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

Iva Stoeva, Radka Tincheva, Daniela Avdjieva, Reni Koleva

University Paediatric Hospital Sofia

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 ill (upper respiratory infections). Enuresis nocturna; No difficulties with neck- rotation, involvement mainly of the axial skeleton. Hormonal Growth hormone (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- lumbal kyphoskoliosis. Treatment with rhGH (Norditropin) started at 5 years and 5 months with 0.05 U/kg/d. Disappearence 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.

fig.1 Disproportional short stature

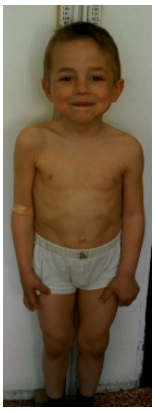


fig.2 X-ray spine and pelvis (AP view)

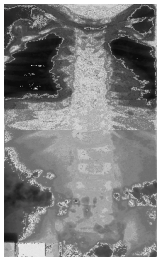


fig.3 X-ray spine and pelvis (lateral view)

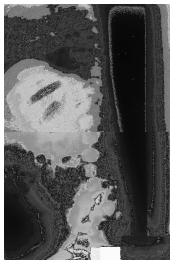


fig.7 X-ray hand and wrist: bone age delay

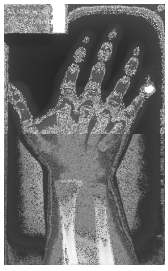


Table 1 Hormonal investigation before rhGH treatment (glucagon test)

minute	0	30	60	90	120	150
BG mmol/l	4.5	8.3	7.1	2.8	3.7	-
GH mU/l	1.66				9.36	5.77
TSH mU/l	2.6					
T_4 nmol/l	132					
FT_4 pmol/l	16.9					

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 (25rd 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_h: - 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: diastemomyelia ? (Diagnosis by radiologist)
X-ray of the spine and pelvis (AP view): at the level Th7-Th12:
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 spinosi (fig.3)
Evaluation by neurosurgeon and orthopedist – no treatment offered
Next presentation (4 yr 4 mo)
Enuresis nocturna;
Height 91.6 cm, SDS_h: - 2.6
Disproportionate short stature (fig.4): big forehead (fig.5), cervical lordosis;
sleek thoraco-lumbal kyphosis; deformation of the thorax with
dilated lower aperture; acromicria; 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 - lumbal kyphosis because
of *defects at* the level of Th12 - L1
Differential diagnosis:
Spondylo-costal dysplasia;
Mucopolisacharidosis IVB Morquio: excluded
Next presentation (5 yr 1 mo)
Progressing growth delay (fig.6) and nocturnal enuresis;
persistent skeletal deformities
Investigations:
X-ray of the hand; BA delay about 1 year 5 months; (fig.7)
bullet shape of middle and distal phalanges;
homogenous osteoporosis
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)
US of the thyroid gland: normal structure
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: Enuresis nocturna disappeared during the first 2 weeks.
The growth velocity, below the third percentile before treatment, accelerated
Significantly. First year-7.14 cm/yr (90-th 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)

fig.4 Auxology up to 4 yrs

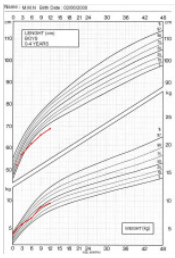


fig.5 Head circumference up to 4 yrs

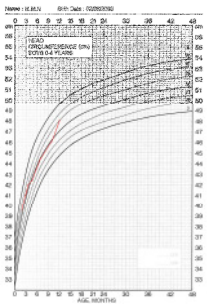


fig.6 Progressive growth delay

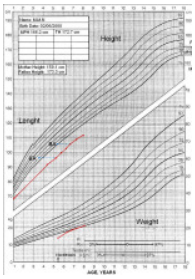
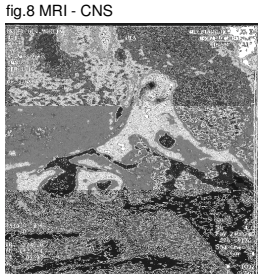


fig.8 MRI - CNS



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**