A boy with disproportionate short stature, skeletal abnormalities, normal mental development, pituitary hypoplasia and partial growth hormone deficiency

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SUMMARY

Auxology and phenotype: key feature: early and slowly progressing disproportionate short stature (at birth: length 47 cm - 3rd centile, weight 3010g - 50th centile, head circumference 50th centile; 6 and 12 months: length < 3rd centile, weight 25th centile, head circumference 50th centile; 4 years: length < 3rd centile - SDSp – 2.6, 5 years: length < 3rd centile, weight < 3rd centile, growth velocity < 3rd centile). Slow, progressive delay also in bone maturation (BA 3 months at 1 year of age and BA corresponding to 1.5 years at 5 years chronological age). Mid-parental height 166.2 cm, Target-height 172.7cm. Younger sister: normal growth and development, Normal mental development. Seldom III (upper respiratory infections). Enuresis nocturna: No difficulties with neck-rotation, involvement mainly of the axial skeleton. Hormonal Growth hormone deficiency (GH) testing revealed Growth hormone deficiency (max GH 9.6 mU/l after glucagon), isolated so far. MRI: hypoplastic hypophysis and infundibulum, no neurohypophyseal ectopy, insufficient development of Th12-L1 bodies. Thoraco-lumbar kyphoskoliosis. Treatment with rhGH (Norditropin) started at 5 years and 5 months with 0.05 U/kg/d. Disappearance of Enuresis nocturna during the first 2 weeks of treatment. Possible etiological candidate genes: DLL3, LHX3, 4. Clinical interdisciplinary (paediatric endocrinologist, orthopedic surgeon, rehabilitation) follow up team critical for optimal outcome.

CONCLUSIONS

• The patient represent a rare condition: GHD associated with spondylo-costal dysplasia;
• Despite early diagnosis and treatment, a substantial growth and development delay is still evident
• The mechanisms for the growth velocity deceleration during the third year of rhGH treatment remain to be elucidated
• Such patients should be characterized thoroughly in respect of phenotype-genotype relations
• Their optimal integration needs extensive integrative efforts of the society: medical, social, educational

Family history:
Mother’s height: 159.1 cm, father’s height: 173.3 cm, midparental height: 166.2 cm (3rd centile), target height -172.7 cm (25th centile);
Younger sister: healthy; proportionate stature, height at the 50th centile

Past medical history:
Birth: uneventful pregnancy, delivery in 42nd gestational week with cerebral oedema. Length: 47 cm (3rd centile), Weight: 3050g (50th centile), head circumference 50th centile;
Poor growth during the first year, despite the good appetite

Evaluation by paediatric endocrinologist (1 yr 6 mo), because of growth delay
SDS, -1.6;
Disproportionate short stature with relatively larger head and shorter legs (fig.1); shorter fingers with modified shape

Assessment of the neurodevelopmental status – normal
X-ray of the spine: diastematomyelia ? (Diagnosis by radiologist)

X-ray of the spine and pelvis (AP view); at the level Th7-Th8: wide interpedicular spaces; at the level Th8-Th9: spina bifida, short diskal space, deformation of ribs (fig.2)

X-ray of the spine and pelvis (lateral view): at the level L2-L3: wide diskal spaces; at the level L3-L5: knitting processes spinoi (fig.3)

Evaluation by neurosurgeon and orthopedist – no treatment offered

Next presentation (5 yr 1 mo)
Progressing growth delay (fig.6) and nocturnal enuresis;

Differential diagnosis:
Spondylo-costal dysplasia;
Mucopolisacharidosis IVB Morquio: excluded

Next presentation (4 yr 4 mo)
Enuresis nocturna;
Height 91.6 cm, SDSp : -2.6

Disproportionate short stature (fig.4); big forehead (fig.5), cervical lordosis; sleek thoraco-lumbar kyphosis; deformation of the thorax with dilated lower aperture; acromia; short fingers; pes planus; truncal obesity

X-ray of the left hand: delay of BA with 8 months;
short, bullet shape of middle and distal phalanges

MRI of the spine: thoraco - lumbar kyphosis because of defects at the level of Th12 - L1

Diagnosis:
Partial GH deficiency with spondylo-costal dysplasia

Hormonal GH testing revealed GHD (max GH 9.6 mU/l after glucagon). (table 1)

MRI of the head: hypoplastic pituitary and infundibulum

without neurohypophyseal ectopy (fig.8)

Diagnosis: Partial GH deficiency with spondylo-costal dysplasia

Treatment: rhGH 0.05 U/kg/d as starting dosage at 5 years and 5 months.

Effect of treatment: Enuresia nocturna disappeared during the first 2 weeks. The growth velocity, below the third percentile before treatment, accelerated Significantly. First year-7.14 cm/yr (90th percentile according to Prader) Second year-6.8 cm/yr (75-90th percentile)

Third year-3.8 cm/yr

Surgical correction of the scoliosis at 8 years of age;

Future problems to be solved:

1. Reasons for the unsatisfactory growth during the third year of rhGH;
2. Etiological diagnosis (DLL3, LHX3, 4)

Table 1 Hormonal investigation before rhGH treatment (glucagon test)

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