CASE REPORT

Touraine-Solente-Gole Syndrome in Two Siblings

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ABSTRACT

Hypertrophic Osteoarthropathy secondary to various causes is not a common entity but primary hypertrophic osteoarthropathy (also called Touraine-Solente-Gole Syndrome) is an extremely rare genetic disorder. It was first described in 1868 by Friedrich and has premier features of clubbing, periostosis and pachydermia. Based on clinical manifestations Touraine Solente and Gole distinguished it into three forms as complete, incomplete and fruste form. Most of the cases described up till now had onset in late adolescence. This report describes two siblings having symptoms consistent with Touraine-Solente-Gole Syndrome which had onset in early childhood.

Key Words: *Touraine-Solente-Gole syndrome. Periostosis. Pachydermia. Hypertrophic osteoarthropathy. Siblings.*

INTRODUCTION

Hypertrophic Osteoarthropathy (HOA) is a clinical syndrome of clubbing of the fingers and toes, enlargement of the extremities and painful swollen joints. The disease falls in two groups i.e. primary HOA (3 - 5%) and secondary HOA (95 - 97%).[1,2]

Primary hypertrophic osteoarthropathy is a familial disorder with predominance in men. It has three clinical presentations or forms. This condition is also known by other names like idiopathic hypertrophic osteoarthropathy, pachydermoperiostosis, hereditary hypertrophic osteoarthropathy and Touraine-Solente-Gole syndrome.[3]

We are reporting a case of two siblings who presented with features consistent with this rare syndrome at a very early age.

CASE REPORT

Two siblings, a brother and a sister aged 8 and 10 years respectively, resident of Bahawalnagar presented with the complaints of clubbing, enlargement of fingers (Figure 1) and toes and excessive sweating of both hands and feet for 4 years. Parents noticed that these symptoms gradually progressed over this period. There was also history of bone pain and arthralgia.

There was no history of cyanosis, respiratory distress, chronic cough, blood in stools, rash, restlessness, weight loss or anorexia. They were born to consanguineous parents with unremarkable birth history. These kids were vaccinated and developmentally normal. The boy had been operated for Patent Ductus Arteriosis (PDA) at the age of 2 years.

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Received: October 31, 2013; Accepted: May 07, 2014.

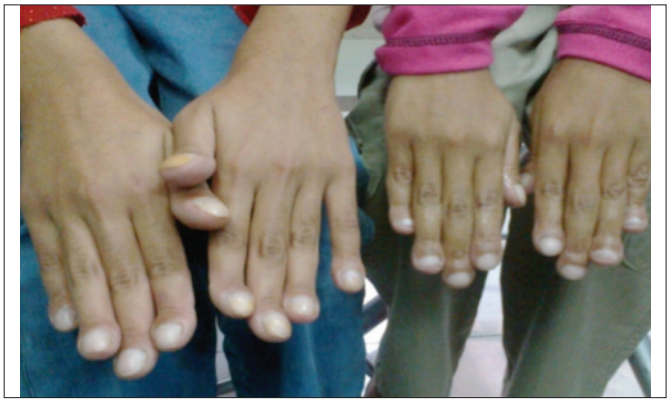

Figure 1: Digital clubbing in both siblings.

Both of them were of average built having height and weight falling at the 50th centile (WHO standards). Both had clubbing of hand and feet with extreme degree of sweating of extremities. They had disproportionate enlargement of hand and feet compared to body size. Rest of the systemic examination was unremarkable.

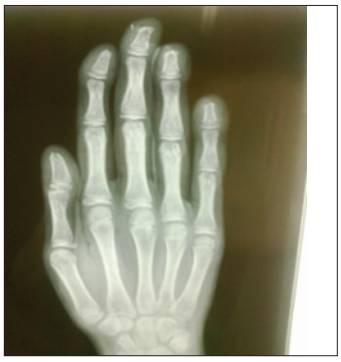

Figure 2: Radiograph of hand showing acro-osteolysis.

Laboratory investigations done in both patients were CBC, serum calcium, phosphate, alkaline phosphatase and thyroid function tests which were normal. In radiological survey plain X-rays showed evidence of acro-osteolysis (Figure 2). Bone scan was done which was normal.

Patients were managed conservatively with NSAIDs to alleviate the symptoms of pain. COX-2 Selective NSAIDs (Etorixocib) may be prescribed for long-term if things do not improve. To prevent further bone resorption treatment with oral bisphosphonate is planned.

