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BRIEF REPORT

Growth hormone producing prolactinoma in juvenile cystinosis: a simple coincidence?

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Abstract Juvenile cystinosis was diagnosed in a patient who presented with severe headache attacks and photophobia. Treatment with oral cysteamine and topical cysteamine eye drops was started. One-and-a-half years later, he developed unilateral gynecomastia and elevated prolactin and growth hormone levels. A pituitary macroprolactinoma was discovered and successfully treated with the dopamine agonist cabergoline. Increased serum growth hormone levels were attributed to enhanced growth hormone production by the prolactinoma and somatostatin inhibition by cysteamine. Although the occurrence of prolactinoma in this patient could be a simple coincidence, it might also be a rare yet unrecognised complication of cystinosis.

Keywords Cystinosis · Cysteamine · Prolactinoma · Growth hormone · Headache

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Abbreviations

GH	growth hormone
IGF-1	insuline-like growth factor 1

Introduction

Cystinosis is a rare autosomal recessive disorder caused by mutations of cystinosis gene (*CTNS*, 17p13.3), encoding the lysosomal cystine carrier. This results in the intralysosomal accumulation of cystine throughout the body and intracellular crystal formation. Three clinical forms of cystinosis varying in severity and age of onset are distinguished. In the most severe, infantile form (MIM 219800), patients develop renal Fanconi syndrome during the first year of life and, when untreated with cysteamine, end-stage renal disease before the age of 10 years. Patients with the intermediate, juvenile form (MIM 219900) generally develop symptoms at a later age and have a slower rate of renal disease progression. As well as renal disease, patients with cystinosis suffer from extrarenal complications involving cornea, brain, retina, muscles, thyroid, pancreas and liver. In the ocular form of cystinosis (MIM 219750), only the cornea is affected, and other organs are spared. The incidence of cystinosis is 1:200,000; the juvenile and ocular forms are seen in less than 5% of all patients [1]. Treatment with the amino thiol cysteamine depletes intralysosomal cystine content, decreases the rate of renal disease progression, improves growth and protects extrarenal organs [1, 2].

Prolactinomas are functioning pituitary adenomas, which produce either prolactin, prolactin and growth hormone (GH) or prolactin and adrenocorticotrophic hormone. Their occurrence in children is extremely rare [3]. Until now, the

occurrence of prolactinoma has not been reported in patients with cystinosis. Here we report a patient with the association of juvenile cystinosis and prolactinoma with coproduction of GH.

Case report

A 10-year-old adopted Brazilian boy with congenital deafness, possibly due to congenital cytomegalovirus infection, presented with weekly attacks of severe headache and photophobia. At that time, his height was 133 cm (−1.5 SD), weight 23.4 kg (−2.5 SD) and blood pressure 110/75 mmHg. Further physical examination, including neurological examination, was normal. Urine examination demonstrated proteinuria of 4 g/l without signs of proximal tubular dysfunction such as aminoaciduria, glucosuria or phosphaturia. Cerebral computed tomography (CT) was considered normal.

The diagnosis of juvenile cystinosis was made after finding corneal cystine crystals on ophthalmologic examination and elevated cystine levels in both polymorphonuclear (PMN) leukocytes and cultured fibroblasts measured by high-performance liquid chromatography (2.46 and 2.94 1/2 cystine/mg protein respectively). The diagnosis was later confirmed by mutational analysis of the *CTNS* gene (hom 537del21). The patient was subsequently treated with phosphocysteamine (Laboratory of Pharmaceutical Chemistry, University Hospital, Leuven) and topical cysteamine eye drops. Phosphocysteamine was administered instead of cysteamine bitartrate (Cystagon®), because the latter drug was badly tolerated, causing severe gastrointestinal discomfort and an increase in headaches. Cystine levels measured in PMN on phosphocysteamine (40 mg/kg per day cysteamine base divided in four doses) were between 0.50 and 1.76 1/2 cystine/mg protein.

At the age of 10.5 years, headaches increased and were interpreted as migraines, as they were accompanied by nausea and pain in the eyes. There were no signs of other neurological disorders, especially not of increased intracranial pressure. Treatment with the calcium channel antagonist flunarizine and sumatriptan brought no improvement. At the age of 11.5 years, the patient developed enlargement of the left breast. His height was 141 cm (−2 SD) and weight 28.7 kg (−2 SD), his height velocity had not increased (Fig. 1). Serum prolactin level was 109,265 mE/l (normal: 80–420 mE/l), random serum GH 33 mE/l (normal: <2 mE/l), insulin-like growth factor 1 (IGF-1) 53.5 nmol/l (normal value for age and pubertal stage: 13–23 nmol/l). Creatinine clearance at that time was 80 ml/min per 1.73 m^2.

