Severe Kyphosis Secondary to Glucocorticoid-Induced Osteoporosis in Adolescent Twins with Congenital Adrenal Hyperplasia - A Case Report and Literature Review

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Abstract

Patients with Congenital Adrenal Hyperplasia (CAH) need a life-long treatment with glucocorticoids (GC) which affects bone quality and bone density. We report the clinical cases of twin sisters diagnosed at birth with CAH (simple virilization form). They both received treatment with GC and were diagnosed with severe Hyperkyphosis; they underwent transpedicular vertebral instrumentation, Ponte osteotomies and posterior autograft spinal fusion. Post-surgery evolution was favourable. After 3 years, one of the patients suffered a spinal implant infection that needed debridement and drainage. Patients with long term treatment with GC have a higher risk for osteoporosis than the general population. While monitoring the patients we should take into consideration the bone’s status and preventive measures against osteoporosis. It is important to diagnose the deformities of the spine at a young age in order to be able to try a conservative treatment because, for these patients, surgery comes with a higher risk of complications. It is necessary to have paediatric orthopaedic checkups for children with long term GC treatment.

Keywords: Congenital Adrenal Hyperplasia (CAH); Glucocorticoids; Secondary osteoporosis; Hyperkyphosis

Introduction

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder caused by a mutation in the encoding of steroidogenic enzymes involved in the glucocorticoid synthesis. There are three forms of 21-OHD: classic salt wasting; classical simple virilization form and the least severe nonclassical CAH [1,2]. The simple-virilizing form manifests with precocious pseudo-puberty and advanced bone age in early childhood. Pubertal onset is at 9-10 years of age, the adult patients are usually overweight and the mean adult height in females is shorter than that of the general population [3,4].

The goal of the treatment is to replace the lack of glucocorticoids and mineralocorticoids, so that the patient can have a normal growth and achieve normal puberty. The management of the glucocorticoid (GC) treatment is difficult. Undertreatment means an increased adrenal androgen production with accelerated bone age and loss of growth potential. Overtreatment may result in growth suppression, truncal obesity, increased blood pressure and osteopenia because of the effects of steroids on bone metabolism. Both overtreatment and undertreatment have effects on bone metabolism [5,6].

GC treatment is one of the most frequent cause of osteoporosis. The most important effect is the decreased bone formation which may involve several mechanisms: they affect the differentiation and activity of the cells of osteoblast lineage and other cells within the bone; they also affect the transcription of many genes that encode the synthesis of the matrix of osteoblasts like type 1 collagen and osteocalcin; they affect the synthesis of indulin-like growth factors and IGF binding proteins (IGFB-3, -4, -5) [7].

In a study that determined the prevalences of osteocyte apoptosis in femoral heads, obtained from patients who underwent prosthetic hip replacement because of osteonecrosis (due to chronic glucocorticoid treatment), it has been determined that the bone is not necrotic, instead it has apoptosis of cancellous lining cells and osteocytes [8]. The osteoclast function decreases with prolonged treatment and bone resorption is accelerated. The proliferation of osteoclast and also the production of type 1 collagen is also decreased [9].

In a systemic review and meta analysis the authors concluded that ongoing GC therapy associates with lower bone mineral density (BMD) of the spine in children, compared to controls. There are studies that measure changes in spine BMD and/or spine Z score related to GC therapy, that report patients having inconstant reduction in spine BMD or Z score across studies [10].

A study that followed metabolic markers and BMD in 38 adults with 21 OHD, determined that BMD values were decreased in three patients but this is explained by the decreased height and not the GC treatment [11]. Another study evaluated the effect of GC on BMD and concluded that there is no influence on BMD and other factors should be evaluated such as: daily calcium (Ca) intake, polymorphism of vitamin D receptor, ethnic factors, socioeconomic status, and 24 h urinary free cortisol level [12].

Microarchitectural bone measured by Trabecular Bone Score (TBS) seems to be more important than BMD. Patients with GC induced osteoporosis have a significant deterioration in the microarchitectural bone structure [13]. Vertebral fractures are an important issue in children with GC induced osteoporosis, but the BMD values may not be able to adequately reflect the increased risk of fractures. The alteration in bone microstructure must be considered when assessing the risk of fracture and can be measured with TBS, that can be extracted from DXA images of the lumbar spine [14,15]. A low bone density or deterioration to the bone microstructure of the vertebrae and possible vertebral fracture can lead to deformities of the spine. A study that tested the correlation between spinal deformity, such as hyperkyphosis, and the BMD in pre and postmenopausal patients, observed that, as the regional bone mineral density decreases, the thoracic or lumbar curvature increases [16].

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Received April 18, 2017; Accepted June 24, 2017; Published June 28, 2017


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Considering their immunosuppressant effect, the use of high doses of GC have an increased risk of complications, such as infections. In a meta-analysis of 21 randomised controlled trials and 42 observational studies on the association between systemic glucocorticoid therapy and the risk of infections in patients with rheumatoid arthritis, the authors concluded that the patients with GC therapy have an increased risk of infection which is not related to rheumatoid arthritis [17].

Case Report

Our patients are twin sisters diagnosed at birth with congenital adrenal hyperplasia (simple virilizing form). They both received treatment with GC preparations that mimic the diurnal cortisol secretion profile. The patients received corticosteroids treatment with hydrocortisone, the dosage varied but, generally, the dosage was situated at the upper limit of the average dosage (10-25 mg/m²/d) or even higher, in order to treat the symptoms of adrenal insufficiency.

