Congenital growth hormone deficiency associated with hip dysplasia and Legg-Calve-Perthes disease

Short title: Hip disorders and growth hormone deficiency

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Summary

Objective: Growth hormone deficiency (GHD) is usually treated with recombinant human GH (rhGH), and this has been rarely associated with hip disorders. We analysed the clinical data of patients with congenital GHD receiving rhGH who had associated hip dysplasia or Legg-Calve-Perthes disease (LCPD), with a view to determining whether the hip dysplasia was associated with the underlying disease or with rhGH treatment.

Design: We performed a retrospective analysis of paediatric and adolescent patients seen between 1992-2018 with congenital GHD and hip disorders. Data were collected through a review of the patients' medical records and included demographics, clinical and imaging data, and the time frame between the onset of the symptoms related to the hip disorders and the onset of GH treatment.

Results: Of the 13 patients with hip disorders, hip dysplasia was present in ten patients and LCPD in three. Hip dysplasia was diagnosed before rhGH was initiated in 50% of cases. These patients had bilateral hip dysplasia and isolated GHD. LCPD was diagnosed in one patient before rhGH was commenced and did not progress. In two patients, LCPD was diagnosed after rhGH was started and did temporarily progress in one of them, but rhGH was not discontinued because LCPD did not seem to be related to rhGH treatment.

Conclusions: This study suggests that hip dysplasia could be a manifestation of an underlying GHD. Additionally, rhGH treatment may not necessarily be causative of LCPD.

Key words: Hypopituitarism; growth hormone; pituitary hormone deficiency; septo-optic dysplasia; pituitary diseases; hip dysplasia; Legg-Calve-Perthes Disease.

Introduction

Congenital hypopituitarism is defined by the partial or complete insufficiency of one or more pituitary hormones. The phenotype can be highly variable and may consist of isolated hypopituitarism, or more complex disorders such as septo-optic dysplasia (SOD) [1]. Growth hormone deficiency (GHD) is the commonest pituitary hormone deficiency [2,3] . Children diagnosed with GHD may require recombinant human GH (rhGH) treatment for a variable period, ranging from a few years to lifelong, and in this respect, the surveillance of the long-term side-effects of rhGH treatment is particularly important. Orthopedic complications may occur following the commencement of rhGH [4], but some patients may develop hip disorders before rhGH is started, suggesting that untreated GHD/hypopituitarism may be associated with hip pathology.

The aims of our study were to identify those patients with congenital GHD receiving rhGH treatment at our tertiary centre over a 25-year period in whom hip dysplasia or Legg-Calve-Perthes disease (LCPD) has been documented, and to then determine whether GHD and hip dysplasia or LCPD occur coincidentally, or whether the hip dysplasia could be a manifestation of the underlying neuroendocrine developmental disorder or a potential adverse effect of rhGH.

Methods

We conducted a retrospective study of paediatric and adolescent patients with congenital GHD and hip disorders presenting from 1992 to 2018 to the London Centre for Paediatric Endocrinology and Diabetes (LCPED), incorporating two tertiary paediatric and adolescent endocrinology centres based at Great Ormond Street Hospital for Children and University College London Hospitals.

Data were collected retrospectively through a review of the patients' medical records and included demographics, associated endocrine diagnoses, clinical features of the hip disorder, the time frame between the onset of the hip symptoms and the time rhGH was started, and imaging data.

From over 300 eligible patients with congenital GHD, including approximately 170 patients with septo-optic dysplasia (SOD), 13 patients were identified as having a hip disorder. GHD was diagnosed if a sub-optimal growth velocity and a low IGF-I concentration for age and sex (below -2 standard deviation scores) were documented in association with sub-optimal GH responses to provocation (peak GH <6.7 µg/L) [2,5,6]. In these cases, brain magnetic resonance imaging was performed to search for structural pathologies of the central nervous system. rhGH was initiated at a dose of 15-20 mcg/kg/day for GHD [7] in the majority of cases, and the dose was subsequently adjusted according to insulin-like growth factor I (IGF-I) concentrations (targeting the upper half of the normal range) based on assays available during the studied period., as well as growth velocity, which was also monitored to avoid accelerated or suboptimal growth. In one case, rhGH was prescribed in the context of small for gestational age, and in two cases with peak GH at glucagon stimulation test >6.7 µg/L, but associated with low or borderline low IGF-I and reduced growth velocity, GH was also commenced.

