Unexpected growth patterns in branchio-oto-renal syndrome

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Introduction

- Branchio-oto-renal (BOR) syndrome is a rare inheritable condition affecting the ears, 2nd branchial arch structures and the urinary system.
- Recognised features include hearing loss, structural defects of the ear, branchial defects, and a variety of renal malformations.
- Causative genetic variants include SIX1 and EYA1 which cumulatively account for ~49% of all cases of BOR syndrome.
- Short stature has not commonly been described in BOR syndrome, but is associated with oculo-facial-cervical syndrome and oculoauriculovertebral syndrome, which have demonstrated allelism with BOR due to mutations involving the EYA1 gene.
- We present data from two unrelated pedigrees, seven individuals in total, who exhibit phenotypes clinically suggestive of BOR syndrome who demonstrate a pattern of delayed and suboptimal growth.

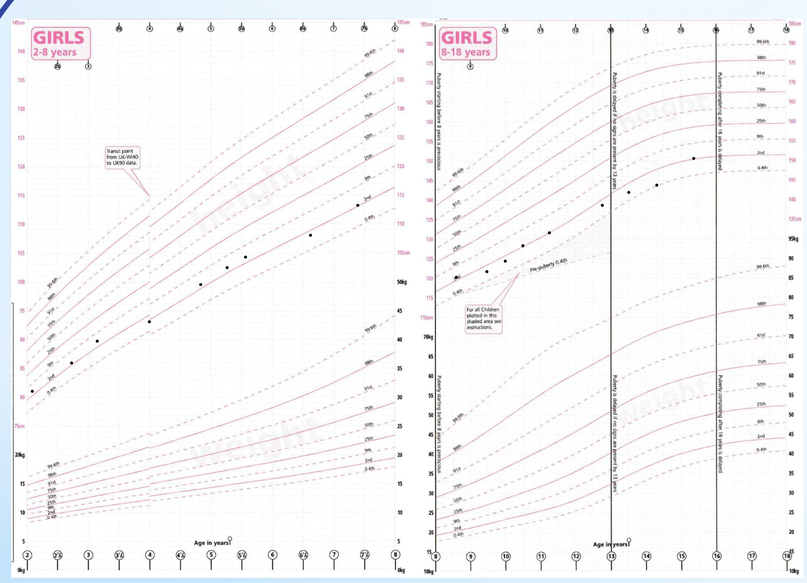
Methods

Data was collected on 2 probands and their siblings attending Paediatric Endocrinology for concerns regarding growth.

This included:

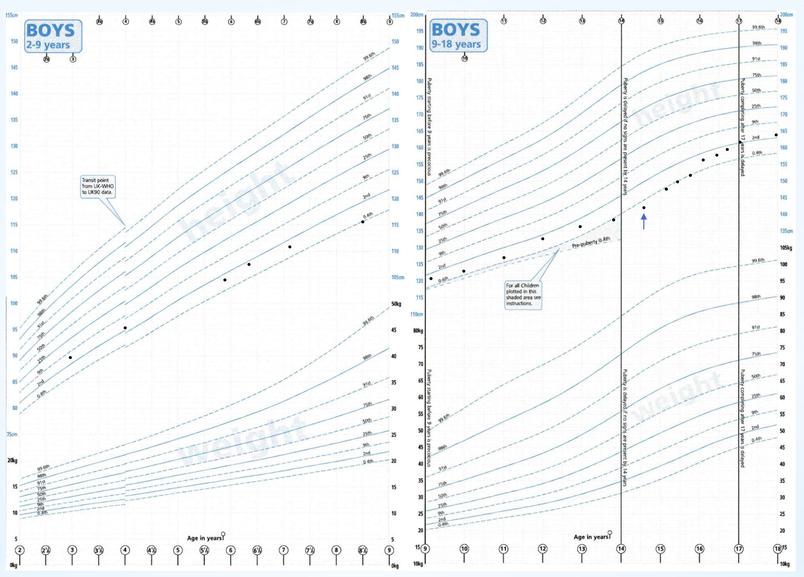
- Auxology data
- Annual growth velocity
- Final height where available
- Bone age
- Growth factors
- Midparental height (MPH)

