Refractory Hyperinsulinaemic Hypoglycaemia in Beckwith-Wiedemann Syndrome due to Imprinting Control Region 1 Gain of Methylation: severity discordant to genotype.

Louise S Conwell1,2, Craig A McBride2,3, Kelvin Choo2,3, Shawn C Tadgell1, Michelle E Fuery4, Janene R Davies5.

1 Department of Endocrinology and Diabetes, Queensland Children’s Hospital, Brisbane, Australia 2 School of Clinical Medicine, Faculty of Medicine, University of Queensland, Brisbane, Australia 3 Department of Paediatric Surgery, Queensland Children’s Hospital, Brisbane, Australia 4 Department of Dietetics and Food Services, Queensland Children’s Hospital, Brisbane, Australia 5 Anatomical Pathology, Pathology Queensland, Brisbane, Australia

Case

- Beckwith-Wiedemann syndrome (BWS), suspected antenatally was confirmed postnatally in a female
  - 35 weeks gestation
  - unaffected parents
  - natural non-consanguineous conception
  - no family history of hypoglycaemia or BWS

- Cardinal Beckwith-Wiedemann spectrum1 features
  - macroGLOSSIA
  - no exomphalos, lateralised overgrowth or placental mesenchymal hyperplasia

- Suggestive Beckwith-Wiedemann spectrum1 features
  - macrosomia
diastasis recti
  - umbilical hernia
  - no polyhydramnios, nephromegaly, ear creases / pits or facial naevus simplex

Molecular genetic testing

- Molecular defect
  - gain of methylation at H19/IGF2 intergenic differentially methylated region (IGDMR), known as imprinting control region 1 (ICR1)

- This genotype
  - accounts for 5% of BWS
  - low frequency of exomphalos
  - high Wilms’ tumour risk (24%)1

Hyperinsulinaemic Hypoglycaemia

- Unexpected for genotype, she had severe hyperinsulinaemic hypoglycaemia
  - refractory to medical therapy (diazoxide, octreotide)
  - No ABC2 or KCNJ11 variants were detected
  - Genotype would predict diffuse, not focal disease

Clinical Course

- Complications included catheter-related bloodstream infections and thromboses
  - MacroGLOSSIA
  - exacerbated feeding difficulties
  - impeded expressive language development
  - contributed to mixed sleep-disordered breathing requiring oxygen in sleep
  - Subtotal pancreatectomy (80-85%) was performed at 11 weeks of age
  - in this context, reducing endocrine tissue mass may suffice3

- Histology was atypical for diffuse / focal Congenital Hyperinsulinism (CHI)
  - large, numerous islets as previously observed in BWS (Figure)
  - CHI continued to be refractory to medical management
  - Octreotide trialled again
  - brief use of Rapamycin (Sirolimus)
  - exacerbated transaminits and anaemia
  - ceased at the onset of a sepsis episode

- [18F]-DOPA PET/CT scan did not indicate the unlikely scenario of ectopic disease
  - Further resection to the equivalent of a 95% pancreatectomy was performed two weeks after the initial resection (13 weeks of age)
  - exocrine pancreatic insufficiency
  - CHI persisted: medical support included intragastric feeds / dextrose, Octreotide

- Lanreotide commenced at 8 months, with discharge home at 9 months of age
  - Tongue reduction surgery at 14 months
  - At 19 months of age
    - oral feeding, gastrostomy reversed
    - pancreatic enzymes
    - fat-soluble vitamins
    - Lanreotide 30mg monthly deep S/C
    - tumour surveillance negative

- no evident neurocognitive impairment

Conclusion

- The severity of CHI was discordant to that previously reported for this genotype of BWS
- Although clinical heterogeneity has been described in the different genotype of ICR2 hypomethylation (accounts for 50% of BWS), these cases were still diazoxide-responsive4

References


Presented at the Annual European Society of Paediatric Endocrinology Meeting, Vienna, Austria, September 2019.

A/Prof Louise S. Conwell, Louise.Conwell@health.qld.gov.au

Figure

A. Representative section of pancreas showing minimal increase in islets - without nuclear enlargement and without focal adenomatous hyperplasia, H&E, 40x
B. Islets demonstrated with antibody to insulin, 40x
C. p57 expression in islets retained, 40x
- retained in normal islets and in diffuse CHI
- loss of expression in focal CHI

Poster presented at:

Poster P2-151

P2-151

P2-151