Hip dysplasia and LCPD were diagnosed based on clinical findings and imaging. Hip dysplasia was suspected when infants presented with abnormal gait, asymmetric sitting, localized pain or discomfort, difficulty in weight-bearing, or delayed walking, and the diagnosis was confirmed by radiography [8].

According to the appearance on anteroposterior and frog-leg lateral radiographs, assessing the Putti triad and in particular the Shenton line and the Hilgenreiner angle, infants were classified as having acetabular dysplasia (without subluxation), subluxated with

associated acetabular dysplasia, or dislocated hip(s) [9]. The Putti triad comprises three radiographical signs: (1) hypoplasia/delayed appearance of the femoral nucleus (usually appears in the first 6 months of life); (2) acetabulum index > 35 degrees, measures the inclination of the acetabulum. This is the most useful parameter of the acetabulum displacement up to 6 years of age. It is formed by the Hilgenreiner epiphyseal angle (the angle formed by a line drawn through the triradiate and a line drawn through the epiphyses of the femoral head); (3) Interruption of Shenton line which is an imaginary curved line drawn along the inferior border of the pubic ramus (superior order of the obturator foramen) and along the inferomedial border of the neck of femur.

LCPD was suspected when localized pain in the thigh was present. The affected femoral head in LCPD can undergo varying degrees of necrosis [10]. LCPD was diagnosed based on radiographs or magnetic resonance showing an abnormality of the femoral head based on the Catterall classification [11]. Patients with underlying conditions known to be associated with hip deformities, slipped capital femoral epiphysis and pelvic fracture were excluded.

During follow-up, radiographs were assessed to determine the progression of the hip disorder.

The data that support the findings of this study are shown in Tables 1-3.

Results

Presenting signs and symptoms of the hip disorder

Ten patients had hip dysplasia; none had hip dysplasia diagnosed during the newborn period. Three presented with abnormal gait, two with asymmetric sitting, two with localized pain, one with difficulty or discomfort in weight-

bearing, and one with delayed walking. Patient #10 was diagnosed with hip dysplasia during follow-up of a left femoral fracture.

A diagnosis of LCPD was made following presentation with localized pain in the thigh in all three affected patients.

<u>Patient characteristics and birth history</u>

The affected patients included four females and nine males. All patients had midline brain and/or hypothalamo-pituitary defects. Ten patients (77%) had SOD. The remaining three patients (23%) had hypothalamo-pituitary defects (ectopic/undescended posterior pituitary with two also having anterior pituitary hypoplasia) on magnetic resonance imaging, with multiple anterior pituitary deficiencies. Seven patients were born by normal delivery, two by an elective C-section (twin birth; breech position) and two by an emergency C-section (due to maternal eclampsia). Three patients were born preterm (<37 weeks of gestation) and by C-sections. None of the patients had a birth weight > 4 kg (Table 1). None of the children had a history of trauma during delivery. Three patients were born to first-degree consanguineous parents. One patient had a monozygotic dichorionic healthy twin. All pituitary hormone deficiencies were adequately replaced in all patients. Thyroxine concentrations were normal with treatment.

Ten out of 13 patients had hip dysplasia, six (60%) of whom had bilateral disease, three (30%) had left sided involvement and one (10%) patient had right hip dysplasia. Of these ten patients, five (50%) patients had acetabular dysplasia (without subluxation), one (10%) patient had subluxated hip(s) with associated acetabular dysplasia, and four (40%) had dislocated hip(s). Four patients underwent surgery, one was treated with a hip splint which resolved his hip dysplasia (patient #10), a further one is scheduled to undergo surgery and four have no hip

reconstruction planned to date (Table 2). No family history of hip dysplasia was present in any of the patients.

Hip dysplasia was diagnosed at a mean age of 5.0 years (range: 0.3-13.5). rhGH was started at an average age of 5.2 years (range: 1.4-13.2).

Five patients (50%) had developed hip dysplasia at a mean of 3.8 years (0.5-10.2) prior to initiating rhGH treatment. Four had bilateral hip dysplasia and isolated GHD. One patient (patient #10) had left hip dysplasia which resolved with a hip splint before rhGH was started (Table 2).

Five patients developed hip dysplasia after rhGH was commenced, and received rhGH doses that ranged from 5.9 to 55.8mcg/kg/day. The rhGH doses showed a wide range, but this reflects the course of treatment, whereby doses were individually assessed based on IGF-I concentrations.

Three patients had LCPD (two on the left side); all were males. LCPD was diagnosed at the ages of 3, 15.4 and 18 years. rhGH was started at age 4, 10.3 and 14.6 years, respectively. One patient had developed left-sided LCPD one year prior to initiating rhGH treatment (Table 3).

