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Slipped Capital Femoral Epiphysis after 2 Months from Starting Growth Hormone Therapy

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Abstract

Recombinant growth hormone (GH) is a widely used hormonal therapy for children and adolescents with GH deficiency or short stature related to certain conditions. Generally, GH therapy has a good safety profile; however, it could have rare but significant orthopaedic complications including slipped capital femoral epiphysis (SCFE). Pediatric endocrinologists are aware of these possible complications, and they are responsible for appropriately counseling their patients before commencing this hormone. However, the pediatric endocrinologist may not be the first clinician who encounters the orthopaedic complications of GH, as the patient may seek an emergency medical opinion from people from other specialties. Here, we report the case of a 13-year-old Iraqi adolescent boy who presented with limping that appeared only 2 months after receiving GH (0.035 mg/kg/d). He was diagnosed with SCFE in a relatively very short time after commencement of the treatment. Despite this, the patient was not considered to be at high risk of SCFE. A careful evaluation of SCFE in patients complaining of a limp or hip and knee pain during GH therapy is highly recommended.

Keywords
- limping gait
- hip joint pain
- slipped femoral epiphysis
- atraumatic limp
- growth hormone therapy
- case report

Introduction

Recombinant growth hormone (GH) therapy is an important pharmacological intervention to stimulate linear growth in children with GH deficiency (GHD).[1] The mechanism of action of GH involves interaction with GH receptors in different organ systems and utilizing several metabolic pathways. The diverse action of GH on the different target tissues during growth promotion may, however, be associated with unwanted side effects. For example, GH therapy can be causing some serious but uncommon side effects such as increased intracranial pressure, slipped capital femoral epiphysis (SCFE), impaired glucose tolerance, hypothyroidism, and gynecomastia.[1,2] Indeed, there is an increased prevalence of SCFE in children treated with GH.[2]

SCFE is the most common hip disorder in children aged between 9 and 15 years.[3] SCFE is a slippage and separation of the metaphysis from the epiphysis of the proximal femur. The epiphysis remains in the acetabulum, while an outward rotation of the femur occurs with an extension.[4] The etiology of SCFE appears to be multifactorial; however, some factors that are identified as causally related to SCFE include obesity (whether in boys or girls) and endocrine disorders such as hypothyroidism, GHD, and hypopituitarism.[5] One of the risk

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factors for developing SCFE includes a height below the 10th percentile before the age of 10 years or after the 16th birthday.[6]

In addition to SCFE, GH therapy could be associated with other various orthopaedic complications including scoliosis, and carpal tunnel syndrome. Therefore, it is important to provide proper counseling before commencing the treatment, followed by close clinical monitoring during treatment with GH.[2,7]

Here, we report the case of an Iraqi adolescent patient who developed SCFE during GH therapy. To our knowledge, this is the first case report from Iraq about this complication of GH treatment. Worldwide, the patients who developed SCFE usually received higher doses of GH and received it for at least 2 years.[8] It was rarely reported in patients who received it for a short period of time.

Case Presentation

An adolescent boy, age 13 years and 9 months, gained weight significantly over 1 year, with poor correspondence to his linear growth, for which he was referred to a pediatric endocrine clinic for an evaluation. His growth velocity was 3 cm/y. His height 1 year ago was 147 cm (–1 standard deviation score [SDS]), and at the time of referral it was found to be 150 cm (–1.5 SDS). His midparental height (MPH) is 173 cm (–0.5 SDS), while his body mass index (BMI) was 30.2 kg/m^2, exceeding the 95th percentile. Bone age is between 11 and 12 years. His sexual maturity rating is 3 for gonads and 3 for pubic hair with a testicular volume of 10 mL bilaterally.

Evaluation of pituitary hormonal functions showed a GHD (basal GH of 0.05 ng/mL, and the peak with stimulation was 0.45 ng/mL). Insulinlike growth factor 1 (IGF-1) was 185 ng/mL (within the normal reference range for age and gender), thyroid function was normal, and there was adequate adrenal reserve. Brain magnetic resonant imaging (MRI) study was normal, indicating no pituitary gland abnormalities or any space-occupying lesion (e.g., tumor). Therefore, the child was diagnosed with isolated GHD. GH treatment was started with a dose of 0.035 mg/kg/d.

Two months later, the patient presented to the clinic with limping and left hip joint pain with limitation of movement for a week. However, his condition was not associated with any previous trauma or fever, or skin rash. He responded to GH, and he grew by 2 cm. A bilateral hip X-ray revealed irregular left femoral epiphysis with more density in the frog position, suggesting an SCFE (►**Fig. 1**). GH therapy was discontinued, and surgical intervention was advised.

Discussion

SCFE occurs more frequently in periods of rapid height gain. Children and adolescents treated with GH are at greater risk of developing SCFE.[9] A previous report indicated that 52 of a total of 57,968 children treated with GH were diagnosed with SCFE. The total incidence of SCFE was found to be 73.4 per 100,000 patients per year,[10] while the prevalence in the general population is 10.8 cases per 100,000 patients per year.[9] A careful clinical evaluation is recommended for children treated with GH and complaining of pain in the hips or knees. SCFE is usually diagnosed based on clinical history, and clinical examination, as there would be a limitation of the internal rotation of the affected leg. The condition is usually confirmed by a bilateral hip X-ray, which typically shows a widening of the physis, reducing the height of the epiphysis, and loss of the concavity of the anterior femoral head–neck junction. SCFE is a surgically corrected condition using in situ fixation with hip screw.[9]

In the current case report, the GH treatment in this adolescent patient was not the only risk factor for SCFE. BMI of the patient was high, and obesity is known to play a significant role in the occurrence of SCFE. A cohort study by Perry et al in Scotland on 597,017 school children aged 5 to 6 years and 39,468 aged 11 to 12 years showed a higher risk of SCFE in high BMI children.[11] On the other hand, the risk of SCFE was very low among children with low BMI. Therefore, a strong correlation between childhood BMI and SCFE is evident from such large-scale study.

