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*Brief Report*

# Familial primary hypertrophic osteoarthropathy in association with congenital cardiac disease

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**Abstract** It is rare to find congenital cardiac disease in association with familial primary hypertrophic osteoarthropathy. We have now encountered three siblings, two of whom had digital clubbing, patent arterial ducts and delayed closure of the cranial fontanels. The third infant was unusual in that there was no clubbing, or cranial abnormality, despite a small ventricular septal defect. To the best of our knowledge, this association has not previously been observed.

Keywords: Familial occurrence; patent ductus arteriosus; arterial duct; ventricular septal defect

ALTHOUGH CASES OF PRIMARY IDIOPATHIC hypertrophic osteoarthropathy occurring in families have been documented over the years, it is nevertheless a rare condition in young children.[1,2] It is all the more unusual when associated with congenital cardiac disease.[2,3] We have now encountered three siblings, two of whom had digital clubbing, hyperhidrosis, delayed closure of the cranial fontanels, and patent arterial ducts. In the third infant there was no clubbing, but he had a small ventricular septal defect that underwent spontaneous closure.

## Descriptions

Our first patient was the first child born to Asian parents, who are first cousins. Birth occurred at 33 weeks gestation, with the baby weighing 1.6 kg. Polyhydramnios was noted during the pregnancy, but an amniocentesis at 27 weeks was normal. After birth, a murmur typical for patent duct was heard, and this persisted despite a course of oral Indomethacin.

On examination at the age of 8 weeks, he was acyanotic, and there were no signs of congestive cardiac failure. The continuous murmur through the patent duct was still audible. The respiratory rate was increased at 70 per minute, and his weight had risen to 2.58 kg. The chest X-ray and the electrocardiogram were within normal limits. He was managed conservatively. At the age of 4 months, he still had the murmur of a patent duct. The skull sutures were thought to be somewhat splayed. Cardiac catheterisation at 8 months of age confirmed persistent patency of the duct, which was 6 mm in diameter, with significant pulmonary hypertension. Surgical ligation was undertaken 10 days later.

At the age of 6 months, he was noted to have clubbing of the fingers and the toes, while both the posterior and anterior fontanels were still wide open. The clubbing persisted, and excess sweating of the hands and feet was documented when he was 2 years and 3 months. The anterior fontanel was still patent at 3 years of age, and finally closed shortly before his fifth birthday. The fingers and toes of both parents were normal.

He was given a trial of oral propanolol, which was not very effective in controlling the hyperhidrosis. X-rays of the hands and feet revealed some tufting of the distal phalanges, but there was no periosteal reaction in the distal radius and ulna.

When aged 7 years and 4 months, he underwent bilateral thoracoscopic sympathectomies. The

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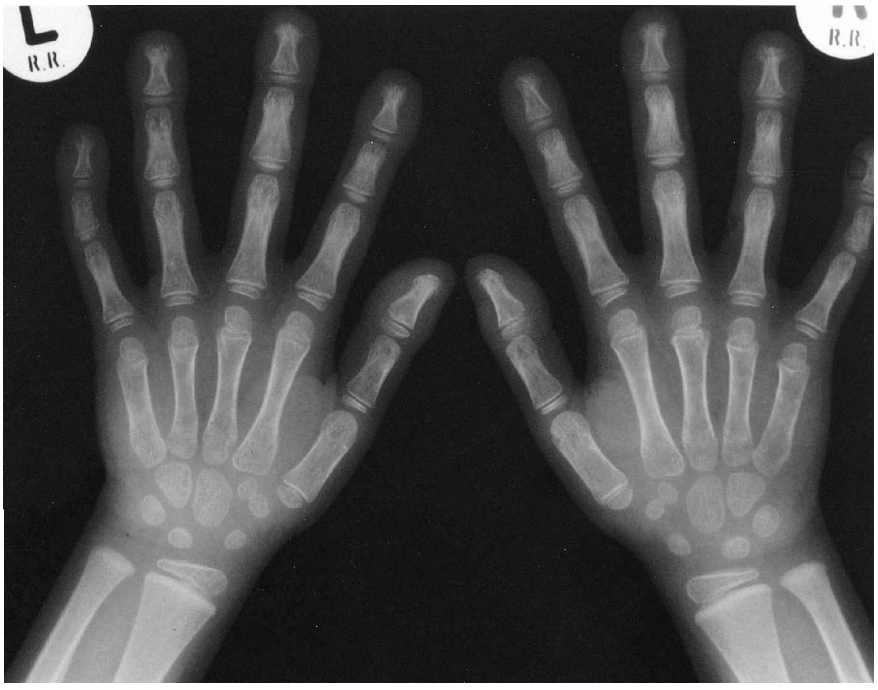