No patient had a family history of LCPD. LCPD progressed in patient #11 from 21.4 years to 22.3 years of age, but not from 22.3 years old to 23.1 years. No medical intervention was needed. In this case, rhGH was not discontinued as LCPD did not seem to be a consequence of rhGH treatment (LCPD worsened 6.0 years after initial diagnosis of LCPD, and 11.1 years after commencement of rhGH). Additionally, even with rhGH treatment, contralateral disease did not emerge. In patient #12, it did not progress, even on rhGH replacement treatment. In patient #13, LCPD was diagnosed at 18 years of age, when rhGH had already been stopped.

Overall, seven patients developed the hip disorder after rhGH treatment was initiated, of which two discontinued the rhGH treatment permanently because growth had stopped and the patients opted not to continue rhGH in adulthood (patients #6 and #13).

Radiographic pattern for hip dysplasia

To determine whether hip dysplasia in GHD patients conforms to a particular pattern, plain radiographs were used assessing the Putti triad and in particular the Shenton line and the Hilgenreiner angle. Imaging studies were available in nine patients (with the exception of patient #8). In the examined cases, the diagnosis of hip dysplasia was a late diagnosis and not neonatal as is usually observed. A left-sided preference for hip dysplasia was noted, but no particular pattern was observed.

Discussion

This study presents clinical data on a cohort of 13 children and adolescents with congenital GHD, ten of whom had SOD, and a co-existing hip disorder managed in a tertiary paediatric endocrinology centre. Ten patients had hip dysplasia and three had LCPD. None had a traumatic birth. The majority of patients were male, but this may reflect the male predominance observed in patients with congenital hypopituitarism. Hip dysplasia was diagnosed before rhGH was initiated in half of our patients; all but one had bilateral hip dysplasia and isolated GHD with no other pituitary hormone deficiency. LCPD was diagnosed in one patient before rhGH was commenced and did not progress. In one patient, LCPD was diagnosed after rhGH was started and did temporarily progress several years post-commencement of rhGH, although LCPD did not seem to be causally related to rhGH.

rhGH replacement therapy can be associated with hip disorders [4]. Whether hip pathology is caused or exacerbated by rhGH therapy, or whether it is simply caused by rapid

growth consequent on GH treatment *per se* remains to be established. However, in some cases, it is clear that hip pathology can develop prior to rhGH therapy. In our study, four patients with isolated GHD developed bilateral hip dysplasia before rhGH was initiated, suggesting that hip dysplasia could possibly be a manifestation of the underlying neurodevelopmental disorder (GHD) rather than a consequence of GH therapy.

Hip dysplasia

In the general population, its incidence is 1.28 per 1000 live births[12]. The etiology of hip dysplasia is unknown, but is considered to be multifactorial, involving both genetic and intrauterine environmental factors [13]. By reason of the progressive nature of the condition, it is also known as developmental dysplasia of the hips (DDH).

DDH describes the spectrum of structural abnormalities that involve the growing hip [14], including frank dislocation, subluxation and instability, and dysplasia of the femoral head and acetabulum. In DDH, the hip joint is immature, and the femoral head and acetabulum are neither aligned nor grow normally. Its most severe form is hip dislocation. The normal development of the child's hip relies on congruent stability of the femoral head within the acetabulum. The hip joint will not develop properly if it stays unstable and anatomically abnormal by walking age.

The left side (or bilateralism) seems to be the most frequently affected side in DDH in our study, as also previously reported by Kotlarsky [14]. In contrast to the findings of Kotlarsky, we found a higher incidence of bilateralism (67% versus 20%). Interestingly, four of the five patients who developed hip dysplasia before rhGH was commenced had bilateral DDH and were diagnosed later than usually observed in DDH. This result reinforces our hypothesis that hip dysplasia could be a manifestation of the underlying neurodevelopmental disorder.

Furthermore, it appears as though GH could be important as a factor in the later

development of DDH. The majority of our patients had late presenting DDH if 3 months is considered as a cut off age [15]. Studies show that spontaneous resolution of DDH without intervention is unlikely in children over the age of six months [16]. Therefore, even though DDH is the most common congenital musculoskeletal condition presenting to orthopedic teams in the newborn period [17,18], our patients were not born with DDH, but rather appeared to develop this later.

Additionally, previously described risk factors such as female sex, oligohydramnios and a positive family history [14] were not found in our study. Breech delivery has been associated with GHD and could worsen the severity of pituitary endocrinopathies [19], but in our study, none of the patients were born by breech delivery and the patients born from C-section were not due to breech presentation.

