CLINICAL CASE SEMINAR

Hyperinsulinemic Hypoglycemia in Beckwith-Wiedemann Syndrome due to Defects in the Function of Pancreatic β-Cell Adenosine Triphosphate-Sensitive Potassium Channels


Background: Beckwith-Wiedemann syndrome (BWS) is a congenital overgrowth syndrome that is clinically and genetically heterogeneous. Hyperinsulinemic hypoglycemia occurs in about 50% of children with BWS and, in the majority of infants, it resolves spontaneously. However, in a small group of patients the hypoglycemia can be persistent and may require pancreatectomy. The mechanism of persistent hyperinsulinemic hypoglycemia in this group of patients is unclear.

Patients and Methods: Using patch-clamp techniques on pancreatic tissue obtained at the time of surgery, we investigated the electrophysiological properties of ATP-sensitive K⁺ (KATP) channels in pancreatic β-cells within the pancreas. The focal form of hyperinsulinemic hypoglycemia in infancy; HI, hyperinsulinism in infancy; KATP channel, ATP-sensitive K⁺ channel; TH, tyrosine hydroxylase; UPD, uniparental disomy.

Results: Persistent hyperinsulinism was found to be caused by abnormalities in KATP channels of the pancreatic β-cell. Immunofluorescence studies using a SUR1 antibody revealed perinuclear pattern of staining in the BWS cells, suggesting a trafficking defect of the SUR1 protein. No mutations were found in the genes ABCC8 and KCNJ11 encoding the two subunits, SUR1 and Kir6.2, respectively, of the KATP channel. Genetic analysis of this patients BWS showed evidence of mosaic paternal isodisomy.

Conclusions: In this novel case of BWS with mosaic paternal uniparental disomy for 11p15, persistent hyperinsulinism was due to abnormalities in KATP channels of the pancreatic β-cell. The mechanism/s by which mosaic paternal uniparental disomy for 11p15 causes a trafficking defect in the SUR1 protein of the KATP channel remains to be elucidated. (J Clin Endocrinol Metab 90: 4376–4382, 2005)

HYPERSURFACE IN INFANCY (HI) causes persistent hypoglycemia in infancy and early childhood period. Recent advances in understanding the pathophysiology of this condition have revealed unique insights into the mechanisms regulating insulin secretion from pancreatic β-cells (1, 2). HI is a heterogeneous disease with respect to clinical presentation, molecular biology, and underlying genetics (3). So far, mutations in five different genes have been described, which lead to inappropriate insulin release with respect to the blood glucose concentration (4–8). The commonest cause of persistent HI are mutations in the genes (ABCC8 and KCNJ11) encoding the two components (SUR1 and KIR6.2) of the ATP-sensitive K⁺ (KATP) channel. More than 100 mutations have been described in the ABCC8 gene and about four in the KCNJ11 gene. These mutations affect channel assembly, trafficking, and gating properties (2). Despite these advances, in approximately 50% of all patients with persistent HI, no mutations in either gene have been found.

Histologically, HI can be divided into two major subtypes (9). The diffuse form of the disease is inherited recessively and involves all β-cells within the pancreas. The focal form
(Fo-HI) consists of adenomatous hyperplasia within a limited region of the pancreas, and it is caused by somatic loss of heterozygosity, including maternal Ch11p15 in a β-cell precursor carrying a germ-line mutation in the paternal allele of SUR1 or Kir6.2 (10, 11). Several imprinted genes are located within this chromosomal region, some of which, including p57kip2 and IGF-II, have been associated with the regulation of cell proliferation. p57kip2 is paternally imprinted (i.e. expressed from the maternal allele) in human pancreatic β-cells, and the loss of expression in Fo-HI is caused by loss of heterozygosity, leading to increased cell proliferation and increased IGF-II expression (12).

