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

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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 spectrum[1] features
  - macroglossia
  - no exomphalos, lateralised overgrowth or placental mesenchymal hyperplasia
- Suggestive Beckwith-Wiedemann spectrum[1] features
  - macrosomia
  - diastasis recti
  - umbilical hernia
  - no polyhydramnios, nephromegaly, ear creases / pits or facial naevus simplex

Molecular genetic testing

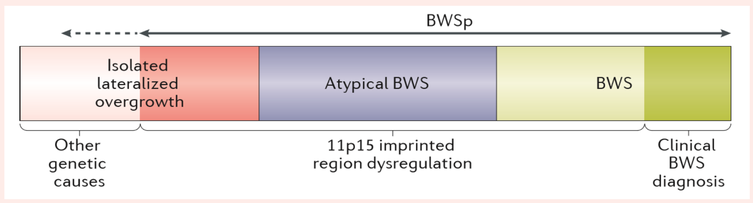
- Molecular defect
  - gain of methylation at *H19/IGF2* intergenic differentially methylated region (IGDMR), known as imprinting control region 1 (ICR1)
- This genotype
  - accounts for 5% of BWS
  - low frequency of exomphalos
  - high Wilms' tumour risk (24%)[1]

Hyperinsulinaemic Hypoglycaemia

- Unexpected for genotype, she had severe hyperinsulinaemic hypoglycaemia
  - refractory to medical therapy (diazoxide, octreotide)
- No *ABCC8* or *KCNJ11* variants were detected
- Genotype would predict diffuse, not focal disease

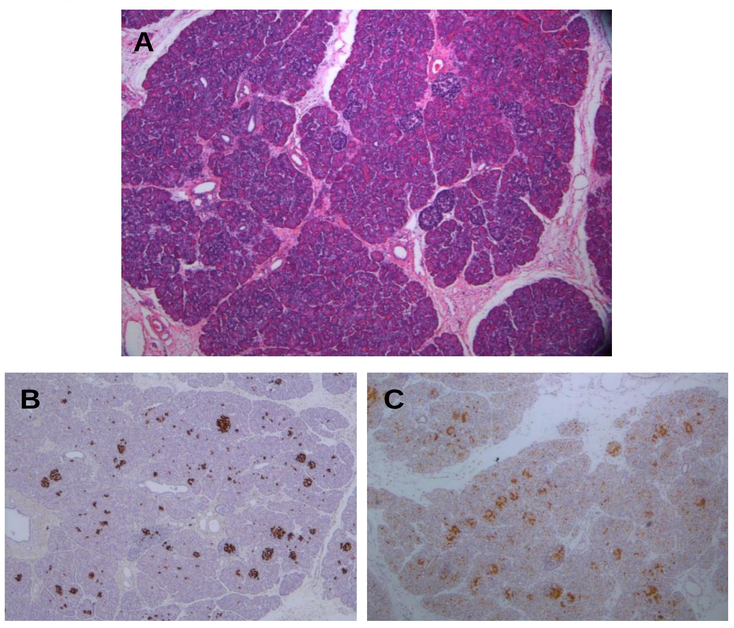
Beckwith-Wiedemann syndrome (BWS)

- A multisystem human genomic imprinting disorder with variable clinical expression and complex molecular aetiology[1]
- An international consensus statement has introduced the concept of Beckwith-Wiedemann spectrum (BWSp)[1]



- Hyperinsulinaemic hypoglycaemia is common (30-60%)
  - 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_{ATP} channel variant but those that do have even more refractory hypoglycaemia
    - ➢ those cases may have large, focal pancreatic lesions[1,2]
  - in BWS due to other molecular defects
    - ➢ hypoglycaemia usually resolves within days
    - ➢ persistent cases are usually diazoxide-responsive[1]

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

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 suffice[3]
- 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 transaminitis 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-responsive[4]

References

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4. Senniappan S *et al.* J Pediatr Endocrinol Metab 2015; 28(1-2):83-6

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