feeding problems, oligondontia, and impaired cardiovascular, renal and genitourinary, gastrointestinal, musculoskeletal, immunologic, and endocrinology functioning.[9]

Hypoglycemia is thought to be a rare manifestation of KS; however it may be under diagnosed. Hypoglycemia in KS patients have been reported secondary to growth hormone deficiency, adrenal insufficiency secondary to adrenocorticotropic hormone deficiency, and hyperinsulinism.[4,9-14] Herein we describe the case of a 5-year-old girl with KS2 in whom persistent hyperinsulinism was diagnosed at 4 years of age, we postulate an epigenetic mechanism for hyperinsulinism in KS2.

Case Report

Our female patient, now 5 years of age, received a clinical diagnosis of KS at 2 years of age on the basis of characteristic facial features, global developmental delay, motor delay with hypotonia and bulbar dysfunction, abnormal dental eruptions, significant joint hypermobility and multiple gut allergies.

During the neonatal period she had symptomatic hypoglycemia in keeping with hyperinsulinism. This required continuous glucose infusions at 12 mg/kg/min to maintain normoglycemia in the first 3 days of life. There was no requirement for diazoxide at this stage, and the working diagnosis was of transient hyperinsulinism.

Over the ensuing 12 months she required enteral feeding via a nasogastric tube and then ultimately a percutaneous gastrostomy (PEG) device. The enteral feeding was instituted due to failure to thrive attributed to poor oral intake and multiple intestinal allergies best described as cow's milk protein allergy. Continuous overnight feeds were supplemented with regular bolus feeds during the day of an elemental formula.

At 4 years of age, concerns about glucose homeostasis were investigated in lieu of behaviors changes and sweating occurring 2 h after a bolus PEG feed. A controlled inpatient hasting study confirmed hypoglycemia [blood glucose 2.1 mmol/L (reference range 3.6-7.7 mol/L)] after 90 min of fasting. Insulin levels at this time were inappropriately elevated (2 mU/L). Calculating her carbohydrate content of her bolus feeds, and continuous overnight feeds indicated that she was receiving 12 mg/kg/h of glucoses, which was also suggestive of hyperinsulinism, given that most children only required 6-8 mg/kg/h of glucose to maintain normoglycemia in normal physiological conditions.

At the time of hypoglycemia a cortisol level was appropriately elevated (600 mmol/L) but she demonstrated a suboptimal growth hormone response (8 mIU/L). Partial growth hormone insufficiency was subsequently excluded with a normal growth hormone stimulation study with excellent growth hormone responses (27 mIU/L) to stimulation of arginine and glucagon. Gastric dumping syndrome was excluded with a normal PEG fluoroscopy study.

Diazoxide was commenced at 50 mg three times a day, which produced a rapid and sustained improvement in glucose homeostasis, with documented capabilities to fast >12 h without developing hypoglycemia. Hypertrichosis has developed as a complication of diazoxide treatment.

Sequencing of the *KMT2D* and the *KDM6A*

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genes were performed by the Manchester Centre for Genomic Medicine, Genomic Diagnostic Laboratory, Central Manchester University Hospitals NHS UK. Using extracted lymphocyte DNA, whole coding sequences of the *KMT2D* and *KDM6A* genes, including the splice donor and acceptor sites, were amplified using long range polymerase chain reaction followed by screening using Next Generation sequencing with Illumina MISeq sequencing by synthesis technology. The whole coding region end flanked by sequences to +/- 15 bp were submitted to a minimum of 100x coverage with mutation and variant calling by a customized bioinformatic pipeline. Mutations and unclassified variants were confirmed via Sanger sequencing (using BigDye version 3.1). Large deletions and duplications of KMT2D were tested via multiplex ligation dependent probe amplification (MLPA) using the P389-A1 MLL2 MRC-Holland probemix, which contains probes for 23 of the 52 exons of *KMT2D*. Large deletions and duplication of *KDM6A* were tested for using MLPA using a custom-designed probemix, which contains Integrated DNA Technologies probes for exons 1, 5, 9, 22, and 29 of *KDM6A*, and these probes were added to the P200-A1 MRC-Holland Human DNA Reference-1 probe mix. Mutations were reported in accordance with the current Human Genome Variation Society guidelines. *KMT2D* sequencing was normal. *KDM6A* sequencing identified a *de novo* pathogenic heterozygous nonsense mutation in exon 6; c.493C>T (p.Arg165Ter).

