A CASE OF HYPOPARATHYROIDISM COMBINED WITH MARFAN SYNDROME IN A 20-YEAR-OLD FEMALE

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Hypoparathyroidism (HP) is an abnormality due to parathyroid hormone (PTH) secretion deficiency, characterized by symptoms of hypocalcemia, hyperphosphatemia and inappropriately low serum PTH concentration. Marfan syndrome (MFS) is a connective tissue disorder. Affected patients are at risk for aortic dissection and severe ocular and orthopedic problems.

Both HP and MFS are rare diseases, with incidences of 4 per 100,000 and 2-3 per 10,000, respectively (Judge and Dietz 2005). Here we report a female patient suffering from both diseases. To our knowledge, this is the first case of HP combined with MFS reported in literature.

Case report

This 20-yr-old female was referred to our endocrinology clinic for the management of hypocalcemia. She developed tetany of both upper limbs, muscle cramps and paresthesias in distal extremities 18 months before admission. The first onset of tetany was in a morning in Aug 2006, with pain and stiffness of bilateral arms. It lasted for about 4 hours and then relieved spontaneously. Several days later, the patient went to local hospital and took blood test which showed hypocalcemia. She was prescribed oral calcium supplements and the tetany did not show again until Oct. 2007. Since then, the patient suffered from symptomatic hypocalcemia (carpal spasm, muscle cramps and paresthesias in distal extremities) every 10 to 30 days, usually starting one or two days before menstruation and lasting for several days. Frequent blood tests showed hypocalcemia and intravenous calglucon injection was used to relieve the symptoms. Despite the oral calcium supplements, symptoms still emerged and aggravated, so the patient subsequently came to our clinic for further diagnosis and treatment.

Her past medical history was remarkable for having suffered from severe myopia since her childhood and being found scoliolotic at the age of ten.

Her parents denied consanguineous marriage and have given birth to 3 children: two daughters and a son. The elder sister of our patient seems normal while her younger brother also presents "tall stature, myopia and spinal column malformation". There is no similar symptom found in other family members by now.

At the time of her clinic visit, physical examination revealed a thin girl who was noted to have long slender limbs (arachnodactyly, both thumb sign (Fig. 1) and wrist sign were positive) and multiple skeletal malformations. The blood pressure was elevated to 160/80 mmHg and pulse rate was 85 bpm. She weighed 50 kg and her height was 169 cm. The skin was dry and rough. There was no facial anomaly but a larger right rima oculi and high-arched palate. She had poor eyesight and horizontal nystagmus was noticed when looking at left side. Ophthalmologic examination revealed subluxation of bilateral lentis. Cardiac, pulmonary and abdominal examination findings were unremarkable. Skeletal abnormalities included pes planus (Fig. 2) and

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pectus carinatum, scoliosis, kyphosis of thoracic vertebra (Fig. 4). The myodynamia was normal while muscular tension was high. There were atrophies of interosseous muscles of hand, the thenar and hypothenar eminences. Chvostek's sign and Trousseau's sign were both positive. She did not have hearing loss.

Laboratory data were obtained while the patient was taking oral calcium supplement. Serum total calcium concentration was low at 1.53 mmol/liter, free calcium concentration was 0.74 mmol/liter, and serum albumin concentration was 40.6 g/liter. Serum phosphorous concentration was elevated at 2.78 mmol/liter, and serum magnesium concentration was normal at 0.71 mmol/liter. Serum PTH concentration was inappropriately low at 3.65 pg/ml (15-65 pg/ml). Twenty-four-hour urinary calcium excretion was high at 1.7 mmol per 24 h. The phosphorus excretion was relatively low at 11.7 mmol per 24 h, while creatinine clearance rate was normal at 138.8 ml/min. Serum ACTH, cortisol, thyroid hormone, gonadal hormones were normal.

Scoliosis and kyphosis (Fig. 3) were also confirmed by X-ray of spinal column (Figs. 4 and 5). Echocardiography revealed aortic sinus dilatation. Ultrasound of thyroid showed nodular goiter. Cerebral CT scan was normal, no calcification of basal ganglia was found.

Based on the findings above, diagnosis of HP and MFS was established.