Pedigree 1



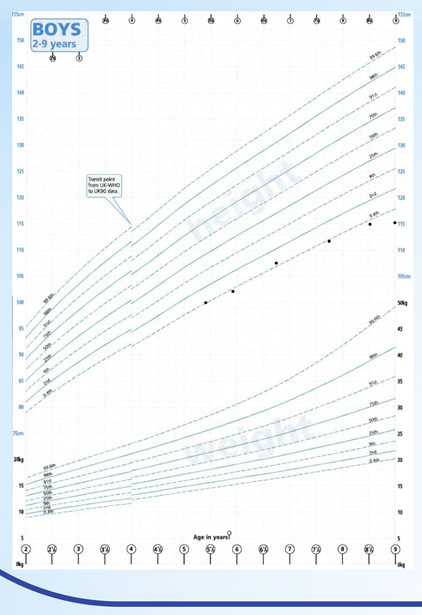
Patient 1 :

- MPH 159.5cm (25th centile)
- Final height 152cm (2nd centile)
- Did not meet criteria for growth hormone



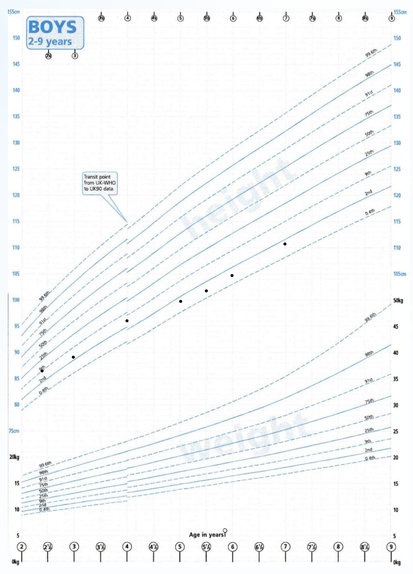
Patient 2 :

- MPH 172cm (25th centile)
- Final height 164.cm (2nd centile)
- Growth hormone started at 14.6 years (↑)



Patient 3 :

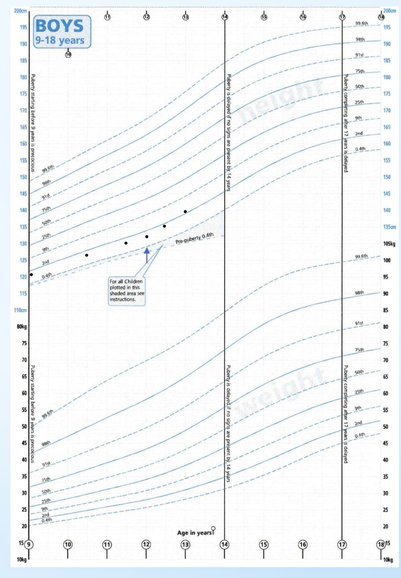
- MPH 172cm (25th centile)
- Current height 115.9cm (<2rd centile)
- Did not meet criteria for growth hormone



Patient 4 :

- MPH 172cm (25th centile)
- Current height 115.9cm (<2nd centile)
- Has not yet had growth hormone testing

Pedigree 2



Patient 5 :

- MPH 170cm (9-25th centile)
- Current height 138.6cm (2rd centile)
- Growth hormone started at 12 years (↑)

- Sibling 1 :
  MPH 157cm (9 -25th centile)
  Final height 152cm (<2nd centile)
- Sibling 2 :
  MPH 157cm (9 – 25th centile)
  Final height 150cm (<2nd centile)

Discussion

- These two families show similar patterns:
  - low height velocity
  - falling below centiles in later childhood
  - failure to reach the predicted mid-parental height
- This is suggestive of suboptimal late childhood and pubertal growth.
- The aetiology for this remains unclear.
- Genetic analysis is in process but yield in BOR syndrome is low.
- Sonic Hedgehog [SHH] mutations have been implicated in mouse studies of pituitary development. EYA and SIX1 are known to function as transcriptional regulators in SHH signalling and the associated GLI family of zinc finger transcription factors. We speculate that a disruption in this pathway could lead to growth reduction in BOR.

Conclusions

- Growth surveillance is advocated in children with BOR. Normal growth in the early childhood years does not guarantee final height attainment.
- We are pursuing auxology data on other families with BOR to ascertain if they display a similar phenotype.
- ? Value of GH replacement despite meeting criteria for same

References

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