*Acta Orthop. Belg.*, 2004, **70**, 299-305

*REVIEW ARTICLE*

# Orthopaedic concerns in children with growth hormone therapy

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**Growth hormone (GH) therapy is widely used in children ; it may have various severe orthopaedic complications. Slipped capital femoral epiphysis, Legg-Calvé-Perthes disease, scoliosis and carpal tunnel syndrome may occur with GH treatment. Before beginning GH therapy, it is important to take into account all the risk factors of the individual patient, as some conditions could contraindicate GH treatment. During GH treatment, close monitoring with both clinical and radiographic examination is mandatory. The paediatric orthopaedic surgeon will frequently be asked about the management of these complications and about the necessity for treatment arrest.**

**The authors review the orthopaedic complications which the orthopaedic surgeon may encounter in patients treated with GH.**

## INTRODUCTION

Growth hormone (GH) is released from the pituitary gland under control of the growth hormone releasing hormone (GHRH). GH is bound to liver receptors, leading to the production of somatomedins (IGFs). IGFs are bound to circulating binding proteins (IGFBPs) and act on growing bones, leading to increased statural growth.

Nowadays recombinant growth hormone (rGH) is widely used in children with GH deficiency. Moreover this therapy is now extended to conditions other than GH deficiency, such as chronic renal failure, idiopathic or other forms of short stature (Turner syndrome, Prader-Willi syndrome,…).

Treatment with GH in children however requires close attention to possible complications. General adverse events associated with GH therapy have been reported in a series of 33 161 children (National Cooperative Growth Study (*3, 15*). The most frequent side effects were idiopathic intracranial hypertension (0.15%), lymphoedema (0.1%), diabetes mellitus and carbohydrate intolerance (0.1%-0.2%), increase in the number and size of naevi (0.07%), gynaecomasty (0.1% of boys) and acute pancreatitis (0.01%-0.05%) (*3, 15*).

Orthopaedic side effects may also occur and the orthopaedic surgeon must be aware of these complications. Slipped capital femoral epiphysis (SCFE), Legg-Calvé-Perthes disease (LCPD), carpal tunnel syndrome (CTS) and scoliosis have been reported in a large number of children treated with GH (*3, 15*). Clinical and radiological follow-up is necessary to allow early diagnosis and treatment

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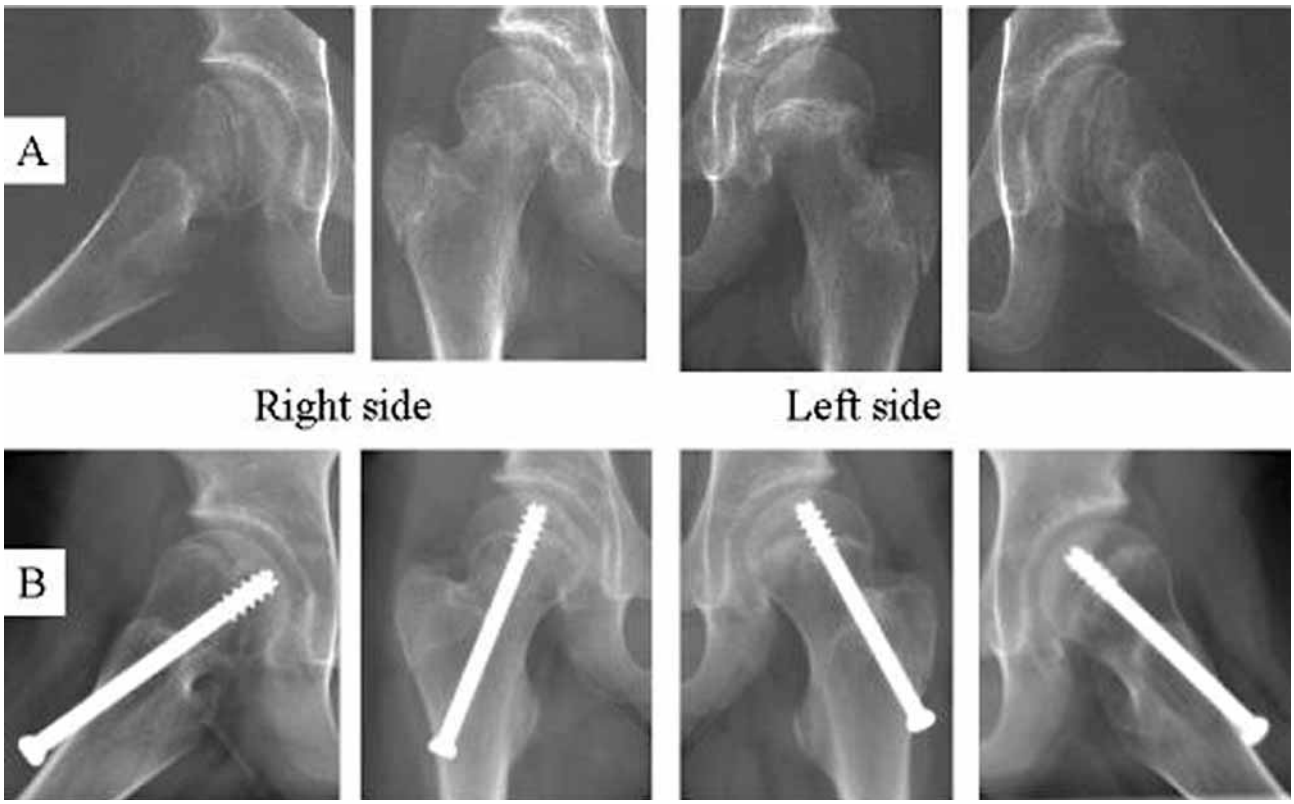


