CASE REPORT

Difficulties in diagnosis and treatment of acromegaly in a patient with a McCune-Albright syndrome. A case report and a review of literature

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Abstract

We describe a female patient aged 43, who at the age of five was diagnosed with polyostotic fibrous dysplasia (FD). The patient was intermittently treated in our department since the age 33, for approximately 10 years, with intravenous bisphosphonates. At the age of 42 acromegaly was diagnosed incidentally, since clinical manifestations were poor, and, if present earlier, they had been related to FD. Only retrospectively, having biochemical confirmation of GH excess, we could relate them to acromegaly. Because of the involvement of the base of the skull there was no possibility of transphenoidal surgery. Long-acting somatostatine analogues were started, but no response was observed, with IGF-1 and GH being even higher during than before treatment. After the 37-year-history of FD, the occurrence of additional endocrine disorder enabled to make diagnosis of McCune-Albright syndrome (MAS) even in the absence of two out of three classical manifestations such as café-au-lait skin pigmentation and peripheral precocious puberty in the past medical history.

INTRODUCTION

McCune-Albright syndrome (MAS) is a rare disorder, more common in girls, classically defined as the triad of peripheral precocious puberty, café-au-lait skin pigmentation and fibrous dysplasia of bone, however not all patients present with all these symptoms (McCune 1936; Albright 1937). Various endocrinopathies such as hyperthyroidism, hyperparathyroidism, Cushing syndrome, acromegaly, hypophosphatemic ricket, hyperprolactinemia and hypogonadotropic hypogonadism have been described in this syndrome (Weinstein *et al.*1991; Shenker *et al.* 1993; Lumbroso *et al.* 2004). Other organs may be also involved resulting in hepatitis, intestinal polyps, and cardiac arrhythmias. Patients with MAS have a somatic postzygotic activating mutation of the GNAS1 gene product, alpha subunit of the G3 protein. Most of the $G_s\alpha$ mutations are point mutations at the Arg 201 position (Levine 1999). cAMP has the ability to stimulate proliferation and differentiation of certain cell types, especially endocrine cells and melanocytes, what results in their overactivity

(Spiegel 1997). The clinical phenotype varies markedly, depending on which tissues are affected by the mutation, but precocious puberty is the most commonly reported manifestation (de Sanctis *et al.* 1999), although not obligatory (Sargin *et al.* 2006). The term gsp oncogene was assigned to these activating Gsα mutations due to their association with certain neoplasms (Landis *et al.* 1989; Yoshimoto *et al.* 1993; Bhansali *et al.* 2003).

Till nowadays only a few dozen cases of MAS and acromegaly were reported. Pituitary tumor was identified in only 40–50% of cases (Bhansali *et al.* 2003).

A CASE REPORT

FD was diagnosed in our patient at the age of five in orthopedic department. Recurrent bone fractures and progressive bones deformation were problems which were present that time. The patient says that some of the fractures she used to treat herself simply by putting the broken limb to a plaster splint and the healing proceeded very quickly. Bones which were involved included: skull, base of the skull, jaw, ribs, humeral, ulnar, lumbar spine, pelvis, femoral, tibial. At the age of 33 and 41 reconstructive jaw surgery were performed and fibrous dysplasia was confirmed microscopically. Markedly elevated alkaline phophatase (1 000–1 500 U/l) was the only abnormal biochemical result. Treatment with i.v. bisphosphonates was introduced and the patient reported general subjective improvement with less bone pain, but concentration of alkaline phosphatase did not decrease. CT of skull was performed and experienced radiologist confirmed the FD, excluding Paget's disease of bones, another disease, which was taken into account basing on clinical grounds (Figure 1). Progressive involvement of the skull resulted in impairment of hearing and vision. In 2005 arterial hypertension and impaired fasting glucose were diagnosed, which progressed to diabetes mellitus in 2009. In 2006 mild hyperprolactinemia was diagnosed and treatment with bromocriptine was started. About that time secondary amenorrhea, hypogonadotropic hypogonadism and breast cancer were diagnosed. Left mastectomy was performed (microscopic result: invasive and in situ ductal cancer). Since 2008 she has noticed increased perspiration and weakness (high-output heart insufficiency was excluded) and slight enlargement of hands and feet. In 2009 the patient was reevaluated. CT of the pituitary with subsequent reconstructions was done, as magnetic resonance was contraindicated because of the ear implant. The examination revealed suprasellar mass 19×26 mm. Biochemically acromegaly was confirmed, basing on GH 26.5 and 16.8 ng/ml (N: 0.01–3.3) and IGF-1 831 and 1 164 ng/ml (N:14–252). Elevated concentration of PTH was also observed 90.99 pg/ml (N:15–65), with normal serum calcium and phosphate concentration, but slightly decreased vitamin D concentration 18.1 ng/ml. Another findings were multinodular goiter (patient refused biopsy) and sinus tachycardia 100 beats per minute.

Treatment with long-acting somatostatine analogues was started, but no response was observed, with IGF-1 and GH even higher than before treatment (IGF-1 1 175, 1 393 ng/ml; GH 38.5; 26.2 ng/ml). Involvement of the skull by the fibrous dysplasia make the patient unsuitable candidate for neurosurgery or radiotherapy, because it is believed that the latter increases the risk of sarcomateous transformation of fibrous dysplasia (Ruggieri *et al.* 1994).

