Hyperinsulinaemic Hypoglycaemia: A New Presentation of 16p11.2 Duplication Syndrome.

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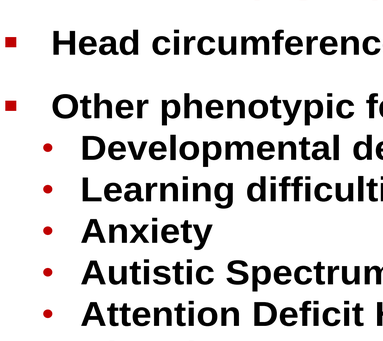
Case

- A term normosomic male was born via assisted vaginal delivery due to failure to progress and fetal distress
  - Maternal history of diet-controlled gestational diabetes
  - Neonatal hypoglycaemia requiring intravenous dextrose for 24 hrs
- Diazoxide-responsive hyperinsulinaemic hypoglycaemia diagnosed at 11 months during a gastrointestinal illness
  - Ammonia and acylcarnitine profile normal
  - Hyperinsulinism ongoing at 9 yrs (7.5mg/kg/day diazoxide)
- Renal tract anomalies diagnosed following a urinary tract infection at 7 weeks
  - Right grade IV vesicoureteric reflux
  - Right bifid collecting system
  - Small right kidney, reduced function
- Persistent low postnatal weight and Body Mass Index (BMI) with continuing selective and restrictive eating behaviours (Figure)
- Head circumference in normal range
- Other phenotypic features:
  - Developmental delays
  - Learning difficulties
  - Anxiety
  - Autistic Spectrum Disorder
  - Attention Deficit Hyperactivity Disorder
- A dilated aortic root was identified at 6 years during cardiac surveillance following prolonged diazoxide use
  - 17 gene aortopathy panel negative
- Both parents clinically unaffected

Figure



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16p11.2 Copy Number Variants

- 16p11.2 <u>microdeletion</u> and <u>duplication</u> syndromes have been described[1]
  - *de novo* and inherited cases
  - spectrum of clinical manifestations
  - incomplete penetrance
  - variable expressivity
- *Shared* phenotypic features[1,2]
  - Autism
  - Developmental delay
- *Mirrored* phenotypic features[1,2,3]
  - ➢ <u>Deletions</u>
    - Obesity
    - Hyperphagia
    - Macrocephaly
  - ➢ <u>Duplications</u>
    - Underweight
    - Feeding / eating disorders
    - Microcephaly
- Two cases of 16p11.2 <u>microdeletion</u> syndrome with hyperinsulinaemic hypoglycaemia, in the absence of pathogenic variants of causative genes, have been reported[4]

Case 1
- paternal inheritance
- neonatal Hirschsprung disease and pyloric stenosis
- hypoglycaemia detected post-operatively on day 30
- diazoxide-responsive
- cessation of diazoxide by 15 months
- no neurological deficits

Case 2
- maternal inheritance
- hypoglycaemia from day 2
- diazoxide-responsive
- cessation of diazoxide by 12 months
- developmental delay
- myoclonic epilepsy
- cognitive impairment
- childhood obesity

- To our knowledge, this is the first case description of hyperinsulinaemic hyperglycaemia in a patient with 16p11.2 <u>duplication</u> syndrome

References

1. Shinawi M *et al.* J Med Genet 2010; 47:332-341
2. Weiss LA *et al.* N Engl J Med 2008; 358(7):667-675
3. Jacquemont S *et al.* Nature 2011; 478:97-102
4. Kostopoulou E *et al.* Clinical Endocrinology 2019; 1-4
5. Rui L. World J Diabetes 2014; 5(4):511-526

Genetic Investigations

- Targeted screening of 16 genes known to cause hyperinsulinaemic hypoglycaemia did not identify a pathogenic variant
  - *KCNJ11, ABCC8, AKT2, GLUD1, GCK, GPC3, HADH, HNF4A, INSR, KDM6A, KMT2D, SLC16A1, CACNA1D, PMM2, TRMT10A, HNF1A*
- A heterozygous interstitial duplication of ~551Kb at chromosome 16p11.2 (Chr16:29,647,342 - 30,198,151) was detected by SNP array (Illumina Whole-Genome Infinium CytoSNP 850K Array)
  - The duplicated region contains at least 30 known genes of which 5 are OMIM listed disease causing genes
    - *KIF22, PRRT2, ALDOA, TBX6, CORO1A*
  - This result conformed a diagnosis of chromosome 16p11.2 duplication syndrome
  - The duplication was paternally inherited

Conclusions

- Our case expands the clinical spectrum of phenotypic abnormalities observed in the 16p11.2 duplication syndrome
- The two reported cases of hyperinsulinaemic hypoglycaemia in 16p11.2 microdeletion syndrome were diagnosed neonatally and ceased Diazoxide within 15 months
  - In one of these patients (Case 2), it was postulated that the deletion of *SH2B1*, may have been been contributory[4]
  - *SH2B1* has been associated with developmental delay; and implicated in the regulation of energy balance, body weight and glucose metabolism[5]
  - In our case, *SH2B1* was not within the duplicated region
- Hyperinsulinaemic hypoglycaemia may be a rare feature of 16p11.2 copy number variants.
- The biological mechanisms are unclear

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