POSSIBILITIES AND LIMITS OF THERAPY IN A CASE OF HYPOCHONDROPLASIA

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ABSTRACT

Hypocondroplasia is an autosomal dominant genetic disease caused by mutations in the receptor 3 of the fibroblast growth factor gene. The short stature's negative impact on quality of life can be improved by early diagnosis and prompt recombinant growth hormone therapy. The authors present the case of a teenager who lost the chance of this therapy because of a late diagnosis.

Keywords: hypochondroplasia, short stature, growth hormone.

INTRODUCTION

Hipochondroplasia is a skeletal dysplasia with autosomal dominant inheritance characterized by short stature and a great variability ofclinical and radiological changes over time. Early diagnosis of the disease is essential for the initiation of therapy with recombinant growth hormone which is a chance for the social and professional inseration of these patients.

CASE REPORT

MA, feminine sex, 17 years 8 months old from a rural area was admitted to the II Pediatrics Clinic, "St. Maria" Children Hospital for back pain and arthralgia without inflammatory local changes of the elbows and knees.

History data are incomplete; the mother is deceased; the father's stature is short, but without limb deformities. Birth length is not known. The disease began in the first year of life, but short stature and bone deformities were noted by the family with orthostatic position. After age 2, lower limb deformities had increased; walking became more difficult and she started to walk supported at the age of four years. Walking difficulties prevented school attendance.

Physical examon admission objectified the following pathological aspects: short stature (T136 cm, 5.03 SD below the mean), normal weight for age and sex (45 kg, 0.93 SD below the mean), two "cafe au lait" spots on the trunk, lumbar lordosis, short extremities, short metacarpals, brahydactyly, bilateral coxavara, divergent orientation of the IIIrd and IVth fingers ("the trident aspect"), limited extension of the elbows (Figure 1). She didn't show facial dysmorphia and/or organomegaly.

Exploration revealed normal values for cell blood cells, inflammatory and metabolictests: total calcium 9.6 mg/dl, ionized calcium 4.6 mg/dl, alka linephosphatase (AF) 570U/l, phosphorus 4.9 mg/dl ,parathyroid hormone (PTH) 36.63 pg/ml (normal 15-65 pg/ml), phosphorus clearance 30.45 ml/min and tubular reabsorption of phosphorus (TRP) 80% (normally up to 85%). Renal function was normal: urea 27 mg/dl, creatinine 0.61 mg/dl, creatinine clearance 151 ml/1.73 m^2/min, urinary creatinine 95 mg/dl, urinary phosphorus excretion/24 hours 743 mg/dl (normal 400-1300 mg/dl).

Pelvis and femurra diography (Figure 2) showed significant flattening of the pelvis, low articulation

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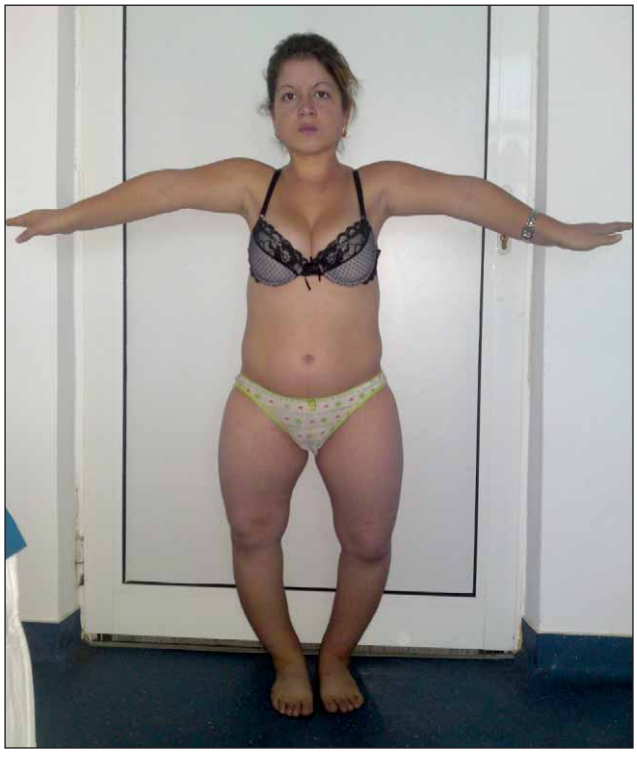

FIGURE 1. *Characteristic clinical phenotype (at the age of 17 years old)*

of sacrum in pelvis, short sacrum, bilateral femoral shortening, discrete clamping of the hip joint spaces, femoral distal metaphyseal areas curvatures in varus and hypertrophy. Rx column lumbar spine (profile) revealed discrete flattening of the dorsal and lumbar vertebral bodies, normal vertebral plates (Figure 3). Skull X-ray (Figure 4) was normal. Rx wrist X-ray (Figure 5) revealed normal bone age, active growth plates with out radiological rickets changes. Osteodensitometry values were normal for age and sex.