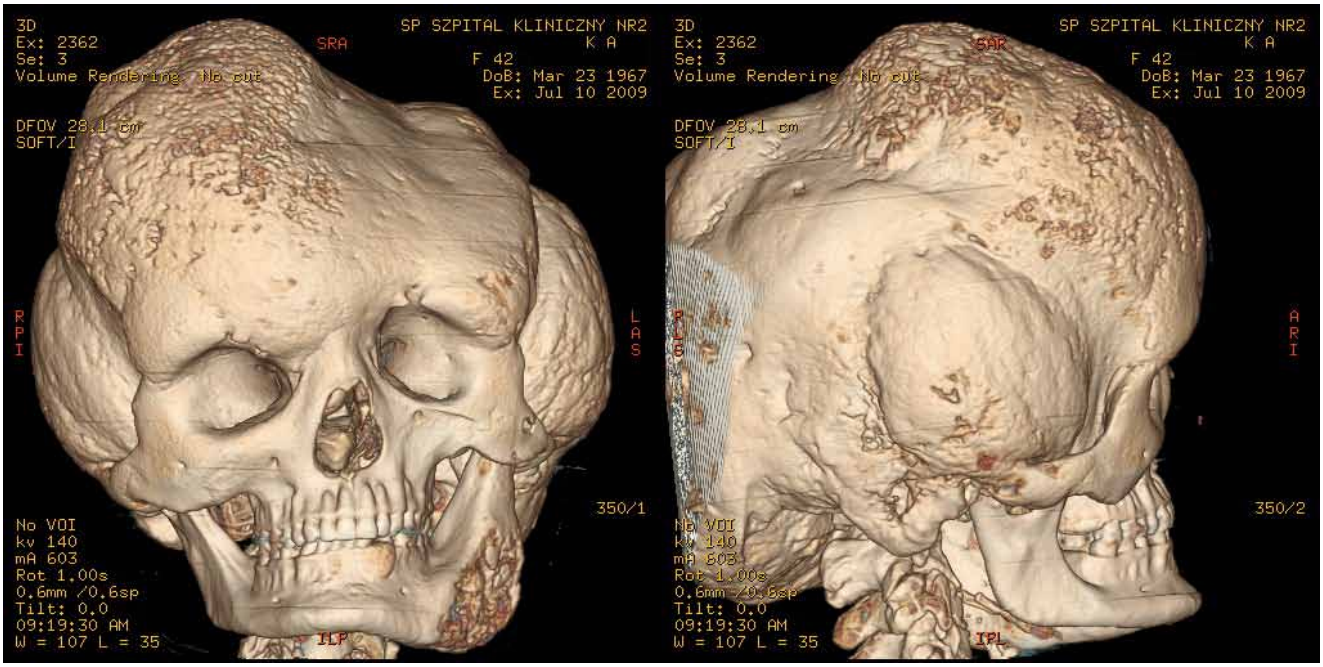

Fig. 1. CT of the skull of the female patient K.A. aged 43 with the McCune-Albright syndrome and acromegaly.

DISCUSSION

We present here many diagnostic dilemmas in a patient with MAS. The first one was the misdiagnosis of FD and Paget's disease. Another problem was decreased alertness toward possible coexisting endocrine disorders. The patient had not presented other abnormalities typical for MAS in childhood. Although the patient was consulted and treated in our department for at least 9 years the diagnosis of acromegaly was incidental. Endocrinopathies such as hyperprolactinemia, hypogonadrotropic hypogonadism and acromegaly were diagnosed approximately at the age of 37, with little or no symptoms. There are reports of patients with MAS in whom other endocrinopaties occured in childhood. It seems necessary to actively screen patients with FD for MAS and other coexisting diseases life-long.

Most patients with MAS and coexisting GH excess caused by gsp mutation usually have cosecretion of PRL and absent pituitary tumors or, if present, the tumors are rather small (Akintoye *et al.* 2002). Unfortunately we can not perform genetic testing because of technical problems. The exposure to excess GH concentration results in higher morbidity related to FD of craniofacial bones i.e. increased risk of vision and hearing deficits (33% vs. 4% in patients with FD and with or without GH excess) (Akintoye *et al.* 2002), thus intensive treatment to normalize GH and IGF-1 is crucial. Long acting somatostatine treatment causes normalization of IGF1 in 50% of patients and in the remaining there is only partial response. It was totally ineffective in our patient. Additive treatment with cabergoline or pegvisomant can be helpful and further decrease IGF1 concentration and improve final outcome (Akintoye *et al.* 2002).

In literature there are only three cases of coexisting breast cancers and MAS in a 40-, 27- and 11-year old patients (Huston & Simmons 2004, Scanlon *et al.* 1980, Tanabeu *et al.* 1998) and in all three cases there had been a history of precocious puberty and enhanced exposure to estrogens. Our patient is the first one in whom breast cancer was not related to early estrogen exposure. Data on possible association between breast cancer and GNAS mutation are lacking.

We conclude that patients with MAS may require lifelong control and screening for all possible endocrine and nonendocrine diseases.

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