***Fig. 1.*** — Bilateral SCFE in a girl aged 13 years and 6 months. A. Anteroposterior and lateral views of both hips showing bilateral stable SCFE. B. Same views 24 months after pinning procedure.

of these complications but no published guidelines exist to date.

The purpose of this article is to review every complication the orthopaedic surgeon may have to deal with in patients treated with GH.

## CASE REPORTS

### Case 1

*Bilateral SCFE during GH therapy in a girl aged 13 years and 6 months (fig 1).*

At 22 months of age, this girl presented a grade 4 neuroblastoma treated by nephrectomy, total body irradiation (10 gray) and chemotherapy followed by bone marrow autograft. She developed failure to thrive and short stature due to the total body irradiation. GH deficiency and hypothyroidism were biologically excluded. At 11 years of age she entered a study protocol of GH therapy for short stature secondary to total body irradiation. Her weight was 20 kilograms (Percentile 3 = 25 kg) and her height was 111.7 centimetres (P3 = 129.5 cm). Given the radiation injury of her growth plates, the GH doses were higher than those usually used for GH deficiency.

She developed right groin pain and limp at 13 years and 3 months of age but she was still able to walk. She was brought for medical advice only three months after onset of her symptoms. Radiographs showed bilateral SCFE. The left side was asymptomatic. *In situ* fixation with pins was performed bilaterally without any attempt to reduce her chronic slip. GH treatment was stopped. Her height at that time was 126 cm (P3 = 145.4 cm) and her weight was 26 kg (P3 = 34 kg). No postoperative complications occurred after a follow-up of 2 years.