Diagnosis of congenital hypochondroplasia was supported by clinical aspects (disharmonic short

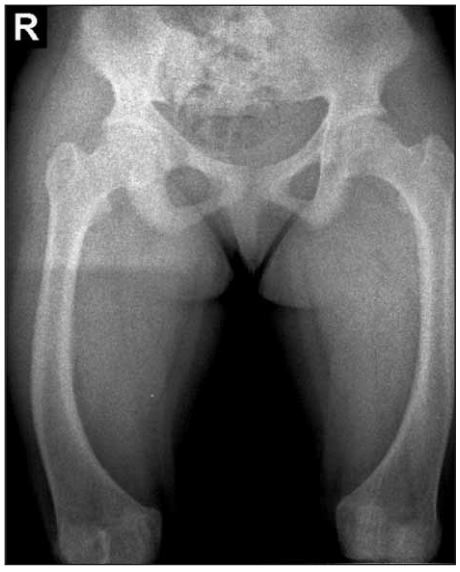

FIGURE 2. *Pelvis X-ray*

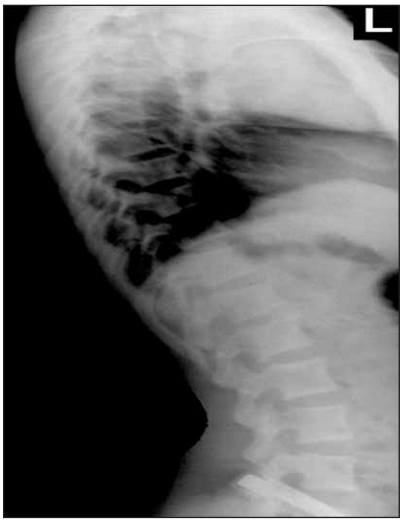

FIGURE 3. *Spine X-ray*

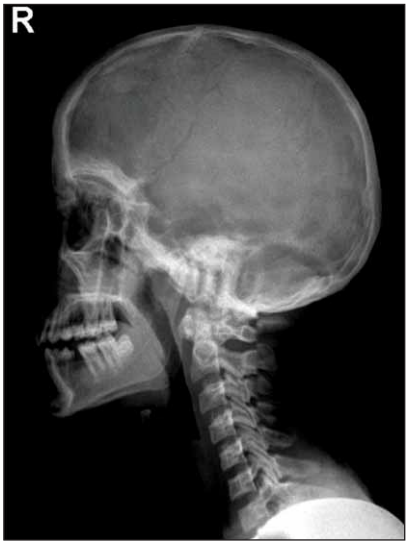

FIGURE 4. *Skull X-ray*

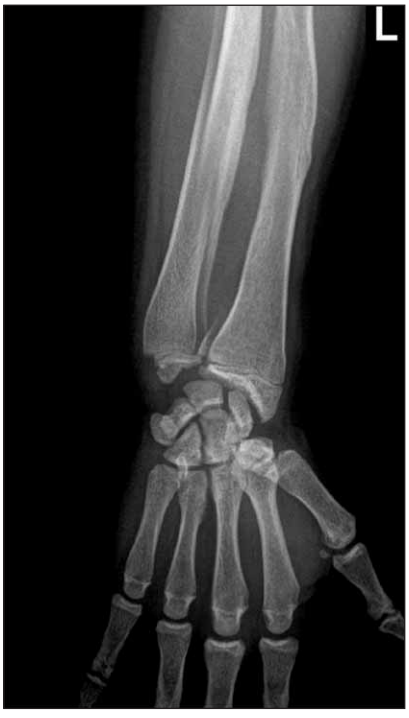

FIGURE 5. *Wrist X-ray*

stature, short extremities, brahydactily, mild generalized joint laxity, limited extension of the elbow-

joints, lumbar lordosis, genuvarum) and radiological features (shortening of the long bones, femoral and iliac wings).

