Kallmann’s syndrome: skeletal and psychological aspects of late diagnosis

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INTRODUCTION

Kallmann’s syndrome (KS) is the most frequent cause of isolated hypogonadotrophic hypogonadism (IHH), which results from severe gonadotropin-releasing hormone (GnRH) deficiency and is associated with anosmia or hyposmia [3, 10]. The syndrome may occur as an inherited or sporadic disorder [9], each exhibiting similar clinical features. In the inherited Kallmann’s syndrome X-linked, autosomal dominant and autosomal recessive modes of inheritance have been described. In the better described X-linked mode of inheritance, the mutated gene (KAL) has been cloned and localised on the Xp22.3 chromosome [2, 4], however the importance of autosomal genes in KS has been recently revealed. The penetration variability of these genes may result in the incomplete expression of the classic features of Kallmann’s syndrome [6, 10].

Several cases of Kallmann’s syndrome have been described up to date [2, 3]. Here, we report the case of a male Caucasian, of age 30, admitted to the Endocrinology Department of the Collegium Medicum, Jagiellonian University in Krakow, Poland, with chief complaints of severe backache and decreased tolerance to physical exercise. He had not been treated prior to admission to our Department.

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We report a case of Kallmann’s syndrome (KS) in a previously untreated 30-year-old Caucasian male, admitted to our Endocrinology Department, presenting with hypogonadotropic hypogonadism and hyposmia, and reporting a history of rickets in early childhood and a rapid growth pattern. On admission, his main complaints were back-pain and a decreased tolerance to physical exercise. The patient gave no family history of hypogonadism or hyposmia, and his case was assumed to be
spermine sulphate) level: 118.5 g/dl (normal range: 35-440; RIA), HGH-9.0 IU/ml (normal range: 0.2-17; IRMA), 330; RIA), HGH-9.0 IU/ml (normal range: 0.2-17; IRMA), PRL-218 IU/ml (normal range: 35-16.5; IRMA), FSH 1.8 mIU/ml (normal range 4-8; IRMA), and serum testosterone level was decreased: 0.1 ng/ml (normal range: 0-0.8; IRMA). The concentrations of the following pituitary hormones were within normal reference ranges: TSH-1.9 IU/ml (normal range 0.2-6.5; IRMA), LH 3.8 mIU/ml (normal range: 1-8; IRMA), a decreased level of LH was observed, the anterior lobe being homogenous after stimulation in terms of testosterone production and release, a provocative test with hCG (chorionic gonadotropin) was performed. Testosterone levels were measured at various time intervals. The basal testosterone level was 0.1 ng/ml and after administration of 2000 IU hCG daily the testosterone level increased to 0.2 ng/ml on day three and 0.9 ng/ml on day five. Calcium and phosphorus serum concentrations and excretion with urine were found to be normal. Rickets was excluded based on normal values of osteocalcin and 25 OH vitamin D. There was no kidney or liver malfunction found based on laboratory tests results. A cytogenetic test showed the patient to have a normal male karyotype. MRI revealed persistent sphenooccipital synchondrosis. The pituitary gland was of normal size and location. Normal signals from the posterior and anterior lobes were observed, the anterior lobe being homogenous after contrast injection. The pituitary infundibulum was of normal width, optic chiasm, optic stria and cavernous sinuses revealing no abnormalities.

As based on an X-ray of his wrist, the patient’s bone age corresponded to that of 15 years. Pelvis X-ray revealed lack of epiphyseal fusion of femur capit. Vertebral column X-ray revealed scoliosis and rotation of thoracic spinous processes as well as subfractures of lumbal marginal laminae. Dysostosis of thoracic and lumbal regions of vertebral column was found as well as thorax malformations, such as kyphosis, scoliosis and costal hump and cobbler’s chest, due to rickets in childhood. As a result of such chest deformations the lung

Key words: Kallmann’s syndrome, hypogonadism, hypoosmia, osteoporosis.

CASE REPORT

Our 30-year-old male patient presented with hypogonadotropic hypogonadism and hypoosmia. He reported a history of rickets in early childhood and a rapid growth pattern that made him the tallest among his peers and family. On admission, his main complaints were back-pain and a decreased tolerance to any physical exercise, due to muscle weakness and bone pain. The GP to whom he turned for medical help referred this patient to an endocrine specialist. The patient gave no family history of hypogonadism or hypoosmia. His case was assumed to be sporadic KS, even though very little was known about his father’s family history. Despite evident signs of hypogonadism, his delayed puberty was of no particular concern to him. The patient and his family had never sought medical advice in this respect. On admission the patient wished that his therapy should not change his physical appearance.

