Beckwith-Wiedemann syndrome (BWS)

- A multisystem human genomic imprinting disorder with variable clinical expression and complex molecular aetiology
- An international consensus statement has introduced the concept of Beckwith-Wiedemann spectrum (BWSp)

Hyperinsulinemic hyperglycaemia is common (30-60%) and usually resolves within a few days
- persistent, severe cases refractory to medical management are usually associated with the paternal uniparental disomy (pUPD11) molecular defect
- majority do not have a paternal inactivating K<sub>ATP</sub> channel variant but those that do have even more refractory hyperglycaemia

Pancreatic mosaicism for pUPD11

Methods

1. Pancreas (region of islet hyperplasia)
   - Targeted MPS hyperinsulinism panel with mosaic variant calling programme on the sequence data (detects variants to level of 1%)
   - KCNJ11, ABCC8, AKT2, GLUD1, GCK, GPC3, a mosaic gain of one copy of chromosome 11p overgrowth
   - Hyperinsulinemic significance unknown

2. Peripheral blood and buccal cells
   - SNP array analysis

Results

1. Pancreas
   - Targeted MPS hyperinsulinism panel
   - maternal ABCC8 variant that was identified in blood was again detected, but only in a small number of reads with skewed allelic frequency suggesting mosaicism

2. Peripheral blood and buccal cells
   - no mosaic paternal uniparental disomy (pUPD) or trisomy 12 identified (cannot exclude low-level mosaicism of <10%)

Conclusions

Pancreatic mosaicism for pUPD11
- Most likely cause of CHI
- With 2 cardinal BWSp features
  - hyperinsulinism >1 week duration, escalating treatment and pancreatic adenomatosis
  - BWSp, pUPD11 predicts a high risk for Wilms tumour and hepatoblastoma, with 3-monthly ultrasonad recommended for 7 years¹
  - a-fetoprotein screening is debated¹²
- Even in the absence of overt 11p overgrowth features, BWSp due to pUPD11 should be considered if
  - persistent, severe CHI without an identified pathogenic K<sub>ATP</sub> channel mutation(s)
  - large focal pancreatic lesions (without with a K<sub>ATP</sub> mutation)
  - atypical histology⁴

Pancreatic mosaicism for trisomy 12
- Unreported previously → significance unknown
- Embryonic lethal when not in mosaic form
- A patient with trisomy 12 in 25% of peripheral blood cells has been reported
- Mild dysmorphic features at birth
- normal development at 6 months of age⁶

References


Case

- A term male (birthweight 3.7kg, 80th percentile) with diazoxide-unresponsive congenital hyperinsulinism (CHI) was born to unaffected parents
  - natural conception
  - non-consanguineous and no family history
  - did not have the cardinal Beckwith-Wiedemann spectrum features of
    - macroGLOSSIA, exomphalos or lateralised overgrowth
  - did not have the suggestive Beckwith-Wiedemann spectrum features of
    - polyhydramnios, macrosomia
    - facial naevus simplex, ear creases or pits
    - umbilical hernia, diastasis recti
    - nephromegaly or hepatomegaly
  - Prenatal ultrasound recommended to assess for size or mesenchymal dysplasia¹
- A targeted massively parallel sequencing (MPS) panel identified a heterozygous maternally inherited K<sub>ATP</sub> channel ABCC8 variant (c.1332+4del) - minimal splicing effect predicted
  - classified as likely benign
- Intensive medical support was required and he could not be medically maintained with a trial of continuous subcutaneous octreotide
- [18F]-DOPA PET/CT imaging of the pancreas - unexpected finding of focal increased uptake in the pancreatic distal body/tail junction (Figure 1A)
- Histopathology of the subtotal pancreatectomy (day 22) showed (Figure 2)
  - focal adenomatous hyperplasia
  - trabeculae and islet nests composed of
    - regular, oval or columnar cells
    - lacking atypia or conspicuous nuclear enlargement
  - adjacent lobules had a relatively normal distribution of islets and exocrine acini
  - chromogranin highlighted the islets
  - aberrant p57 expression in islet cytoplasm
  - nuclear in normal islets and in diffuse hyperinsulinism
- would be negative in focal CHI due to a pathogenic paternal K<sub>ATP</sub> channel variant
- Within 2 weeks, medical support was again required with residual, increased [18F]-DOPA pancreatic uptake (Figure 1B)
- A second regression (5% left in-situ) (day 36) achieved normoglycaemia
- At 24 months of age
  - normoglycaemic with age-appropriate feeding (exocrine pancreatic supplements)
  - normal ultrasonographic appearance of liver and kidneys
  - normal neurodevelopmental progress
- Extended genetic analyses in the context of Beckwith-Wiedemann syndrome (BWS)
  - Congenital Hyperinsulinism focal increased [18F]-DOPA PET/CT pancreatic uptake and
  - atypical histology

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Objectives

- Extended genetic analyses in the context of Congenital Hyperinsulinism focal increased [18F]-DOPA PET/CT pancreatic uptake and
- atypical histology

References


Figures

Figure 1
A. Focal moderate intense [18F]-DOPA uptake at the pancreatic body/tail junction (arrows), consistent with site of hypermetabolic tissue, with a faint focus of [18F]-DOPA uptake at the uncinate process which is more likely physiologic

Figure 2
A. Focal adenomatous hyperplasia (arrow), normal pancreas (without/with a K<sub>ATP</sub> mutation)
B. Islet hyperplasia, H&E, 20x
C. Chromogranin expression in hyperplastic islets (arrow), normal islets (), 4x
D. p57 expressed in hyperplastic islets (arrow) and normal islets (), 4x

1. Pancreas (region of islet hyperplasia)
   - Targeted MPS hyperinsulinism panel with mosaic variant calling programme on the sequence data (detects variants to level of 1%)
   - KCNJ11, ABCC8, AKT2, GLUD1, GCK, GPC3, HADH, HNF4A, INS, KDM6A, KMT2D, SLC16A1, CACNA1D, PM2, TRMT10A, HNF1A
   - Single-nucleotide polymorphisms (SNP) array analysis (Affymetrix CytoCsys 750K)

2. Peripheral blood and buccal cells
   - SNP array analysis

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