Although previous studies have reported that 80% of the affected cohort are female [14], in our study 60% of patients with DDH were male, although this probably reflects the male preponderance associated with congenital hypopituitarism.

GH has anabolic effects on bone, cartilage, and connective tissue growth. Abnormal bone collagen morphology and altered bone geometry were described in rats with isolated GHD [20,21]. Whether similar findings are present in patients with GHD needs further investigation, but results from a human study of muscle and tendon biopsies from patients with GHD or acromegaly indicate a collagen-stimulating role of local IGF-I in human connective tissue, and add to the understanding of musculoskeletal pathology in patients with either high or low GH/IGF-I axis activity [22]. The GH/IGF-I axis also has important effects in the formation and function of cartilage, IGF-I being critical for matrix synthesis and chondrocyte growth [23]. Moreover, in a large cohort of congenital naive GHD individuals, cartilage hypotrophy was observed in the hips, with GHD compromising both growth and cartilage repair [24]. Therefore,

untreated GHD patients may be predisposed to DDH. Hip dysplasia, notably avascular necrosis of the femoral head, was first described in Laron syndrome (GH receptor deficiency) by Rossenbloom et al [25].

Another explanation for the hip dysplasia could lie in its association with hypothyroidism, present in four of our patients. Although well described in association with slipped capital femoral epiphysis, hypothyroidism and hip dysplasia can be seen in the same patient. Thyroid hormones have known effects on proliferation and differentiation of bone and cartilage [26]. Low thyroxine concentrations were speculated to cause abnormal skeletal development in young children with hypothyroidism [27]. Indeed, previous studies have shown that approximately 2-3% of patients with congenital hypothyroidism have hip dysplasia [28,29]. Nevertheless, given that SOD is associated with a wide spectrum of clinical features, and since the pathogenesis of SOD and HD are multifactorial and not fully understood, we acknowledge that a non-endocrine mechanism may link both.

LCPD

The incidence of LCPD ranges from 0.4/100,000 to 29.0/100,000 children under 15 years of age [30]. Its etiology is unknown, but considered multifactorial. The GH/IGF-I axis has also been studied in LCPD patients. Defects in this axis, as well as abnormal increase in serum somatomedin activity with age and low concentrations of circulating IGF-I have been reported in LCPD [31-33]. Indeed, an increased incidence of LCPD has been reported in GHD patients. Bas et al. [34] described a case in which the authors proposed that LCPD could be secondary to IGF-I deficiency.

Similarly, Nishi et al. [35] studied a cohort of 6343 patients with GHD, in which LCPD developed in 12 boys. In this study, nine patients were diagnosed with LCPD prior to receiving rhGH therapy, suggesting that LCPD does not necessarily arise following the commencement

of rhGH. In our study, LCPD was diagnosed in one case before rhGH was commenced. In one patient, LCPD progressed temporarily but did not seem to be related to rhGH treatment because it appeared more than five years after rhGH was commenced and worsened long after LCPD was initially diagnosed. Additionally, continuing rhGH treatment was not associated with contralateral disease.

Retrospective studies have limitations inherent in their design. Some important data were not readily available in medical records, such as maternal primiparity or parental age. Another limitation to our study is the small number of patients, given the rarity of the disorder and, therefore, the inability to generalize concepts found.

In conclusion, only a few studies have addressed the issue of HD and GHD. Hip dysplasia was diagnosed before rhGH was initiated in 50% of our cases. These patients had predominantly bilateral hip dysplasia and isolated GHD with no other pituitary hormone deficiency. Also, LCPD does not seem to be related to rhGH treatment.

This study suggests that hip dysplasia could be a manifestation of an underlying GH deficiency, either isolated or in combination with other pituitary hormone deficiencies (Combined Pituitary Hormone Deficiencies; CPHD). Therefore, hip dysplasia should be considered in children with GHD/CPHD, particularly in those patients with complex midline disorders. Additionally, as previously shown, rhGH treatment may not necessarily be causative in LCPD patients on rhGH treatment. Nevertheless, we recommend monitoring for development of hip disorders in children on rhGH treatment. Clinical and radiological follow-up may be necessary in those children who are symptomatic. Importantly, visual impairment that is a feature in SOD patients may also be associated with an altered gait; however this is unlikely to be related to hip pathology, although exploration of any relationship was beyond the scope of this study. Any complaint of localized bone pain or a limp should nevertheless be taken seriously and thoroughly investigated.

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