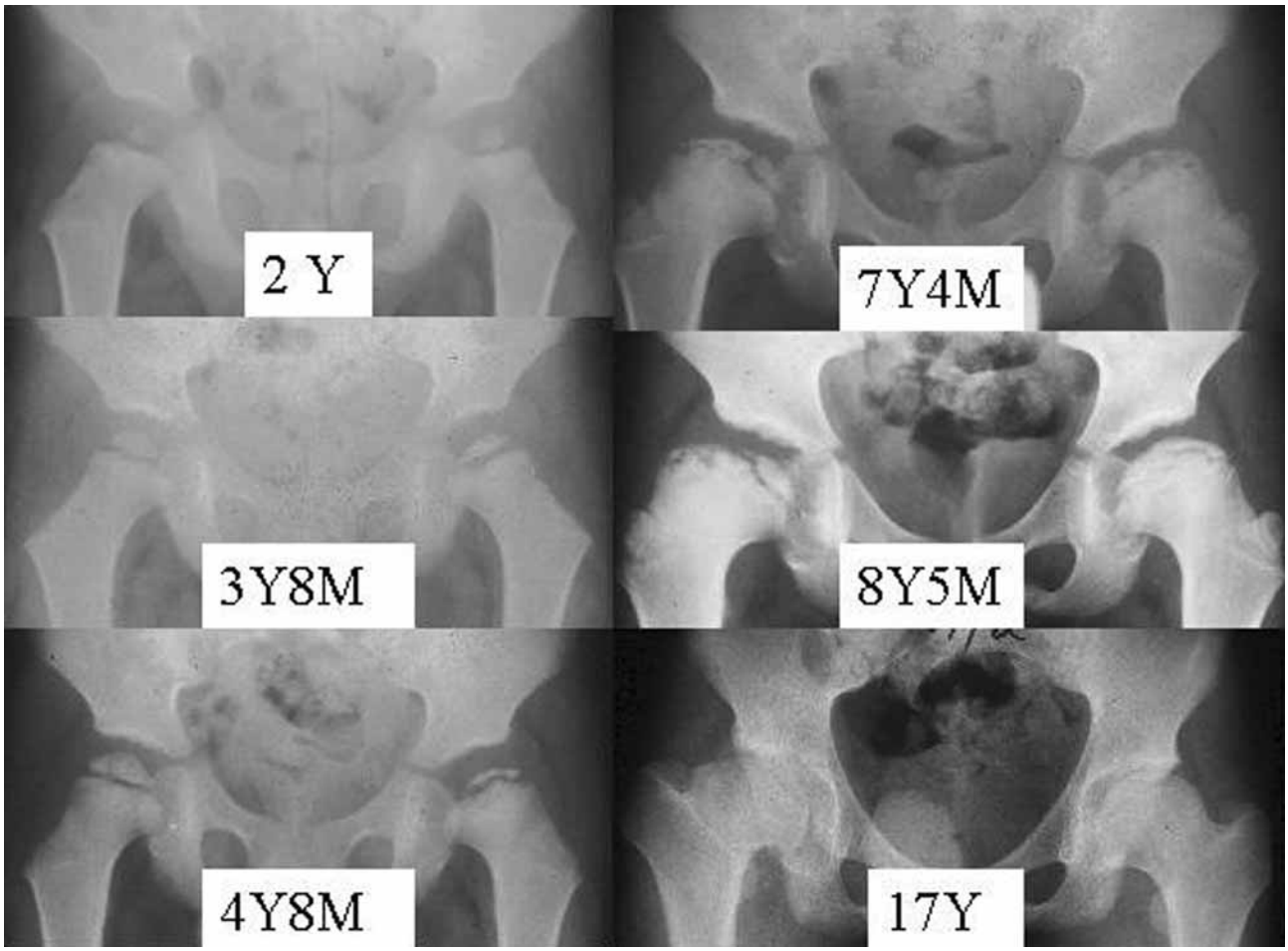


***Fig. 2.*** — Long-term evolution of bilateral LCPD in a boy treated for a short stature due to GH deficiency

**Case 2**

*Bilateral LCPD in a boy treated for a short stature due to GH deficiency (fig 2).*

Treatment began at 9 months of age. His height was 64 cm (P3 = 67.9 cm) and his weight was 8.1 kg (3 < P < 10). He received GH therapy until 16 years of age.

At 3 years and 8 months of age, he developed left groin pain and limp. Left LCPD was diagnosed on radiographs, but GH therapy was nevertheless continued. The right femoral head developed a similar problem one year later. Conservative treatment was applied. The duration of the different phases of the LCP disease were exceptionally long. On the left side, the necrosis and fragmentation stages lasted for one year each and on the right side they lasted for 2 years and 8 months and one year respectively.