Beckwith-Wiedemann syndrome (BWS) is a congenital overgrowth syndrome that is clinically and genetically heterogeneous. Phenotypically, BWS is associated with prenatal and/or postnatal overgrowth, macroglossia, anterior abdominal wall defects, organomegaly, hemihypertrophy, ear lobe creases and helical pits, and renal tract abnormalities. Genetically, BWS is a complex multigenic disorder caused by dysregulation of imprinted growth regulatory genes within the Ch11p15 region (13). Approximately 2% of BWS cases have chromosomal abnormalities involving Ch11p15.5, and 5% of sporadic cases have germ-line mutations in the candidate tumor suppressor gene CDKNIC. About 20% of patients with BWS have paternal uniparental disomy (UPD) for Ch.11p15 (13), and these patients are predicted to have increased expression of the paternally expressed growth promoter IGF2 and reduced expression of the maternally expressed CDKNIC and H19 genes. In all cases with UPD for Ch.11p15, the affected patient is mosaic for a paternal disomy and a normal cell line, indicating that paternal UPD has arisen due to a postzygotic event (14) (see Fig. 1). Up to 60% of sporadic patients have methylation alterations at imprinting control regions, leading to disordered imprinting of IGF2, CDKNIC, or H19 (15).

The incidence of hyperinsulinemic hypoglycemia in children with BWS is about 50% (16). This hypoglycemia can be transient, which, in the majority of infants, will be asymptomatic and resolve within the first few days of life. In about 5% of children, the hyperinsulinemic hypoglycemia can be persistent and extend beyond the neonatal period, requiring either continuous feeding, medical therapy, or, in rare cases, partial pancreatectomy (17, 18). In this group of children, the hypoglycemia can be severe, causing significant brain damage as well as death (19). The underlying mechanism(s) leading to persistent hyperinsulinemic hypoglycemia in this syndrome is unclear.

Using patch-clamp techniques on pancreatic tissue obtained at the time of surgery, we investigated the electrophysiological properties of KATP channels in pancreatic β-cells in a patient with BWS and severely medically unresponsive hyperinsulinemic hypoglycemia. We report a novel case of BWS with mosaic paternal UPD for Ch.11p15 in which persistent hyperinsulinism was found to be caused by loss of function of KATP channels of the pancreatic β-cell.

**Patients and Methods**

**Clinical details**

The patient was born at term with a birth weight of 3.8 kg to non-consanguineous parents. He developed persistent hyperinsulinemic hypoglycemia within 24 h after birth, with a maximum glucose infusion rate of 20 mg/kg/min (normal is 4–6 mg/kg/min). At birth, there were no obvious clinical features of BWS, but, postnatally, he developed right-sided hemihypertrophy, macroglossia, ear lobe creases, and an umbilical hernia. He failed to respond to diazoxide (5–20 mg/kg/dose) or nifedipine (0.25 mg/kg/dose) and had breakthrough hypoglycemia while on continuous sc infusions of octreotide (5–25 μg/kg/dose) and glucagon (5–20 μg/kg/h dose). Normoglycemia could only be maintained on a combination of continuous infusion of 20% glucose and feeds.

Given the severity of his hyperinsulinemic hypoglycemia, it was decided to perform a partial pancreatectomy. He continued to be hypoglycemic after the operation and again failed to respond to maximum doses of diazoxide but eventually maintained normoglycemia on octreotide injections (20 μg/kg/dose) and frequent (two to four hourly) feeds supplemented with 10% Maxijul. Thereafter, it proved possible to progressively reduce the energy content of his diet and to wean down his dose of octreotide such that all therapy was discontinued at the age of 14 months. At that age, a prolonged fast resulted in hypoglycemia (blood glucose, 2.4 mmol/liter at 15 h fasting) associated with an undetectable circulating serum insulin concentration (<1 μU/liter) and a free fatty acid concentration of 2.7 mmol/liter with a total ketone body response of 2.1 mmol/liter. Over the following year, no spontaneous episodes of hypoglycemia have been documented, and he demonstrates normal growth and neurodevelopmental progress. The study was approved by the Ethics Committee of Great Ormond Street Children’s Hospital and the Institute of Child Health; written informed consent was obtained from the parents or guardians.