**Figure 1.**
*X-rays of the hands and wrists of our second patient illustrating tufting of the terminal phalanges of the fingers. There is no periostosis of the radius and ulna. Films taken at the age of 4 years.*

sweating of the hands disappeared, with improvement in his writing and neatness at school. He is now 10 years old, and clubbing of all his digits remains, while his feet continue to sweat. Repeat X-rays show no periostitis of the wrists, hands, tibias and fibulas. Chromosomal analysis was normal.

Our second patient, female, is the second sibling born to this family. Her birth weight was 2.2 kg. Lethargy and mild abdominal distension developed shortly after birth. A cardiac murmur was heard during routine examination. When examined at our cardiac clinic at one week of age, there was no cyanosis and she was not distressed. The pulses were normal in volume. A grade 3/6 systolic murmur was heard along the left sternal border. An electrocardiogram and chest X-ray were within normal limits for her age. The echocardiogram revealed bi-directional shunting across a 4 mm arterial duct. A 2.5 mm defect was also seen within the oval fossa, which permitted some left-to-right shunting. At 7 weeks of age, signs of a significant duct persisted. At that point, she was referred for surgical ligation. Early signs of clubbing of the fingers and toes were observed at 7½ months of age. She also had wide-open anterior and posterior fontanels, with splayed sagittal sutures. There was no hydrocephalus, as the skull circumference was at 2–10th percentile. Digital clubbing was quite obvious at 19½ months, with sweating of the hands. The anterior fontanel was widely patent, and X-rays of the skull revealed a wide anterior fontanel with some wormian bones in the lambdoidal sutures. X-rays of the hands and feet were normal and there was no periosteal reaction.

At 2 years and 9 months, the anterior fontanel was still widely patent, and there were lacunas in the lambdoidal sutures on skull X-ray. At her last attendance, when she was 5 years and 5 months, her weight was at the 25th centile and height at the 50th centile. There was clubbing of the fingers and toes, with hyperhidrosis, and the functional murmur was still present. The anterior fontanel had closed. Repeat X-rays of the hands and wrists showed tufting of the terminal phalanges but no periostitis (Fig. 1). Skull films demonstrated wormian bones of the lambdoidal sutures (Fig. 2a,b). There was no periostitis on X-rays of the tibias and fibulas. She underwent bilateral cervical sympathectomies with cessation of sweating in her hands. Chromosomal analysis was normal.

Our third patient, a male infant, was born at term, by normal vaginal delivery, with a weight of 2.52 kg. At one month of age, he was noted to be tachypnoeic, with some subcostal recession. There was no cyanosis, but on auscultation a grade 3/6 pansystolic murmur was found at the fourth left intercostal space. Chest X-ray and an electrocardiogram were considered to be within normal limits for age. The echocardiogram revealed a 4.5 mm perimembranous ventricular septal defect opening to the outlet of the right ventricle which was undergoing aneurysmal transformation. The peak systolic gradient across the defect was 64 mmHg, when the systemic systolic pressure was 84 mmHg. This indicated a normal pulmonary arterial pressure. At 5 months of age, the pansystolic murmur was foreshortened and grade 2/6, while the fontanels were normal, and there was no clubbing.