Discussion

HP is characterized by PTH secretion deficiency, and encompasses heterogeneous conditions. In adults, the majority of cases of HP are due to acquired conditions such as injury to the parathyroid glands during neck surgery (Mars 2000), sometimes radioactive iodine treatment or external radiotherapy on the cervical region, autoimmunity, maternal hyperparathyroidism, variations in magnesium levels may also lead to HP (Goswami et al. 2004; Maeda et al. 2006).

Some kinds of congenital anomalies may occur with HP in several inherited syndromes (Maeda et al. 2004). The most common one is DiGeorge Syndrome (characterized by thymus and parathyroid dysgenesis, cardiac malformation, and facial dysmorphogenesis, owed to the deletions of locus 22q11.2). Other complex syndromes associated with HP are: **A.** polyglandular autoimmune syndrome type I (HP, mucocutaneous candidiasis, and adrenal insufficiency, related to mutation of AIRE, 21q22.3); **B.** HDR Syndrome (HP, neuro-sensorial deafness, and renal dysplasia, related to mutation in gene GATA3, 10p14-10); **C.** Sanjat-Sakati syndrome (SSS) or hypoparathyroidism-retardation- dysmorphism, HRD, characterized by HP, mental retardation, stunted growth, dysmorphism, and seizures, related to mutation in TBCE gene, 1q43-q44, or 4q35 (Courtens et al. 2006); **D.** Kenny-Caffey Syndrome (SSS plus additional features of osteosclerosis and recurrent bacterial infections, also caused by mutation in TBCE gene (Parvari et al. 2002); **E.** mitochondrial myopathies, such as Kearns-Sayre Syndrome (encephalomyopathy, ophthalmoplegia, retinal pigment dystrophy ataxia and HP, due to mitochondrial DNA deletions (Maceluch and Niedziela) and Pearson's marrow-pancreas syndrome (neutropenia, sideroblastic anemia, vacuolization of the bone marrow cells, and exocrine pancreas dysfunction, also caused by mitochondrial DNA deletions (Becher et al. 1999)

.However, our patient developed HP in her age of 18 and none of the symptoms mentioned above were presented. To the best of our knowledge, there is no literature reporting case of HP combined with MFS or discussing the relationship between these two disorders. So the congenital syndromes were excluded from diagnosis.

MFS was originally described by Dr. Marfan, a French pediatrician, in 1896. It is a relatively common autosomal dominant hereditary disorder. For instance, FBN1 at 15q21.1 was found to cause MFS as early as in 1991 (Lee et al. 1991; Dietz et al. 1991), and later in 2004, TGFBR2 at 3p24.1 was newly identified as the MFS type II gene (Mizuguchi et al. 2004). About 25 % of cases are sporadic due to *de novo* mutations (Judge and Dietz 2005).

A consensus opinion regarding diagnostic criteria was outlined at the International Nosology of Heritable Disorders of Connective Tissue Meeting in Berlin in 1986 (Beighton et al. 1988) and was revised in 1996 (De Paepe et al. 1996). The skeletal, ocular and cardiovascular systems are commonly involved in MFS.

The most important complication of MFS is a progressive dilatation of the aortic root and ascending aorta, leading to aortic valve incompetence and aortic dissection. Early recognition of at risk individuals, either by clinical or molecular investigations, is important in view of the available medical and surgical treatments that can significantly improve life expectancy (Shores et al. 1994; Gott et al. 1999).

Our patient presented ectopia lentis, dilatation of the ascending aorta, pectus carinatum, wrist and thumb signs and pes planus. Thus, she has met the major cri-