**Molecular genetic analysis for BWS**

Evidence of paternal isodisomy was sought by genotyping the patient and his parents with the polymorphic microsatellite markers D11S1984 and tyrosine hydroxylase (TH) in chromosome 11p15.5. Each marker was amplified separately using fluorescently tagged primers described previously (GenBank accession no. G08894) (20, 21). PCR reactions for D11S1984 contained 10 pmol of each primer, 0.2 mm dNTP, 100 ng DNA, 1 PCR buffer (AmpliTaq; Applied Biosystems, Foster City, CA), 1.5 mm magnesium chloride (AmpliTaq), and 0.75 U of Taq DNA polymerase (AmpliTaq) in 10 μL. The PCR cycling was performed using a Tetrad DNA engine as follows: initial denaturation at 95°C for 5 min, followed by 24 cycles of 95°C for 1 min, 57°C for 1 min, 72°C for 1 min, and a final primer extension at 72°C for 5 min. The TH marker was amplified with the cycling parameters described above but with an annealing temperature of 62°C. PCR products were resolved on a 6% denaturing acrylamide gel using the ABI377 (Applied Biosystems) automated sequencer and analyzed using GenScan Analysis Software (Applied Biosystems). For each marker, the parental origin of each allele was determined by comparison to the parental alleles, and each trace was examined for evidence of a ratio in favor of the paternally derived allele. The peak area obtained was used to calculate a dosage ratio of paternal to maternal allele. Given the severity of his hyperinsulinemic hypoglycemia, it was determined by comparison to the parental alleles, and each trace was examined for evidence of a ratio in favor of the paternally derived allele. The peak area obtained was used to calculate a dosage ratio of paternal to maternal allele. A ratio greater than 1.3 in favor of the paternally derived allele is considered to be evidence of mosaic paternal isodisomy.

**Histology of resected pancreatic tissue**

The pancreas was fixed in 10% phosphate-buffered formalin for 24 h, and blocks were processed into paraffin wax. Sections (4 μm thick) were cut and stained with hematoxylin and eosin. Immunostaining was performed using polyclonal antibodies against glucagon (1:200 in 20% normal goat serum; Dako, Glostrup, Denmark), insulin (1:150 in 20% normal swine serum; Dako), pancreatic polypeptide (1:600 in 20% normal swine serum; Dako), and somatostatin (1:200 in 20% normal swine serum; Dako), as well as using monoclonal antibodies against proinsulin (1:1000 in 20% normal rabbit serum; Novocastra, New Castle, UK) and low-molecular-weight cytokeratin clone MNF-116 (1:100 in PBS; Dako). Visualization was obtained using extravidin biotin peroxidase kit (Sigma, Poole, UK). Antigen retrieval was achieved for somatostatin and MNF-116 by previous digestion with 0.02% protease for 5 min at 37°C and for proinsulin by pressure cooking within a microwave oven at full power under pressure for 4 min in preheated citrate/EDTA buffer (pH 6.2).
Immunostaining for p57<sup>Kip2</sup>

Antigen retrieval was accomplished by boiling the sections for 15 min in a microwave oven. Slides were blocked by nonimmune serum for 10 min at room temperature before application of each primary antibody. Slides were double stained for p57<sup>Kip2</sup> (Santa Cruz Biotechnology, Santa Cruz, CA) and insulin (Dako). p57<sup>Kip2</sup> staining was detected with the streptavidin-biotin-peroxidase kit (Zymed Laboratories, South San Francisco, CA) and aminoethylcarbazole as substrate. Insulin was stained using the streptavidin-biotin-alkaline phosphatase kit (Zymed Laboratories, South San Francisco, CA) and 5-bromo-4-chloro-3-indolyl phosphate/nitro blue tetrazolium. To prevent cross-reactivity, avidin-biotin blocking kit was used before incubation with anti-insulin antibody. As negative control, slides underwent the same procedure but were incubated with PBS without anti-p57<sup>Kip2</sup> antibody.