Late follow-up at 17 years of age (fig 2) showed asymptomatic and mobile hips. The patient had a 1.6 cm leg length discrepancy. Radiographs showed a flattened coxa magna and shortening of the femoral neck. The final height was 165 cm (3 < P < 10) and the weight was 64 kg (50 < P < 75) at 21 years of age.

**Case 3**

*Fortuitous diagnosis of LCPD in a 6 year-old boy (fig 3).*

GH treatment was proposed to this boy for hypotonia and obesity secondary to Prader-Willi

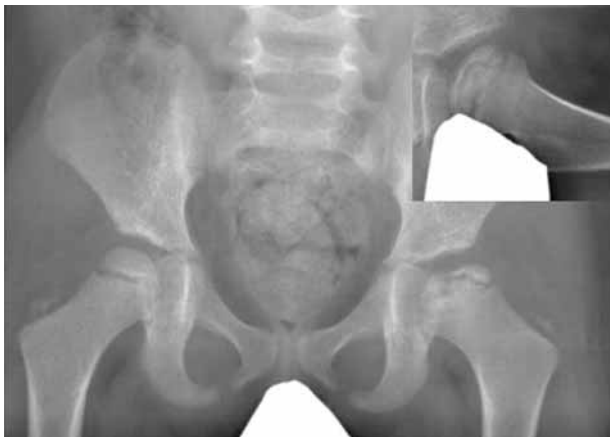

***Fig. 3.*** — Fortuitous diagnosis of LCPD in a 6-year-old boy before beginning the GH therapy.

syndrome. Systematic pelvis radiographs were taken before treatment although the child was asymptomatic. It showed LCPD of the left hip. Pin-hole bone scan staged the disease at Conway stage 3B (27). In this case GH therapy was contra-indicated due to the higher risk of contralateral LCPD. No treatment was applied for LCPD as the child was totally asymptomatic.

**Case 4**

*Rapidly progressive scoliosis in a girl with Prader-Willi syndrome (fig 4).*

Prader-Willi syndrome was diagnosed at 2 years of age. At 9 years of age she developed a pneumonia with respiratory distress requiring intubation and assisted ventilation. Chest radiographs showed severe scoliosis. GH therapy was started at 9 years and 2 months of age with the purpose of decreasing the fatty mass, improving muscular tone and reducing the respiratory problems and the sleep disorders. Her height was 130 cm (P50) and her weight was 79 kg (> P97). At the beginning of the