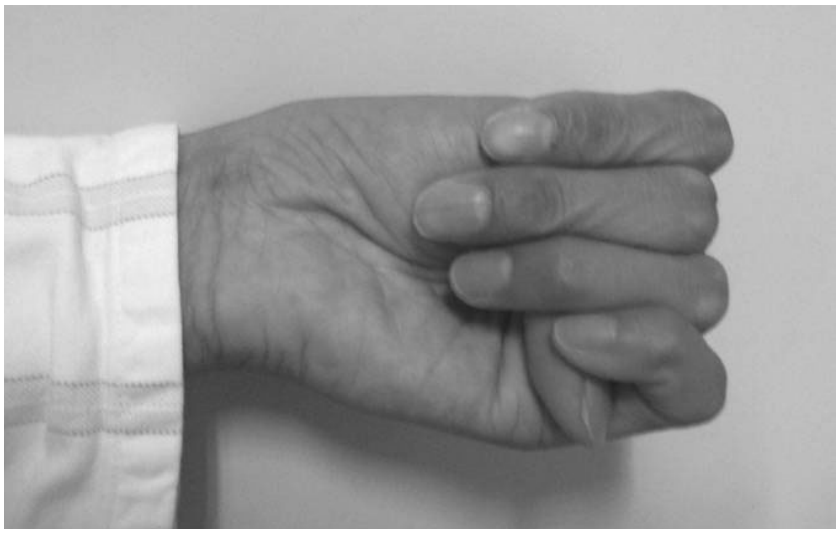

Fig. 1 Thumb sign

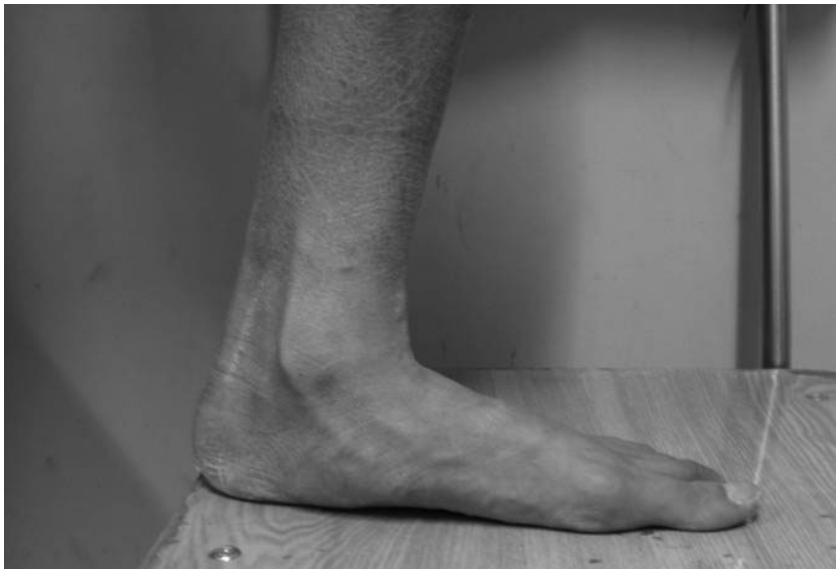

Fig. 2 Pes planus (notice the dry and rough skin)

terion of ocular and cardiovascular system and had skeletal system involved. So she was diagnosed as MFS even without a definite family history.

Several disorders, such as homocystinuria, familial thoracic aortic aneurysm syndrome, Loeys- Dietz aortic aneurysm syndrome and Schprintzen-Goldberg syndrome, are included in the differential diagnosis of MFS on the basis of similar skeletal, cardiac, or ophthalmological manifestations. Patients may present the so called MASS phenotype (emphasising the mitral, aortic, skin, and skeletal manifestations) but do not meet diagnostic criteria for MFS. However, there is no individual refered for these syndromes showing symptomatic hypocalcemia.

The patient was given 600 mg elementary calcium as calcium carbonate (orally twice daily), 90 mg elementary calcium as calcium gluconate (orally three times daily), and calcitriol 0.25 μg (orally twice daily).