Genetics (screening for mutations in ABCC1 and KCNJ11)

All exons and flanking introns of the SUR1 gene and the entire Kir6.2 open reading frame were subjected to PCR amplification and tested for small deletions, insertions, or point mutations using denaturing HPLC (Wave 3500; Transgenomic, Omaha, NE). Samples showing deviating chromatographic patterns were sequenced using the DYEnamic<sup>*</sup> ET dye terminator kit (Amersham Biosciences, Arlington Heights, IL) and analyzed on an automated MegaBaceTM DNA sequencer (Amersham Biosciences).

Functional studies: tissue preparation

After surgery, islets of Langerhans were isolated using a controlled collagenase digestion procedure and were dispersed into single cells as described previously (22, 23). Dispersed cells were incubated at 37°C in a humidified atmosphere of 5% CO<sub>2</sub>/air mixture for up to 4 d and were maintained under standard tissue culture conditions in RPMI 1640 medium supplemented with 10% v/v fetal calf serum, 100 U/ml penicillin, and 100 μg/ml streptomycin.

Electrophysiology

All data were obtained using cell-attached or inside-out recording configurations of the patch-clamp technique as described previously (24). The pipette contained a standard NaCl-rich bathing solution containing the following (in mm): 140 NaCl, 4.7 KCl, 2.5 CaCl<sub>2</sub>, 1.13 MgCl<sub>2</sub>, 10 HEPES, and 2.5 glucose (pH 7.4 with NaOH). The bath solution contained the following (in mm): 140 KCl, 10 NaCl, 1.13 MgCl<sub>2</sub>, 1 EGTA, 2.5 glucose, and 10 HEPES (pH 7.2 with KOH) for all recordings.

Immunohistochemistry

Isolated cells were cultured with poly-d-lysine-coated coverslips (100 μg/ml) for 24 h in RPMI 1640 medium supplemented with 10% fetal bovine serum and 2% penicillin/streptomycin. The cells were fixed by applying Zamboni’s fixative for 50 min and blocked with 1% goat serum in PBS with 0.1% Triton X-100 for 30 min. They were incubated overnight at 4°C with a polyclonal anti-SUR1 antibody used at 1:300 dilution. The cells were rinsed, and the secondary antibody, goat antirabbit FITC-conjugated IgG, was applied at 1:150 dilution (Sigma).

Ca<sup>2+</sup> signaling

Changes in the cytosolic Ca<sup>2+</sup> concentration were monitored by digital imaging microfluorimetry (Roper Scientific, Marlboro, Bucks, UK) of cells loaded with fura 2-AM to a final concentration of 20 μM for 30–40 min at 37°C at which the coverslip formed the base of a perfusion chamber (Warner Instruments, Edenbridge, Kent, UK).

Results

Molecular genetic analysis of BWS

The results of microsatellite marker analysis for markers D11S1984, TH, and D11S1318 are shown in Figure 2. Dosage analysis of patient showed evidence in favor of the paternally derived allele at a ratio of 1.7:1 and 1.5:1 for markers D11S1984 and TH, respectively. The ratios obtained were consistent with a diagnosis of mosaic paternal isodisomy (Figs. 1 and 2).

Histology

Histological examination of the resected pancreas showed throughout the specimen a marked proliferation of endocrine tissue forming irregular nodules rather than discrete islets. These nodules of endocrine tissue contained somatostatin- and glucagon-producing cells in the periphery. In addition, throughout the islets, there were pancreatic polypeptide-immunoreactive cells. Immunostaining for pro-insulin was strong in these nodules, but insulin immunostaining, although present, was weak. An antibody against low-molecular-weight cytokeratin showed the presence of the remaining acinar tissue but also demonstrated that ductular structures were not a prominent feature in the proliferating nodules of endocrine tissue. Figure 3 shows the histological appearance of the resected pancreas.

p57<sup>Kip2</sup> protein was readily identified within the islets by orange-brown nuclear stain. Insulin stain was visualized as purple-black reaction product in the cytoplasm.