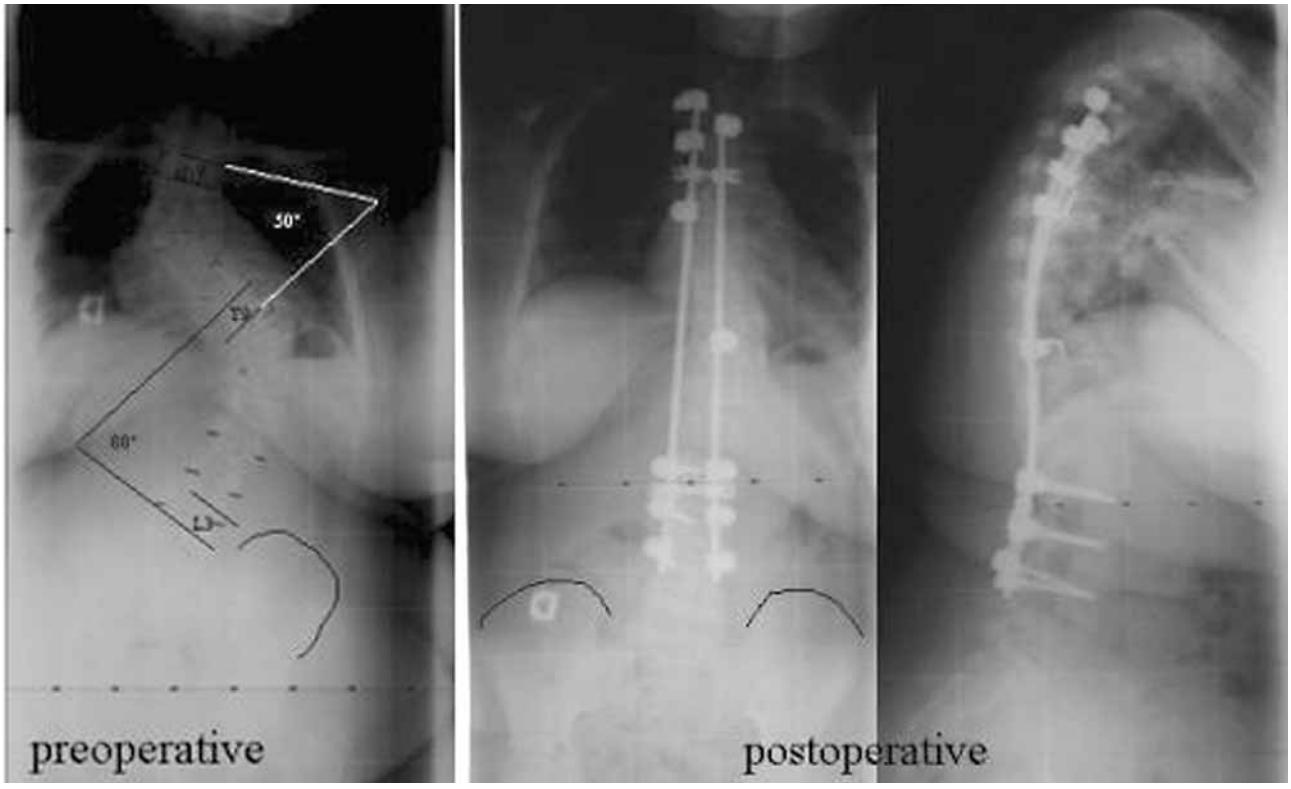


***Fig. 4.*** — Rapidly progressive scoliosis in a 9-year-old girl with Prader-Willi syndrome treated with GH therapy

treatment, the sinistroconvex thoracolumbar curvature measured 62° between T9 and L3. After 6 months of treatment the curvature increased to 88°. In this case bracing was impossible due to her morbid obesity. Instrumented posterior fusion was performed at 10 years of age allowing the GH therapy to be continued.

## DISCUSSION

### Slipped Capital Femoral Epiphysis (SCFE)

SCFE most commonly occurs in children during the peripubertal period. The annual incidence of SCFE in the general population is estimated at 3.41/100 000 with a male predominance (1.88/100 000 in girls and 4.92/100 000 in boys) (*12*). Risk factors in the general population are obesity (*14*) and rapid growth (*12*). Slipping occurs bilaterally in 37% of cases (*13*).

The National Cooperative Growth Study reported an SCFE rate of 135/100 000 (*3*) to 152/100 000 children in children receiving GH-therapy (*15*). This corresponds to an annual incidence of 59.6/100 000 (*3*). Compared to the annual incidence in the normal population (*12*) the relative risk in children receiving GH therapy is about 17.5. SCFE occurs 15 weeks to 10 months after the start of treatment (*21*). SCFE is significantly less common when the indication is idiopathic short stature compared to GH deficiency (*3*) as GH deficiency itself increases the incidence of SCFE (*22*).

Experimental data suggest that GH stimulates chondrocyte proliferation and significantly increases the proliferative and hypertrophied cell zones in both Snell dwarf mice (*25*) and in normal rats (*10*). Thickening of the weakest zone of the growth plate reduces its ability to resist shearing force.

In case 1, the girl was at high risk for SCFE and the GH treatment in this case was questionable. The first major risk factor in this case was total body irradiation. Chapman *et al* (*6*) have shown that the incidence of SCFE reaches 10.4 % after pelvic radiotherapy with 60% of bilateral slip. Slipping occurs after a mean latency period of 6 to 8 years after irradiation with doses of more than 25 grays (*2*).

The authors recommend a pelvis radiograph before beginning GH therapy, because chronic SCFE may be asymptomatic and the child may still be walking, as our case.