A similar case was reported by Mazzarello et al, in which an adolescent male with short stature and partial GHD developed SCFE during GH treatment. He was treated surgically using Moore's pins for epiphysis fixation. Although SCFE occurs in different age groups, SCFE is highly prevalent among adolescent patients.[12]

Treatment with GH for other indications such as Turner's syndrome (TS) might also cause SCFE. A case reported by Nasrallah et al indicated that TS itself is a risk factor for SCFE and therefore the prescribing physicians of GH should be vigilant and careful.[13] The patient reported in Nasrallah et al was a girl age 12 years and 1 month who was diagnosed with SCFE. TS is described to be associated with cardiovascular, renal, cognitive, and orthopaedic conditions such as scoliosis, Perthes' disease, and SCFE.[14]

The time from the initiation of GH therapy and the occurrence of SCFE varies among the reported cases. In the present case report, SCFE occurred only 2 months after starting GH treatment. In contrast, three other patients were reported in Taiwan by Wang et al. Two patients had hypopituitarism and were treated with GH starting at the age of 15 years and 6 months and 13 years and 9 months. SCFE developed 4 years and 1 year after GH therapy in the two patients. There was another patient in Wang et al's report who had Prader–Willi syndrome with obesity and hypogonadism and was started on GH at the age of 12 years and 11 months. SCFE developed 2 months after starting GH therapy.[2] These reports perhaps indicate no relationship between the duration of therapy and the onset of SCFE.

Our patient was started on 35 µg/kg/d, which could be argued that it was a high dose to start with since the recommended dose for patients with GHD ranges between 23 and 39 µg/kg daily as per the British National Formulary (BNF). However, Sävendahl et al referred to those patients experiencing SCFE who usually received higher doses of GH (43.7 µg/kg/d) compared with the whole patient population (30.9–38.6 µg/kg/d).[8] Further studies looking at the gradual increase of the GH dose and association with SCFE are

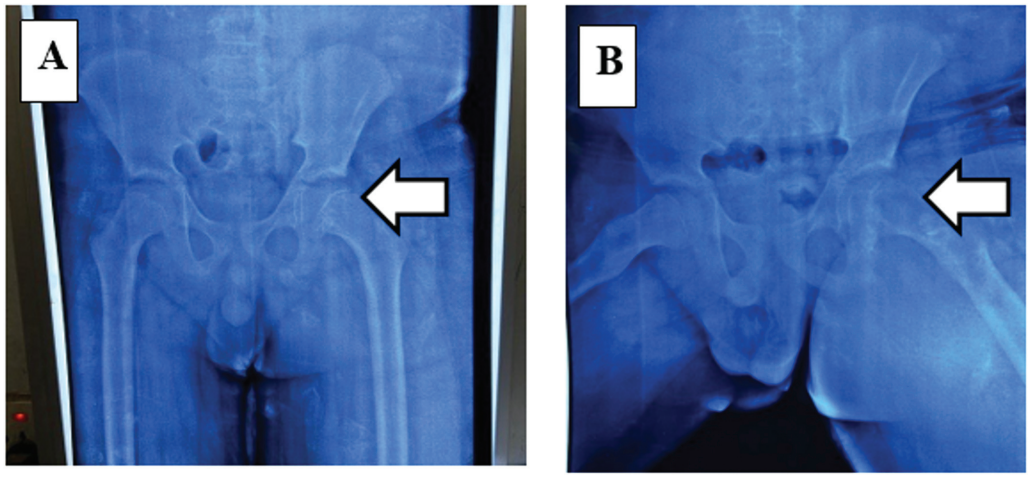

Fig. 1 (**A**) Anteroposterior view. (**B**) Frog view of the pelvis. X-ray of bilateral hips shows displacement of epiphysis between the left femoral head and the femoral neck (*arrow*).

warranted, especially in GH-sensitive patients who may show rapid growth velocity or acute joint changes. Nevertheless, there is a call to study alternative dosing strategies in the obese patient population as they might just benefit from the calculated dose based on their ideal weight.[15] Therefore, if this was taken into consideration in our case, then we could have administered a lower total dose of recombinant GH, which could have been associated with a lower risk of developing side effects.

One of the limitations of this case report is that no other cases from our center who received a similar starting dose of GH developed SCFE. Starting a relatively higher dose of GH is going to be associated with a higher risk of developing SCFE. Another limitation is the rarity of similar conditions from the neighboring countries.

Conclusion

SCFE can occur in patients who receive recombinant GH as early as 2 months after its commencement. Regular monitoring and careful clinical evaluation of patients complaining of a limp or pain over the hip and knee while they receive GH therapy is indeed essential. Clinicians should have a low threshold to investigate for SCFE when it is suspected. Starting patients on a lower dose of GH and building up gradually could minimize the risk of developing unwanted complications.

Patients Consent Statement

We would like to thank our patient and his parents for their cooperation with us and for providing consent for publication. Consent was obtained from the father of the patient and assent was also signed by the child.

Compliance with Ethical Principles

No prior approval is required for single case reports.

Data Availability Statement

It will be made available on request.

Authors' Contribution

W.H.A. is the treating physician, who initially drafted the manuscript. H.A. reviewed the manuscript and finalized it. Both authors agreed on the final version.

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Conflict of Interest

None declared.

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