DISCUSSION

Hypertrophic osteoarthropathy was first described in 1868 by Friedrich who termed a familial case of HOA as 'hyperostosis of the entire skeleton'. In 1935, Touraine-Solente and Gole individualized Pachydermoperiostosis (PDP) as primary form of HOA and distinguished it into three forms. Complete form comprises of 40%, having clubbing along with skeletal and skin manifestation. Fifty four percent fall in the incomplete form in which there is no pachydermia but only skeletal changes along with clubbing. Fruste form is present in 6% of cases and presents with pachydermia and minimal skeletal changes.[3,4]

It is a very rare genetic disorder. Up till now only 204 cases have been reported. Thirty eight percent of cases have family history of PDP. Although autosomal dominant model with incomplete penetrance and variable expression has been proved, both autosomal recessive and X-linked inheritance have also been suggested. This is augmented by a study in which out of 204 patients, 37 were confirmed to have autosomal dominant mutation and rests were suggested to have autosomal recessive form.[5]

Pathogenesis was not fully understood until its relation was shown with mutation in HPGD (Hydroxy Prostaglandin Dehydrogenase) gene. Previously two theories prevailed as possible mechanism. Neurogenic theory and humoral theory. Neurogenic theory proposed stimulation of vagus nerve which leads to vasodilatation, increased blood flow and PDP. Humoral mechanism proposes that mediators such as growth factors or inflammatory mediators are increased leading to fibroblast proliferation and PDP.

Recently, it has been suggested that locally acting PGE_2 plays role in pathogenesis of PDP. In these patients, high levels of PGE_2 and decreased levels of PGE-M, a metabolite of PGE_2 was also observed. PGE_2 mimic activity of osteoblast and osteoclast leading to periosteal bone formation and acro-osteolysis respectively. PGE_2 has vasodilatory affect too, which is consistent with the local vasodilatation and digital clubbing.[3]

Mutation on chromosome 4q33, 34 in HPGD gene is considered to be the main culprit. This gene encodes 15 hydroxyprostaglandin dehydrogenase, the main enzyme for prostaglandin degradation.[6] Once there is no enzyme for prostaglandin degradation, high levels of PGE_2 leads to aforementioned manifestations.

PDP has many obvious clinical manifestations. In addition to digital clubbing, skin can be involved in the form of pachydermia; coarse and oily skin, seborrheic hyperplasia and hyperhidrosis. Skeletal involvement can be in the form of periostosis, acro-osteolysis, thick toes and finger bones, joint effusion, arthralgia and bone pain.[5]

A number of patients have been described to have PDA likely resulting from increased PGE_2 as was present in one of these patients.[6] Clubbing in conjunction of acro-osteolysis helps to differentiate primary HOA from all other causes of acro-osteolysis except Hajdu Cheney syndrome.[7]

Diagnosis is based on clinical features, radiology, biochemical markers and mutation analysis. Before pronouncing Primary Hypertrophic Osteoarthropathy (PHOA), it is mandatory to exclude the secondary form as it is associated with serious prognosis. Clues like age of disease onset and positive family history can point towards the diagnosis.[8]

Predominant radiographic features of PHOA is periostosis (symmetric osseous thickening) which commonly extends into epiphysis, an important distinguishing point from SHOA, in which periostosis mainly involves diaphyseal and metaphyseal periostosis. Other important findings are Acro-osteolysis and periosteal proliferation. Chest X-ray and CT scan can help to rule out any underlying cardiac and pulmonary abnormality if indicated.[1,2]

Elevated levels of PGE_2 are related with PDP urinary PGE_2, a useful marker for this disease.[5] HPGD mutation is found in majority of patients with typical PHOA. Sequencing of HPGD gene is highly specific first line investigation particularly in children.[9] Testing for HPGD mutation and biochemical testing for HPGD deficiency in patients with unexplained clubbing might help to obviate extensive searches for occult pathology.[6]

As there is no curative treatment available, the authors were obligated to restrict themselves to symptomatic treatment until the gene therapy is available. For inflammation and pain NSAIDs and corticosteroids have been used with good results. These drugs inhibit cyclo-oxygenase activity and thereby prostaglandin synthesis. To avoid gastropathy cox 2 selective NSAID etorixocib is preferred.[5] For bone formation and pain reduction bisphosphonates such as pamidronate and risedronate can be used. These inhibit osteoclastic bone resorption and, therefore, decrease bone remodelling.[5]

Retinoid have been used to improve skin manifestation. These act on retinoid nuclear receptors and thus regulate transcription.[3] Surgical correction of clubbing has been mentioned in literature. Reconstructive surgery for aesthetic reason can also be performed.[10]

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