Wells *et al* (*31*) propose bilateral pinning with prophylactic pinning of the uninvolved hip because 100% of patients with endocrine disorders eventually develop bilateral slip. The authors think that systematic bilateral fixation could allow to continue the treatment with the same posology.

### Legg-Calvé-Perthes Disease (LCPD)

LCPD generally occurs in children aged 4 to 10 years. An increased incidence of LCPD has been reported in GH deficiency (*5, 18, 19, 23*) and in chronic renal failure (*4*) which can be indications for GH treatment. Treatment with GH has been shown to be associated with a further increase in the incidence of LCPD in case of renal osteodystrophy and hyperthyroidism (*16, 17*). To date the mechanism by which the endocrine abnormalities and the GH therapy cause femoral head avascular necrosis in children remains unknown.

In case 2, GH treatment should have been stopped when the diagnosis of LCPD was made. Indeed the continuation of GH favoured contralateral disease and delayed the healing process. This boy had a major risk factor, as he was GH deficient.

Before beginning GH therapy, a radiograph of the pelvis is needed, as asymptomatic LCPD could be present (as in case 3). The authors think that the occurrence of LCPD should lead to complete arrest of GH therapy to give the best chance to the contralateral femoral head not to develop the disease and to optimise the healing of the femoral head necrosis.

### Scoliosis

Adolescent idiopathic scoliosis, defined as a lateral spinal curvature greater than 10 degrees accompanied by vertebral rotation is present in 1.7 to 4% of children between 10 and 16 years of age (*24, 26, 32*).

Controversies persist about the risk of scoliosis progression in case of GH therapy. Vidil *et al* (*29*)

and Allen *et al* (*1*) are of the opinion that no conclusion can be made regarding a possible relationship between GH treatment and scoliosis progression. Efficacy of the bracing treatment is reported in some cases (*29*). On the contrary Dymling *et al* (*9*), Nishi *et al* (*19*), and Wang *et al* (*30*) conclude that growth hormone may increase the risk of scoliosis progression. Scoliosis develops in 4% of patients under GH therapy (*30*). Curves are progressive in 50% (*29*) to 60% of cases (*30*) and require bracing treatment. Despite bracing, progression continues in 50% of the cases and is frequently severe (*30*).

In case 4, the girl was at high risk for scoliosis progression and in this case GH treatment was contraindicated before surgical correction. In Prader-Willi syndrome, the prevalence of scoliosis is 86% (with progression in 15 to 20% of cases) (*11*). Other major risk factors for curve progression were present in this case : curve greater than 30 degrees, skeletal immaturity and female gender (*24, 26*).

The authors think that treatment of scoliosis in case of GH treatment is no different than treatment for classic idiopathic scoliosis but requires special vigilance from the physician. GH treatment should be stopped if scoliosis progression continues despite the treatment.

### Carpal Tunnel Syndrome (CTS)

Contrary to adults, CTS is uncommon in children (*28, 20*). In case of GH therapy in children, the incidence of symptomatic CTS remains low : 27/100 000 children without sex predominance (*3*). The syndrome occurs 3 months to 5.5 years after starting GH treatment (*3*). The rare occurrence of symptomatic CTS in children treated with GH is different from the situation in adults, in whom CTS (3-12%) is far more frequent (*7, 8*). Further studies are needed to assess the incidence of asymptomatic CTS in children with GH therapy.

Clinical examination is mandatory at every consultation with the paediatric endocrinologist. Electrophysiologically confirmed CTS in a child needs surgical treatment if symptomatic.

## CONCLUSION

GH therapy has become a widely used treatment ; its indications are numerous. GH therapy exposes the child to side effects : SCFE, LCPD, scoliosis and CTS may occur during GH treatment, and close follow-up by a paediatric orthopaedic surgeon is mandatory.

Contraindications to GH treatment exist. The authors think that a previous history of pelvic radiotherapy or of LCPD, as well as significant progressive scoliosis or kyphosis should contraindicate any GH treatment.