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**Fig. 1.** Principle of mosaic paternal isodisomy. A, A somatic mosaicism is manifested by a cell line having two identical copies of a paternal chromosome 11 (P1,P1) and a cell line with a paternal and a maternal allele (P1,M1) (B). Mosaic paternal isodisomy is demonstrated by microsatellite markers (MSM) and the expression of the paternally imprinted p57<sup>Kip2</sup> protein from the maternal allele in position 11p15.5.
p57Kip2 stain was clearly positive in β-cells with very few positively stained nuclei outside the islets. p57Kip2 staining is shown in Figure 4.

**Genetics**

Denaturing HPLC analysis of ABCC8 and KCNJ11 genes revealed deviating banding patterns in SUR1 exons 16, 23, and 33; additionally, three variants were disclosed in Kir6.2. Sequencing revealed all patterns to be polymorphisms seen in the general population at large. Both of the polymorphisms in the six codons of the ABCC8 and KCNJ11 genes were seemingly paternally derived, and no maternal polymorphisms were seen in the ABCC8 and KCNJ11 genes. No silent mutations or rare intron variations were found.

**Functional studies**

Figure 5 summarizes the expression of $K_{\text{ATP}}$ channels in isolated cell membrane patches by electrophysiology. In control human β-cells, $K_{\text{ATP}}$ channels are present, and the average current value per patch of membrane was 25.5 ± 1.48 pA ($n = 263$). In contrast, no $K_{\text{ATP}}$ channels were recorded in the patient tissue. Similar data were obtained in the HI β-cells with truncations of the C-terminal domain of SUR1 (Fig. 5A), whereas in other HI patient tissue, a modest level of channel activity was recorded. The loss of functional $K_{\text{ATP}}$ channels in BWS β-cells was correlated with immunofluorescence data using a SUR1 antibody that showed a perinuclear pattern of staining (Fig. 5B). We also examined the control of Ca$^{2+}$ signaling events in BWS β-cells (Fig. 6). These data showed that responses to glucose and tolbutamide were impaired. For example, 10 mM glucose induced a 34 ± 4 nM rise in cytosolic Ca$^{2+}$ in 26 of 38 experiments, whereas only...
31 of 66 cell clusters responded to 0.1 mM tolbutamide \([\text{[Ca}^{2+}]_i = 27 \pm 3 \text{ nM}]\). Most cells, however, were responsive to 40 mM KCl-induced depolarization of the cell membrane, suggesting that voltage-gated Ca\textsuperscript{2+} channels were unaffected by the loss of K\textsubscript{ATP} channels.

**Discussion**

Our data show that the mechanism of hyperinsulinemic hypoglycemia in this patient was due to the loss of functional K\textsubscript{ATP} channels in the pancreatic \(\beta\)-cells. Loss of function of pancreatic \(\beta\)-cell K\textsubscript{ATP} channels is a major cause of congenital HI (25). In tissue isolated from our patient, operational K\textsubscript{ATP} channels were not recorded, suggesting that either the number of channels at the cell membrane were limited or that they were absent from cells. Immunofluorescence images using a SUR1 antibody revealed marked differences between control and patient tissue in that BWS cells presented with a perinuclear pattern of staining. This distribution of the SUR1 protein correlates with an absence of functional electrophysiological recordings of K\textsubscript{ATP} channels at the plasma cell membrane of the \(\beta\)-cell.

We were also able to show impaired responses of BWS \(\beta\)-cells to glucose and tolbutamide, which is consistent with the ion channel data. However, the fact that some cells were able to respond to tolbutamide and glucose does imply an ability of cells to express normal channels. Collectively, we would suggest that hyperinsulinism is related to aberrant expression of sufficient numbers of channels at the cell surface. HI-causing mutations in the \textit{ABCC8} and \textit{KCNJ11} genes (encoding SUR1 and Kir6.2, respectively) impair the function of the K\textsubscript{ATP} channel by affecting channel density, channel expression, channel trafficking from the Golgi apparatus and endoplasmic reticulum, channel gating properties, and channel activity in response to changes in the concentrations of intracellular nucleotides (26, 27). Mutations in these genes are, however, only found in about 50% of patients with HI (28). Despite extensive search, no mutations were found in the genes \textit{ABCC8} or \textit{KCNJ11} in this patient. Mutations in the promoter region of \textit{ABCC8} or \textit{KCNJ11} were, however, not excluded with the methods in use. Another possible genetic cause could be a mutation in an unknown gene affecting trafficking of the SUR1-Kir6.2 complex.