Other causes of short stature with disproportionate limbs were eliminated:

- achondroplasia associates facial dysmorphism (skull bulky, bulbous nose) and radiological changes (excessive development of the skull, settling of the vertebral bodies), but length rarely reaches 110 cm, even in adulthood.
- pseudoacondroplasia evokes some common features like normal facial appearance, short limbs, short phalanges and deviations in the axis of the lower limbs. It was eliminated by length (usually not exceeding 110 cm), absence of arthrosis in the hip and knee joints and characteristic radiological changes (long bones with bold diaphyseal, small irregular epiphyseal nuclei, irregular vertebral body plates).
- familial hypophosphatemic vitamin D resistant rickets is characterized by legs deformities, walking difficulties, short stature, normal or slightly low serum calcium, but also by low phosphorus levels, greatly increased alkaline phosphatase and parathyroid hormonelevels and low TRP.
- mucopolys accharidoses present craniofacial dysmorphia, neurological impairment, enlarge organs such as liver or spleen; all of these are absent in this case.

Pain fulsymptoms were improved by administration of NSAID sand individualized physicalt herapy. Vital prognosis of the caseis good, but the long-term prognosis is encumbered by the late diagnosis which affects growth hormone therapy's results and also the occurrence of static disorders, arthrosis and pseudoarthrosis with a negative impact on quality of life. Follow-up involves assessment of the height, weight and head circumferences using special standardized curves, neurologic examination for signs of spinal cord compression or sleep apnea (indications for CT or MRI brainscan) and regular ly orthopedic examination.

DISCUSSIONS AND CONCLUSIONS

Skeletal sysplasias involves more than 200 forms which differ in their pathogenic mechanisms, inheritance patterns, natural hystory and variable prognosis (1). Recent progresses in the molecular genetic field lead to to the classification of the sediseases according to the affected gene and/or protein(2).

The existence of variable phenotypes caused by different genetic mutations is essential for the moment of the diagnosis. Short disharmonious stature (on average, 145-165 cm in males, 133.4 to 150.6 cm in females at adult age, child 2-3 SD below the mean), rhisomelic or mesomelic limb shortening, limiting the forearm extension arms, brahydactily, joint laxity, macrocephaly with normal aspect of viscerocranium are clinical suggestive features of the diagnosis. Less common, but significant signs are scoliosis, genu varum, lumbar lordos is evident since the adoption of orthostatic position, learning difficulties, *acanthosis nigrigans*, temporal lobe epilepsy (3). Common radiological changes (shortening of the long bones, dorsal concavity of the lower lumbar vertebral bodies, short femoral neck and shortened ilia) are similar to those of achondroplasia, but attenuated. All of these could be absent in infant and toddler period (4).

The diagnosis in the case presented was madelate, only after the appearance of symptoms caused by static difficulties.

Genetic diagnosis is possible. 70% of patients are heterozygous for the mutation of the receptor 3 of fibroblast growth factor gene ($FGFR_3$) situated on the chromosome 4 (4p16.3) (5,6). The binding of FGF to its receptor activates the intracellular tyrosine kinase with a significant role in the regulation of enchondral ossification. Gene mutations activate the receptor in the absence of growth factor and causes abnormal development of the long bones. The type of mutation determines the severity of skeletal abnormalities (7).

Growth hormone (rGH) therapy was approved in skeletal displasia as well as in GH deficiency, chronic renal failure, Turner syndrome, Prader Willi syndrome, small size for gestational age and growth failure at the age of two years. Studies prove the effectiveness of therapy by improving growth velocity waist (from 1.2 SD to 2.6 SD), weekly subcutaneous administrated three years (7.2 cm/year in the first year, 6.3 cm/ year in the second year, 5.7 cm/year in the third year of treatment) (8). rGH therapy may be continued up to the maximum possible height (growth velocity < 2 cm/ year and/or bone age of 16 years in boys and 14 in girls). Growth hormone is beneficial not only for a better length on the adult age, as well as the direct stimulation of bone stock in longitudinal growth at the growth plate, subperiosteal bone formation and increasing bone mineral content (9,10).

In this case, social and economic conditions, lack of family's interest and poor collaboration with primary care units reduced the patient's chance for this therapy with a positive impact on quality of life, schooling and opportunities for social and professional integration.

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