Even if no contraindications are present, pretreatment evaluation of the child is mandatory. This should include thorough clinical examination, with focus on the hips and the spine. A systematic radiograph of the pelvis is necessary, as asymptomatic LCPD or stable SCFE may be present. Full spine radiograph is performed if clinical examination is abnormal.

Monitoring is essential during GH therapy to allow early diagnosis and treatment of adverse events. Clinical and radiographic follow-up (with hip radiographs every 4 to 6 months) are necessary. Any complaint of bone pain or limp should be assessed aggressively.

In case of complications, immediate treatment is recommended. If SCFE is diagnosed, bilateral pinning must be performed. Prophylactic contralateral pinning should allow continuation of the GH therapy. In case of LCPD, treatment should be immediately stopped to prevent contralateral disease and to decrease the severity of the condition. In case of scoliosis, the treatment is similar to treatment for idiopathic scoliosis and GH-treatment may be continued except in case of severe scoliosis progression despite treatment. CTS is very rare in GH treated children. In case of symptoms, electrophysiologically proved CTS should lead to surgery.

## REFERENCES

1. **Allen DB.** Safety of human growth hormone therapy : current topics. *J Pediatr* 1996 ; 128 (5 Pt 2) : S8-13.
2. **Berard J, Brunat-Mentigny M, Cocchi P, Naoury A.** Epiphysiolyse de la hanche après radiothérapie pratiquée pour tumeur pelvienne dans la première enfance. A propos de 5 nouveaux cas. *Chir Pédiatr* 1985 ; 26 : 163-166.