Patient A. The patient was diagnosed at 1 year of age with congenital adrenal hyperplasia due to 21-hydroxylase deficiency, simple virilizing form, and started receiving treatment with GC. At the age of 3 she was diagnosed with clitoral enlargement, labial fusion, and vesicoureteral reflux and underwent surgery. She developed precocious pseudo-puberty with accelerated growth, between the age of 8 to 12, and a diminished growth due to premature closure of the epiphysis, resulting in a smaller than normal final height.

Clinical evaluation at the age of twelve, showed a back deformity—angled kyphosis, best observed in the lateral Adam bending test. The kyphosis did not correct on dorsal hyperextension. For the evaluation of the hyperkyphosis we performed the following radiographic exams: A lateral standing of the spine; an AP view of the spine, to evaluate associated scoliosis (Figure 1); lateral view of the thoracolumbar spine in hyperextension; plain radiography of the pelvis. On an MRI of the spine we evaluated the spinal cord; we used a CT scan for preoperative planing to measure the length and width of the vertebral pedicles.

On the lateral standing view of the spine we measured a Cobb angle of 87 degrees and 4 vertebrae (T10, T9, T8, T7) measuring a wedged angle of more than 5 degrees (Figure 2). On the pelvic view, the Risser Score was stage 4. On the MRI, no modifications of the spinal cord were found. After excluding other different diagnosis like Pott Disease or congenital kyphosis the patient underwent surgery for hyperkyphosis.

Before surgery, we performed standard blood and urine tests for determining glucocorticoid and mineralocorticoid values. During surgery, the patient received increased doses of corticosteroid because of the hypothalamic–pituitary–adrenal atrophy, through feedback inhibition and the inability to normally produce cortisol in response to the surgical stress.

The patient underwent transpedicular vertebral instrumentation from L3 to T2, Ponte osteotomies at T12-T6 and posterior autograft spinal fusion (Figure 3). Post-surgery evolution was favourable with normal healing of the surgical wound. Recommended follow ups had favourable outcomes with no complications.

Three years and six months after surgery, the patient checked in the ER with back pain, fluctuant tumefaction on the spinal area, and increased inflammatory markers. The ultrasound and MRI features suggested infection (Figure 4). After 10 days, we removed the last NPWT dressing; considering that the local tissue presented no signs of...
persistent infection, we decided to close the wound. During this period all the swab cultures were negative and the patient received 2 weeks of empiric large spectrum intravenous antibiotics, then oral antibiotics for 4 weeks. At the checkup, there were no clinical signs of local infection.

Patient B. Similar to her sister the patient came to our clinic with hyperkyphosis. The patient developed precocious pseudo-puberty with premature closure of the epiphysis, resulting in a lower than normal final height and her GC treatment was similar in dosage with her sister's.

The same imaging investigations were performed (Figure 5). On the lateral standing view of the spine we measured a Cobb angle of 98 degrees and 5 vertebrae (T11, T10, T9, T8, T7) showing a wedged angle of more than 5 degrees. On the pelvic view, the Risser Score was 4. No abnormalities were found on the MRI scan. She underwent surgery for hyperkyphosis. During surgery, the patient received increased doses of cortisol.

The patient underwent transpedicular vertebral instrumentation from L3 to T2 and Ponte osteotomies at L1-T5 and posterior autograft spinal fusion (Figure 6). After surgery, her evolution was favourable with normal healing of the surgical wound. The patient continued her treatment with GC.

Discussion

Patients with congenital adrenal hyperplasia need to have a lifelong treatment with GC. These patients have a higher risk of complications caused by the CAH and the GC treatment compared to the general population.

Secondary osteoporosis is increasingly recognized as a complication of chronic diseases such as CAH treated with long term GC. Published data suggested that this treatment is associated with lower or normal BMD; whether children taking GC have lower BMD compared to children with the same diseases and not requiring GC is not yet certain. In our reported cases, both patients had normal BMD. The microarchitectural structure of the vertebral bone is usually associated with the GC treatment and the bone quality seems to be more important for the outcome than the bone density.

In the previously presented clinical cases, the patients received constant doses of GC with no interruption of treatment. Excessive Hydrocortisone dosage can lead to growth disturbances, truncal obesity, osteopenia and reduction of bone turn over [1].

We evaluated the growth of the patients using www.medcalc.org growth charts. First patient had a weight percentile of 69% and a stature percentile of 15%. This data showed a normal weight velocity growth and a short stature. For the second patient, the weight was situated on the 86% percentile, showing that the patient is overweight; the stature percentile was 9%, close to the inferior limit of the appropriate growth velocity, showing a lower than normal growth rate.

Vertebral compression fractures, that frequently appear in osteoporosis, could be a cause for the spinal deformity [15]. The hyperkyphosis in these cases are similar to the Scheuermann kyphosis with a fixed angular kyphosis presenting an anterior wedging of the vertebral. Apart from the patient's medical history, we had no other criteria for a differential diagnosis with Scheuermann disease.

Conclusion

Even though we do not have an exact status of the bone in patients with Congenital Adrenal Hyperplasia and long-term treatment with GC, these patients have a high risk for osteoporosis. While monitoring the patients we should consider the bone status and preventive measures against osteoporosis (calcium, Vitamin D and bisphosphonates) should be taken into consideration from the beginning of the GC therapy. It is important to diagnose these deformities of the spine at a young age to be able to try a conservative treatment because for these patients, surgery comes with a high risk of complications. It is necessary to have pediatric orthopedic checkups for children with long term GC treatment.

References