CT of the pituitary gland revealed a macroadenoma of 26×14 mm. A thyrotropin-releasing hormone test and oral glucose tolerance test were performed, both showing an abnormal rise of GH. Review of cerebral CT performed at the age of 9 years revealed the presence of pituitary microadenoma (<10 mm). Treatment with the dopamine receptor agonist cabergoline was initiated. According to the treatment protocol of prolactinoma, no cranial surgery was performed. Analysis of the multiple endocrine neoplasia type 1 (*MEN-1*) gene revealed no mutations.

After 2.5 years of cabergoline treatment, IGF-1 levels were still increased. To distinguish between cosecretion of GH by pituitary adenoma and an increase of GH levels due to the somatostatin inhibiting effect of cysteamine, GH profiles were performed under cysteamine administration (40 mg/kg per day) and 4 weeks after cysteamine withdrawal. The treatment with cabergoline was continued during the test. Under cysteamine treatment, the mean GH level over 12 h was 24.1 mE/l (normal 6–16 mE/l), whereas it was 8.4 mE/l after cysteamine withdrawal. Abnormally high GH peak values (>60 mE/l) were observed both with and without cysteamine administration after 220 and 520 min, respectively. Baseline GH levels were normal in both profiles.

On follow-up after 1 year of treatment, the size of the prolactinoma had decreased to 7–8 mm on cerebral magnetic resonance imaging (MRI). Control MRI, performed at the age of 13.5 years, demonstrated no visible prolactinoma. At that time, the patient no longer complained about headaches. A bone age test performed at the age of 13 years and 10 months revealed a bone age of 12 years. Frequent ophthalmologic investigations never showed papillary oedema, and a lumbar puncture confirmed a normal intracranial pressure (13 cm H_2O). A cardiac ultrasound was performed because of the prolonged use of cabergoline, which might induce cardiac valve regurgitation [4], and showed no abnormality. Due to successful treatment with cabergoline, serum prolactin and IGF-1 levels fell to minimal 929 mE/l and 17.7 nmol/l, respectively. During the treatment period, creatinine clearance declined to 33 ml/min per 1.73 m^2.

Discussion

This is the first reported case with the association of cystinosis and prolactinoma. Although central nervous system disease is a recognised complication in cystinosis, the occurrence of prolactinoma has not yet been reported. Cystinotic encephalopathy might present with mental deterioration and motor difficulties (cerebellar ataxia or spasticity) or acute cerebral ischaemia [5]. Pituitary resistance to thyroid hormone is also described in patients treated with thyroxin, indicating pituitary dysfunction [6]. Furthermore, nonabsorptive hydrocephalus and pseudotumuor cerebri are reported, which might lead to headache [7, 8]. Both latter