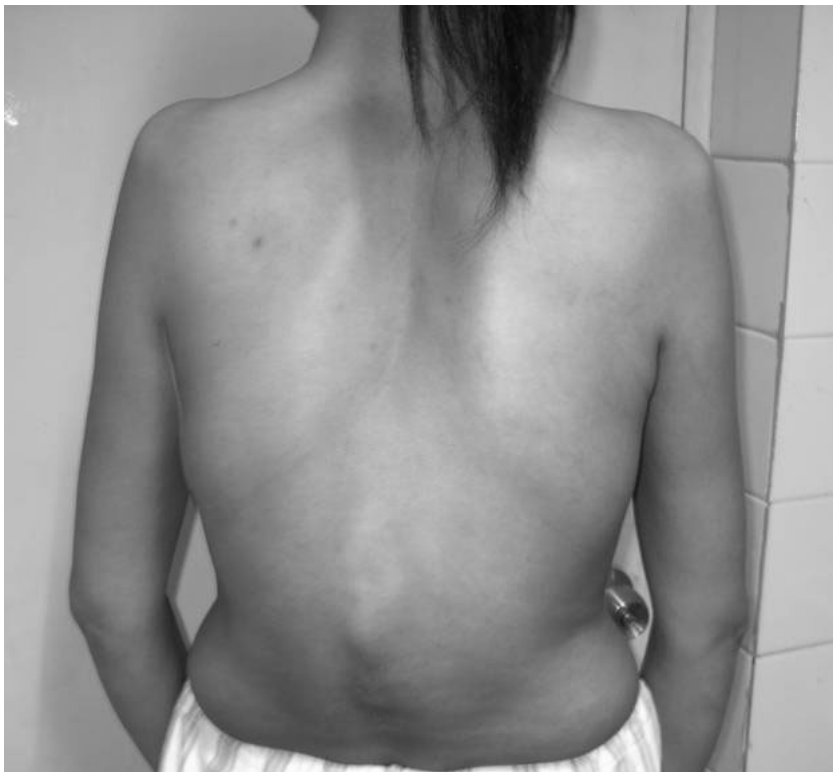

Fig. 4 Spinal colum malformation (scoliosis and kyphosis of thoracic vertebra)

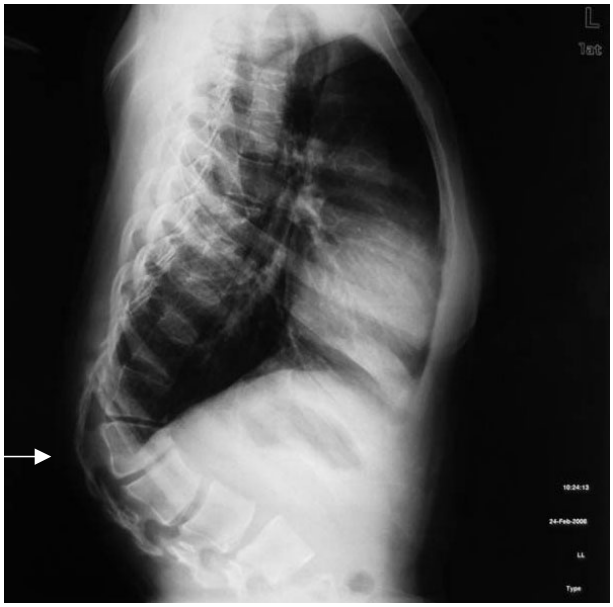

Fig. 6 X ray of spinal column at lateral position showing kyphosis of thoracic vertebra

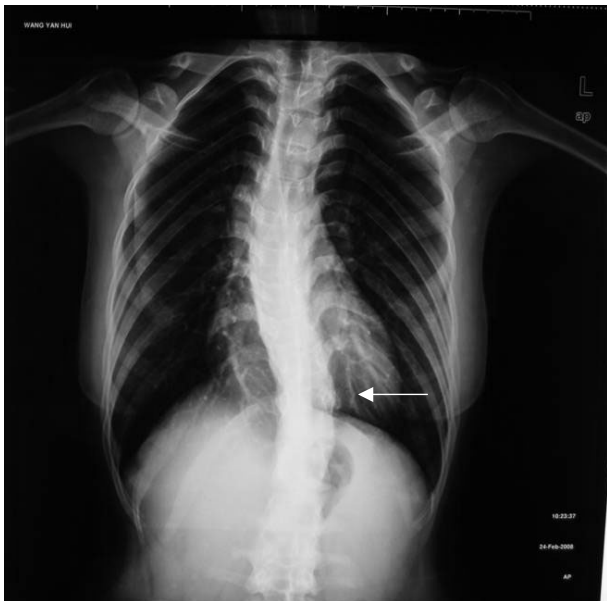

Fig. 5 X ray of spinal column at posteroanterior position showing scoliosis

Metoprolol (12.5 mg orally once daily) was given to control the blood pressure and heart rate for slowing down the progression of aortic dilatation and preventing dissection. Repeated laboratory evaluation showed a slight rise in total and free serum calcium concentration. Blood pressure remained normal and she did not present any symptomatic hypocalcemia.

Since in the literature we did not find any similar case of HP combined with MFS, and the genetic loci associated with these two disorders do not overlap with each other, we assumed that our patient mignt develop HP and MFS independently. However, more cases should be collected and further study should be done to understand the etiology of such diseases in the future.

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