3. **Blethen SL, Allen DB, Graves D, August G, Moshang T, Rosenfeld R.** Safety of recombinant deoxyribonucleic acid-derived growth hormone : The national cooperative growth study experience. *J Clin Endocrinol Metab* 1996 ; 81 : 1704-1710.
4. **Boechat MI, Winters WD, Hogg RJ, Fine RN, Watkins SL.** Avascular necrosis of the femoral head in children with chronic renal disease. *Radiology* 2001 ; 18 : 411-413.
5. **Burwell RG, Vernon CL, Dangerfield PH, Hall DJ, Kristmundsdottir F.** Raised somatomedin activity in the serum of young boys with Perthes' disease revealed by bioassay. A disease of growth transition ? *Clin Orthop* 1986 ; 209 : 129-138.
6. **Chapman JA, Deakin DP, Green JH.** Slipped upper femoral epiphysis after radiotherapy. *J Bone Joint Surg* 1980 ; 62-B : 337-339.
7. **Cohn, Feller AC, Draper MW, Rudman IW, Rudman D.** Carpal tunnel syndrome and gynecomastia during growth hormone treatment of elderly men with low circulating IGF-1 concentrations. *Clin Endocrinol* 1993 ; 39 : 417-425.
8. **De Boer H, Blok GJ, Van der Veen EA.** Clinical aspects of growth hormone deficiency in adults. *Endocr Rev* 1995 ; 16 : 63-86.
9. **Dymling JF, Willner S.** Progression of a structural scoliosis during treatment with growth hormone. A case report. *Acta Orthop Scand* 1978 ; 49 : 264-268.
10. **Harris RW.** The endocrine basis for slipping of the upper femoral epiphysis. *J Bone Joint Surg* 1950 ; 31 : 5-11.
11. **Holm VA, Laurnen EL.** Prader-Willi syndrome and scoliosis. *Dev Med Child Neurol* 1981 ; 23 : 192-201.
12. **Kelsey JL.** The incidence and distribution of slipped capital femoral epiphysis in Connecticut. *J Chronic Dis* 1971 ; 23 : 567-578.
13. **Loder RT, Aronson DD, Greenfield ML.** The epidemiology of bilateral slipped capital femoral epiphysis. A study of children in Michigan *J Bone Joint Surg* 1993 ; 75-A : 1141-1147.
14. **Loder RT, Greenfield ML.** Clinical characteristics of children with atypical and idiopathic slipped capital femoral epiphysis : description of the age-weight test and implications for further diagnostic investigation. *J Pediatr Orthop* 2001 ; 21 : 481-487.
15. **Maneatis T, Baptista J, Connelly K, Blethen S.** Growth hormone Safety update from the National Cooperative Growth study. *J Pediatr Endocrinol Metab* 2000 ; 13 Suppl 2 : 1035-1044.
16. **Mehls O, Ritz E, Krempien B, Gilli G, Link K, Willich E, Scharer K.** Slipped epiphyses in renal osteodystrophy. *Arch Dis Child* 1975 ; 50 : 545-554.
17. **Mehls O, Broyer M.** Growth response to recombinant human growth hormone in short prepubertal children with chronic renal failure with or without dialysis. The European/Australian Study Group. *Acta Paediatr Suppl* 1994 ; 399 : 81-87.
18. **Neidel J, Schonau E, Zander D, Rutt J, Hackenbroch MH.** Normal plasma levels of IGF binding protein in Perthes' disease. Follow-up of previous report. *Acta Orthop Scand* 1993 ; 64 : 540-542.
19. **Nishi Y, Tanaka T, Fujieda K, *et al.*** Slipped capital femoral epiphysis, Perthes' disease and scoliosis in children with growth hormone deficiency. *Endocr J* 1998 ; 45 Suppl : S167-169.
20. **Poilvache P, Carlier A, Rombouts JJ, Partoune E, Lejeune G.** Carpal tunnel syndrome in childhood : report of five new cases. *J Pediatr Orthop* 1989 ; 9 : 687-690.
21. **Prasad V, Greig F, Bastian W, Castells S, Juan C, Avruskin TW.** Slipped capital femoral epiphysis during treatment with recombinant growth hormone for isolated, partial growth hormone deficiency. *J Pediatr* 1990 ; 116 : 397-399.
22. **Rappaport EB, Fife D.** Slipped capital femoral epiphysis in growth hormone-deficient patients. *Am J Dis Child* 1985 ; 139 : 396-399.
23. **Rayner PH, Schwalbe SL, Hall DJ.** An assessment of endocrine function in boys with Perthes' disease. *Clin Orthop* 1986 ; 209 : 124-128 ..
24. **Reamy BV, Slakey JB.** Adolescent idiopathic scoliosis : review and current concepts. *Am Fam Physician* 2001 ; 64 : 111-116 .
25. **Smeets T, Van Buul-Offers S.** The influence of growth hormone, somatomedins, prolactin and thyroxine on the morphology of the proximal tibial epiphysis and growth plate of Snell dwarf mice. *Growth* 1983 ; 47 : 160-173.
26. **Soucacos PN, Zacharis K, Soultanis K, Gelalis J, Xenakis T, Beris AE.** Risk factors for idiopathic scoliosis : review of a 6-year prospective study. *Orthopedics* 2000 ; 23 : 833-838.
27. **Tsao AK, Dias LS, Conway JJ, Straka P.** The prognostic value and significance of serial bone scintigraphy in Legg-Calve-Perthes disease. *J Pediatr Orthop* 1997 ; 17 : 230-239.
28. **Van Meir N, De Smet L.** Carpal tunnel syndrome in children. *Acta Orthop Belg* 2003 ; 69 : 387-395.
29. **Vidil A, Journeau P, Soulie A, Padovani JP, Pouliquen JC.** Evolution of scoliosis in six children treated with growth hormone. *J Pediatr Orthop* 2001 ; 10-B : 197-200.
30. **Wang ED, Drummond DS, Dormans JP, Moshang T, Davidson RS, Gruccio D.** Scoliosis in patients treated with growth hormone. *J Pediatr Orthop* 1997 ; 17 : 708-711.
31. **Wells D, King JD, Roe TF, Kaufman FR.** Review of slipped capital femoral epiphysis associated with endocrine disease. *J Pediatr Orthop* 1993 ; 13 : 610-614.
32. **Yawn BP, Yawn RA, Hodge D, *et al.*** A population-based study of school scoliosis screening. *JAMA* 1999 ; 20 ; 282 : 1427-1432.