Histological examination of the pancreas showed strong proinsulin and weak insulin immunostaining, suggesting that the \(\beta\)-cells were secreting large amounts of insulin. The
disomy of the 11p15.1 region causes a KATP trafficking defect
uniparental heterodisomy of the 11p15.1 region. uniparental isodisomy in the 11p15.5 region and paternal
our patient may represent a unique case of mosaic paternal
The mechanism(s) in which paternal uniparental hetero-
11p15.1 region gave rise to a K_{ATP} trafficking defect and
It is suggested that one of these genetic errors in the 11p15.1 region gave rise to a K_{ATP} trafficking defect and
became homozygous in a majority of the cells. A search for
in the ABCC8 promoter region will be performed
to investigate this possibility.
In summary, we have described a novel case of BWS with
persist, severe HI, together with the typical mosaic paternal
in the 11p15.5 region, resulting in a Beckwith-Wiedemann phenotype and an atypical diffuse islet cell histology.

Fig. 6. Ca^{2+} signaling in BWS β-cells. The data show voltage-
dependent Ca^{2+} entry in BWS β-cells and cell clusters stimulated by
exposure to 40 mM KCl, which depolarizes the cell membrane and
activates voltage-dependent Ca^{2+} channels (n = 4). In this typical
experiment, simultaneous recording of 13 data points are illustrated.
Note that, although all cells responded to KCl, few showed any re-

duction with a possible undiscovered partial gene de-

proliferation of endocrine tissue was reminiscent of the ap-
pearsances seen in Fo-HI. However, in this patient, prolifer-
atating islets were seen throughout the pancreas, and ductular
structures were not a feature within these nodules and there
was no evident of fibrosis. Thus, the changes seen in our
patient are different from those seen in typical Fo-HI. Be-
cause \( p57^{kip2} \) is paternally imprinted in human pancreatic
β-cells and there is the loss of expression in Fo-HI, the fact
that \( p57^{kip2} \) protein expression was readily demonstrated
throughout the pancreas also excludes focal forms of the
disease.

The genetics of the BWS in this patient showed that, in the
lymphocytes, the paternally derived allele had a ratio of 1.7:1,
5:1, and 1.2:1 for markers D11S1984, TH, and D11S1318,
respectively. The ratios obtained were regarded as evidence of
mosaic paternal isodisomy. The expression of \( p57^{kip2} \) in the
β-cells suggests that, at least in the β-cells, there was no
loss of the maternal 11p15.5 region, thus further supporting the
expression of mosaic paternal UPD. The inheritance pat-
terns of the polymorphisms in the \( ABCC8 \) and \( KCNJ11 \) genes
gave, however, evidence of paternal heterodisomy in the
region 11p15.1 and loss of maternal 11p15.1. Accordingly, our
patient may represent a unique case of mosaic paternal
uniparental isodisomy in the 11p15.5 region and paternal
uniparental heterodisomy of the 11p15.1 region.

The mechanism(s) in which paternal uniparental hetero-
disomy of the 11p15.1 region causes a \( K_{ATP} \) trafficking defect
remains to be elucidated. Both of the \( ABCC8 \) and the \( KCNJ11 \)
alleles were paternally derived, and the father was healthy.
In one of the alleles of the child, the areas 11p15.5 and 11p15.1
arose from two different paternal alleles, suggesting a break
of continuity with a possibly undiscovered partial gene de-
letion in \( ABCC8 \) in the area of exon 33 to exon 39, in which
no polymorphisms were seen. This could have a dominant
action and explain the persistent, severe hyperinsulinemic phenotype and the impaired trafficking of the SUR1-Kir6.2
complex.

Another possibility is a mosaicism of paternal isodisomy
and paternal heterodisomy in 11p15.1, which would allow a
recessive undiscovered mutation in \( ABCC8 \) or \( KCNJ11 \) to


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