Discussion

Persistent hypoglycaemia is a rare finding in Kabuki Syndrome, most commonly reported in the neonatal period, but is a more common finding in KS2.[4,11] There are sparse published cases of hypoglycemia in Kabuki Syndrome in the infancy period,[7] with causes being attributed to combined pituitary hormone deficiency,[8] growth hormone deficiency,[9] and adrenal insufficiency.[9-14] Persistent hypoglycemia secondary to hyperinsulinism is a rare event in KS.

Persistent hyperinsulinism is a clinically and genetically heterogeneous disease, with etiologies including monogenic, syndromic, metabolic, and secondary processes. There are now 11 genes associated with monogenic forms of hyperinsulinism (*ABCC8, KCNJ11, GLUD1, GCK, HADH1, UCP2, MCT1, HNF4A, HNF1A, HK1, PGM1*).[15] Hyperinsulinism has been reported as clinical feature in an eclectic array of syndromes including Turner syndrome, Beckwith-Wiedemann syndrome, Sotos syndrome, Costello syndrome, Simpson-Golabi-Behmel syndrome, Ondine syndrome, Usher syndrome, Perlman syndrome, Timothy syndrome, and the congenital disorders of glycosylation.[16,17] The monogenic and syndromic causes of hyperinsulins have provided valuable insight into the cellular mechanisms associated with hyperinsulinism, which broadly rest with perturbations at three levels: channelopathies, enzyme anomalies, and transcription factor defects.[17] Channelopathies affect the subunits of an adenosine triphosphate (ATP)-sensitive potassium (KATP) channel set through the plasma membrane of the pancreatic b-cells *i.e.,* the sulfonylurea receptor and the inward rectifying potassium channel.[15,17] When closed, the KATP channel depolarizes the plasma membrane which induces insulin secretion. Enzymes anomalies or other metabolic diseases can produce hyperinsulinism by affecting ATP/adenosine diphosphate (ADP) ratio within the b-cells, which determines controls the opening of the KATP channel.[15,17] Transcription factors may induce hyperinsulinism by altering KATP channel subunit expression.[15,17] How syndromes such as KS2 induce hyperinsulinism remains unclear at this junctures.

The *KMT2D* and *KDM6A* genes are both histone modifiers integral to normal development and embryogenesis.[5] Histone modification include molecular processes such as methylation, acetylation, phosphorylation, and ubiquitination, which are essential process to coordinate translational and signaling networks required for appropriate cellular differentiation during embryogenesis.[18] The tissue specific expression of chromatin genes is marked with an active histone modification like H3K4 methylation and H4 acetylation, while chromatin states of the same genes are enriched with repressive marks such as H3K27 methylation.[18] The *KDM6A* gene encodes a lysine-specific demethylase that specifically demethylates the H3K27me3/me2 mark and aims to induce a steady state of H3K27me3 in proliferating cells.[19] The endocrine pancreatic cells demonstrate an increase in the number of H3K27me3 domains during differentiation *in vivo*.[20] Disruption in this expression dynamic can lead to altered pancreatic beta-cell development, and *EZH2* and *KDM6A* are known to act as epigenetic switches in mesenchymal stem cell differentiation.[21] The mechanisms of transient and persistent hyperinsulinism, in genetic syndromes such as KS2, remain to be fully elucidated. The *KDM6A* gene is an important modifier, which induces a multisystem clinical phenotype in KS2. Hoe pathogenic sequence variants in the *KDM6A* gene cause perturbations in b-cell insulin release remains to be clarified, with potential mechanisms including alerting KATP channel function, altering the ATP/ADP ratio, or altered demethylation of the H3K27me3/me2 mark.

Conclusions

Given that hypoglycemia appears to be more common in KS2, we propose that all KS2 children be screened for persistent hypoglycemia, as failure to recognize and manage hypoglycemia can generate preventable otherwise adverse neurological outcomes. Clinician awareness of hyperinsulinism in KS2 and clinical features of hypoglycemia are essential for screening in the first instance. Pre-meal formal blood glucose measurements or formal fasting studies are other dynamic measure available to the clinician in screening for hyperinsulinism.

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