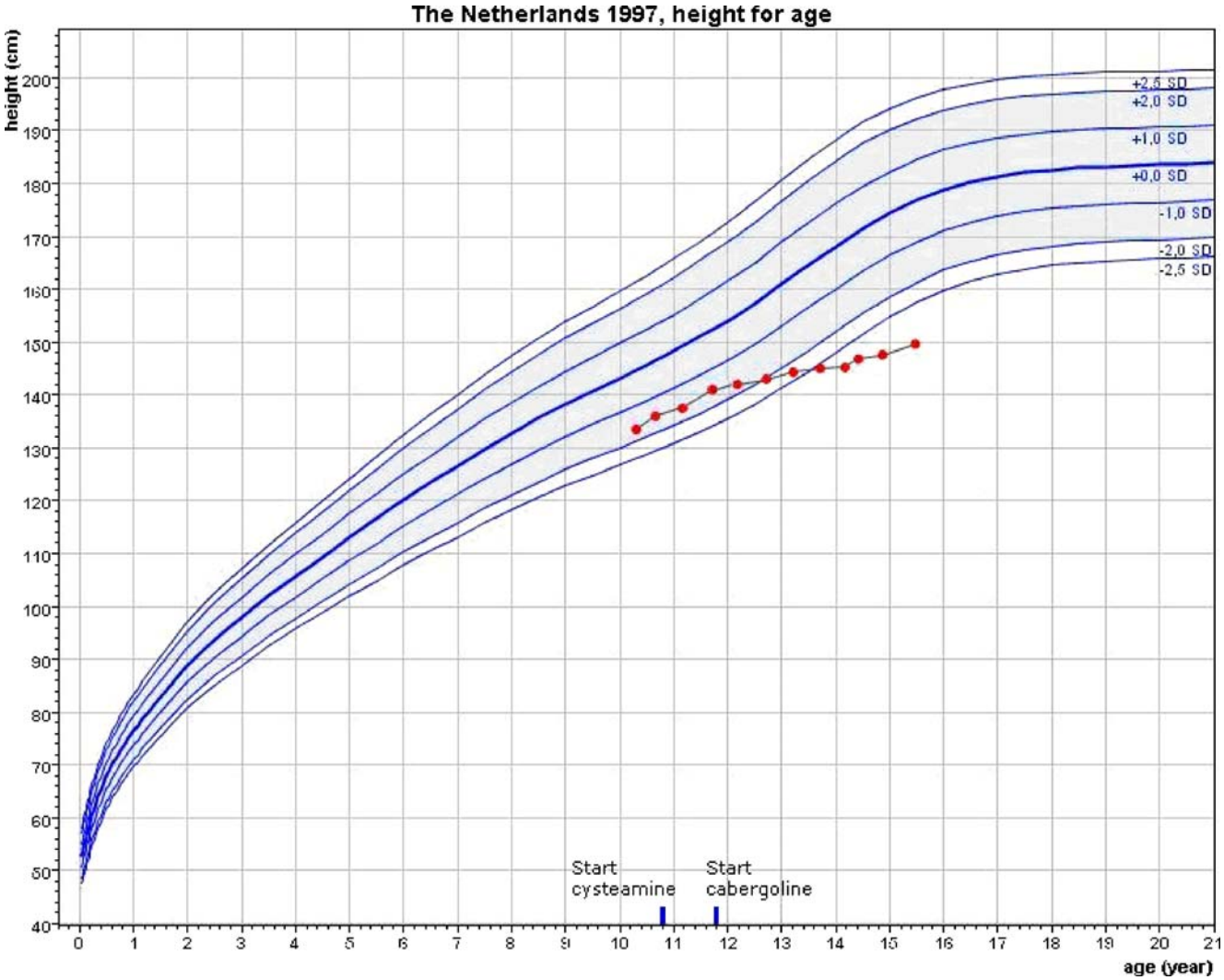

Fig. 1 Growth curve, including the start of cysteamine and cabergoline treatment

possibilities were excluded in our patient by the absence of papillary oedema and normal opening pressure on lumbar puncture. Headache may, however, be the first symptom of pituitary adenoma [9].

The pathogenesis of prolactinomas remains obscure. Mostly, these tumuors comprise of a monoclonal population of cells in which normal mechanisms of growth control are subverted [3]. About 10% of patients with sporadic prolactinomas demonstrate mutations in the tumuor-suppressor gene *MEN-1* (11q13) [10]. This genetic abnormality was excluded in our patient. Dysregulation of the hypothalamic–pituitary axis due to cystine accumulation in his brain region might have played a role in tumour development in this patient. A possible causative role of cysteamine administration can be excluded due to the fact that pituitary enlargement was already present on the CT prior to cysteamine administration. Additionally, long-term cysteamine administration is known to result in decreased, rather than increased, prolactin levels [11].

An intriguing dilemma was the origin of his elevated GH levels. Although growth is mostly severely retarded in cystinotic patients, random GH and IGF-1 levels appear to be normal [12]. Treatment with cysteamine is known to improve growth [2]. This effect of cysteamine might be explained by cystine depletion in bones and cartilage, but also by somatostatin inhibition by cysteamine [13, 14].

In children, increased GH levels do not lead to acromegaly as they do in adults but to an increase in growth velocity. Strikingly, the growth velocity of our patient did not increase in spite of elevated GH levels. On the contrary, his growth curve started to decline at the age of 12 (Fig. 1). The increased levels of IGF-1 affirm that his GH levels were indeed elevated and that the GH levels reported were not based on a measurement error. The absence of an increased growth velocity despite elevated GH levels in this patient is puzzling. Growth retardation in cystinosis is generally more pronounced compared with other patients with renal disease, possibly due to cystine

accumulation in bones, the presence of metabolic acidosis and feeding problems [13]. Delayed puberty, commonly seen in boys with either cystinosis [15] or macroadenoma [9] and aggravated by elevated prolactin levels, was seen in this patient but cannot have played a role to this extent at the age of 13. Although unproven, unresponsiveness of bones to the elevated levels of GH and/or IGF-1 can be suggested.

To distinguish between elevated GH due to cysteamine administration and GH production by prolactinoma, we measured GH levels for 12 h overnight while the patient was under cysteamine treatment and 4 weeks after drug discontinuation. In normal subjects, GH is released during the night in a pulsatile fashion and declines to baseline levels below the lower detection limit between peaks. Here we observed an increased mean GH level over 12 h solely under cysteamine therapy, supporting the role of cysteamine administration in the elevation of serum GH. However, the abnormally high GH peak values observed after cysteamine withdrawal argue for elevated GH production by the prolactinoma. Another argument for GH production by the prolactinoma was the parallel decrease of prolactin and IGF-1 under cabergoline treatment. Thus, the increased GH levels found in this patient were probably caused by a combination of enhanced GH production by the prolactinoma, which was enhanced by cysteamine therapy.

Although the occurrence of prolactinoma in our patient could be a simple coincidence, it might also be a rare yet unrecognized complication of cystinosis.

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