132cm final height due to poor pubertal growth: FBN1 is the culprit

Additional features: neurocognitive manifestations

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Introduction and objectives: Very short stature is a common presenting complain that gives rise to numerous investigations. FBN1 heterozygous mutations cause acromelic dysplasia syndromes. The phenotypic spectrum of these growth disorders is broad, ranging from short stature with short extremities, stiff joints, skin thickening with tracheal stenosis and cardiac valvulopathy to nearly isolated short stature. Here, we report on a girl with short stature, aortic bicuspidy, Arnold-Chiari type1 and behavioural and learning difficulties due to a previously described FBN1 mutation.

Methods: case report and literature review. Sanger sequencing and targeted exome sequencing according to standard diagnostic laboratory techniques.

Results: Case Report: A 3.5y-old girl presented with short stature. Her parents were healthy, non-consanguineous, of Caucasian origin. Their height was 175,6 cm (father) and 166,8 cm (mother). She was born at 37 weeks of gestational age by caesarean section after a twin pregnancy obtained by IVF with 1900g and 44,5 cm. Her physical examination at 3.5 years revealed short stature (Height -3.1 SDS, ref Cole 1995), small hands, pseudomuscular build, dry but otherwise normal skin, short nose, broad nasal bridge (Fig. 1) and a relative macrocephaly (head circumference SDS), lumbar hyperlordosis. Parents repeatedly reported behavioural and learning difficulties. She also presented bicuspid aortic valve, asymptomatic Arnold Chiari 1 associated with minor syringomyelia. Growth hormone was administered at 4.9y when her height was at -3.5 SDS with a bone age equal to chronological age. It was given intermittently for a total duration of 6 years (height gain after 1 year: +0.4 SD with 25 mcg/kg/d and +0.5 SD with 50 mcg/kg/d) (growth curve see Fig. 2). Poor response was evident and total pubertal growth was only 11 cm.

CONCLUSIONS

1. Very poor pubertal growth and very short adult height in patients with acromelic dysplasia due to a FBN1 mutation.

2. This case highlights the importance of TGF beta signalling for somatic growth.

3. This mutation has already been described in 2 patients with acromelic dysplasia (de Bruin et al.) and in 1 patient with geleophysic dysplasia (Le Goff et al.). The patient reported by de Bruin had aortic stenosis, mitral and aortic valve insufficiencies. The patients described by de Bruine had some degree of hip dysplasia. Our patient has bicuspid aortic valve, Chiari 1 and neuropsychological difficulties. Identical mutations in the TGF beta5 domain of the FBN1 gene give rise to a variable phenotype sharing severe short stature.

4. This disease is a clinical diagnostic challenge for which targeted exome sequencing is of great help.

5. We confirm that growth hormone therapy response was poor.

6. The cardiac valvular disease being progressive (thickening), it requires follow-up, as do the tendency for carpal tunnel syndrome and hip dysplasia.

7. The neurobehavioral problems of the reported patient could be an aspect of her FBN1-related disease. This requires further study. The previously reported patients had normal development but no details were provided on their behavior. Other FBN1-related diseases include neurocognitive/psychiatric manifestations (Marfan syndrome, Shprinzen-Goldberg syndrome). The macrocephaly present in patients with acromelic dysplasia suggests a CNS effect of FBN1 mutation. This is not surprising, given that fibrillin microfibrils are part of the extracellular matrix which has mechanical functions but also shapes cell behavior and gene expression, in the CNS.

Extensive diagnostic work-up was negative:

- Growth hormone stimulation tests,
- Skeletal survey,
- Cytotype with FISH for SHOX,
- Microarray analysis,
- PTEN11 sequencing,
- FGF3 sequencing,
- 3M syndrome suspicion (bone dysplasia clinic advice).

Recently, targeted exome sequencing showed a de novo c.5183C>T (p.Ala1728Val) heterozygous mutation in the FBN1 gene. This gene encodes the protein fibrillin 1. Fibrillins assemble into microfibrils which perform both structural and regulatory roles in the extracellular matrix. Regulatory roles may be determined by microfibrils-associated proteins which bind to TGF beta, for example. Microfibrils also directly bind bone morphogenetic proteins and growth and differentiation factors.

Figure 1. Photo of the patient at 8 years of age
Figure 2. Growth curves of the patient

Start of puberty: 10.4y of age; 132 cm; bone age: 10yrs (6 and 9).
Final height: 123cm at age 15y (height 6.5SD; BMI 25 kg/m2).

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Growth and syndromes (to include Turner syndrome)
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