On physical examination hypogonadism (micropenis, small testes, no puberty), hypoosmia and severe scoliosis, kyphosis and chest malformations were recorded. No facial hair growth was found nor past voice braking. His skeletal proportions were eunuchoidal, no mid-line defects were found. This case of KS was identified unusually late. Due to patient’s anxiety that his physical appearance might change due to therapy, he was referred to a clinical psychologist who confirmed the patient’s self-perception as a male. The risk of further bone malformations, progression of osteoporosis and consecutive pathological fractures were the main indications for commencing treatment. Psychological support was provided. Six months of treatment with low doses of hCG (500 IU given i.m. twice a week) had elevated his testosterone levels but they still remained below the lower values of the normal reference range for males. Additional treatment with vitamin D and calcium supplementation was continued. A certain improvement of bone density score was observed. The patient noted a marked pain relief and he willingly complied with the treatment. After six months of therapy hCG dose was increased to 2000 IU given twice a week. We conclude that even at such a late diagnosis of Kallmann’s syndrome in a male who accepts his physical appearance and does not wish any treatment in this respect, hormonal therapy is necessary and should be introduced to reduce significant risk of osteoporosis and bone fractures, and also to offset slowly progressing skeletal malformations which result from the lack of epiphyseal fusion.
volume was markedly decreased but without limiting the cardiac space. On spirometry the patient’s FVC reached only 68% of the predicted value (FEV1/FVC - 65%). Osteoporosis was diagnosed from densitometry of a lumbal segment, with a T score of -3.5.

Due to the patient’s anxiety that his physical appearance might change with the therapy, he was consulted by a clinical psychologist who confirmed the patient’s self-perception as a male.

Six months of treatment with low doses of hCG (Biogonadyl, Biomed-Lublin, PL) 500 IU given i.m. twice a week had elevated the patient’s testosterone levels, but they still remained below the lower values of the normal reference range for males. A certain improvement of the bone density score was observed (T score: -2.6), and no changes in the patient’s physical appearance were noted. Additional treatment with vitamin D and calcium supplementation was continued. Marked pain relief was noted by the patient and he willingly complied with the treatment. After six months of treatment the patient was seen by a consulting psychologist again. Improved acceptance of physical changes that might be connected with a more effective treatment was confirmed. At that time the hCG dose was increased to 2000 IU (Biogonadyl, Biomed-Lublin, PL), given i.m. twice a week in order to improve testosterone secretion, skeletal metabolism and increase bone mass. Further psychological support was scheduled and the patient was encouraged to increase his physical activity.

**DISCUSSION**

This case of KS was identified in a patient of 30 years, which is unusually late for this disorder [2, 3]. Such late diagnosis was due to the attitude of the patient’s mother who had accepted his physical appearance and to the reluctance of the mother and the son to earlier seek medical advice. His main complaints: backache, pain in bones and muscle weakness were unusual for the KS and so was his anxiety connected with possible body changes which in typical KS should be the aim of the treatment. Laboratory findings revealed a low serum level of basal gonadotropins, decreased testosterone, poor response to LHRH and delayed but significant response to hCG. There were no other hormonal abnormalities found in this patient and no reasons for his osteoporosis other than hypogonadism. The risk of further bone malformations due to lack of epiphyseal fusion as well as progression of osteoporosis and risk of consecutive pathological fractures were the main indications for commencing treatment. Testosterone is known to increase bone mass in hypogonadal and also in eugonadal men, and physiological effects of androgens in reducing bone resorption and enhancing bone formation are well described [8]. The initial dose of hCG prescribed was very low compared with the therapy of Kallmann’s syndrome that is given in order to restore male gonadal function [1]. The treatment was introduced while the patient refused testosterone substitution in the fear of possible body changes. At that time low dose of hCG was believed to be the best option as pulsatile GnRH was not considered due to its high price. Patient compliance with the treatment was the main issue. Low dose treatment was found to be sufficient to effect significant pain relief, which we assumed was a sign of its metabolic action, but there is no consistent data on testosterone dose-dependent efficacy in bone pain reduction compared with other treatments. Calcium supplementation and vitamin D taken regularly might contribute to this effect but we need to stress that such previous treatment carried out alone had no considerable pain relief effect. The problems described may not be encountered in acquired adult onset idiopathic hypogonadotropic hypogonadism [5], but some cases of late presentation of partial disease were described [7], and associated with spinal osteopenia and segmental disproportion regardless of apparently normal puberty. We cannot be sure to which extent calcium deficit in patient’s bones was due to his childhood rickets and to which extent due to lack of gonadal function resulting in osteoporosis during his rapid growth, but the evident response to hCG treatment is convincing that the latter mechanism played a significant role. In a male of 30 years, not having yet achieved his peak bone mass, it was crucial to institute the most effective treatment and therefore to continue with the full dose hCG, assuring appropriate levels of circulating testosterone, combined with adequate physical activity and nutrient intake. Psychological support was essential to change patient’s attitude towards the treatment and to prepare him for his subsequent body changes.

**CONCLUSIONS**

On the basis of the above findings we conclude that even at such late diagnosis of Kallmann’s syndrome in a male who accepts his physical appearance and does not wish any treatment in this respect, hormonal therapy is necessary and should be introduced to reduce significant risk of osteoporosis and bone fractures, and also to offset slowly progressing skeletal malformations which result from the lack of epiphyseal fusion. At the age of 30 the patient’s peak bone mass may not have yet been achieved, so the treatment should aim at achieving the best possible outcome in this respect. Once hypogonadotropic hypogonadism is established in
patients over 16 years presenting with eunuchoidal skeletal proportions, not only induction and maintenance of secondary sexual characteristics is of importance, but also control of the bone mass and attendance to the psychological aspects of the treatment.

REFERENCES