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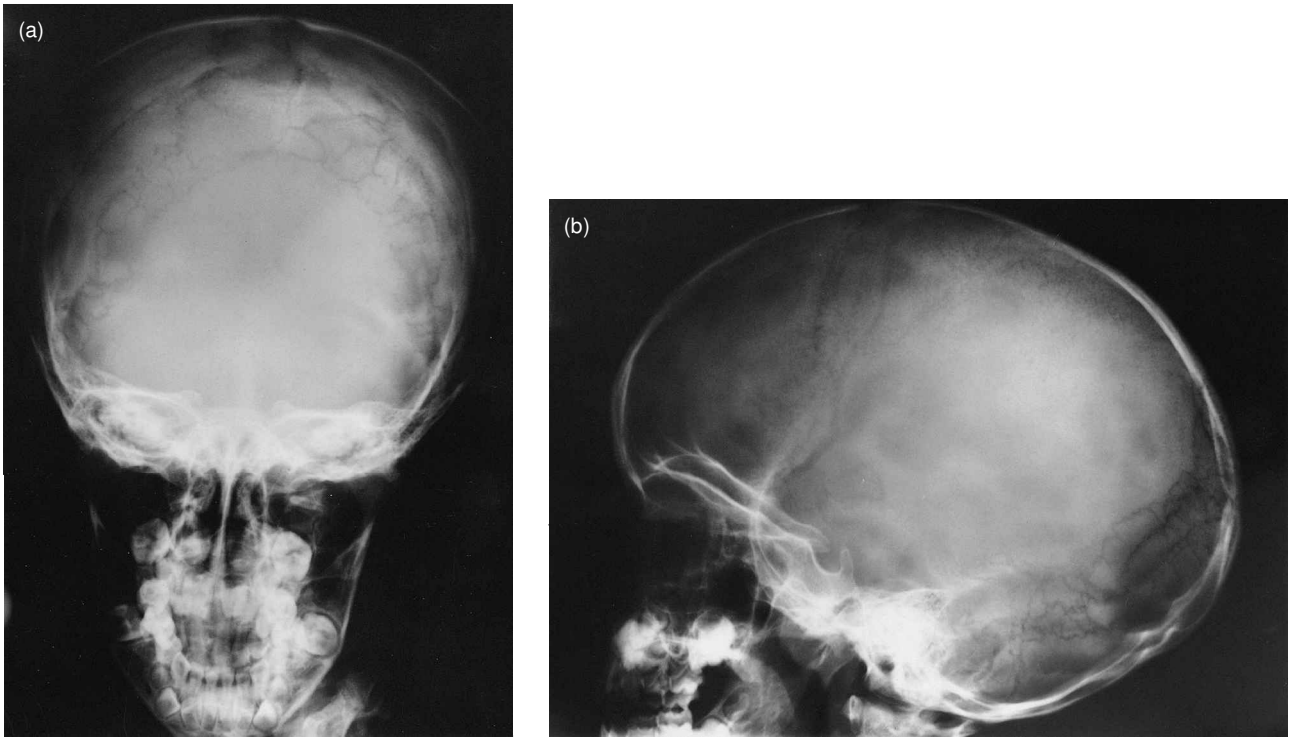


**Figure 2.**
*X-rays of the skull in our second patient taken at the age of 4 years in (a) antero-posterior and (b) lateral projections. Both demonstrate wormian bones involving the lambdoidal sutures, and a patent anterior fontanel.*

When re-examined at the age of 16 months, a grade 1–2/6 functional systolic murmur was audible. An electrocardiogram was normal for his age, and the echocardiogram showed closure of the ventricular septal defect. Chromosomal analysis was again normal.

There are no other children in the family, and neither of the parents has clubbing, nor do they have a congenital cardiac abnormality.

## Discussion

In 1988, Martinez-Lavin and co-workers reported seven of their own patients with primary hypertrophic osteoarthropathy, and analysed 125 cases found in the literature.[1] They found a significant predominance of males, and the age of onset of symptoms had a bimodal distribution, peaking during the first year of life and at the age of 15 years. A positive family history was found in almost two-fifths of the cases. Digital clubbing was reported in nine-tenths, and radiographic periostitis, especially in the tibias and fibulas, in virtually all of the patients.

The authors preferred the term primary hypertrophic osteoarthropathy for the condition, instead of pachydermoperiostitis, or idiopathic, or familial hypertrophic osteoarthropathy.[1] The skin was frequently involved, with the development of coarse facial features. Another interesting feature was the presence of hyperhydrosis. A further associated abnormality might be defects of the cranial sutures.[1,4,5]

By 1993, the team had seen a total of 16 of these patients, four of whom had an associated patent arterial duct. They concluded that primary hypertrophic osteoarthropathy should be included among the heritable disorders that may be associated with patency of the arterial duct.[2] There is only one other report from Finland,[3] where a patient underwent surgical closure of an arterial duct at the age of 2 months, developed digital clubbing at the age of 5 years, and hypertrophic osteoarthropathy at the age of 18 years. A low ratio of T-helper to T-suppressor cells was found in this patient, as well as in those family members who had clubbing of the fingers. These authors also found an increased concentration of prostaglandin E-2 in the urine collected over a 3-day period. It is known that prolonged administration of prostaglandin E-2, to maintain patency of the arterial duct in a neonate with cyanotic congenital heart disease, can result in periostitis of the long bones. Thus, it is tempting to implicate this vasoactive factor in the production of some of the observed

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findings in this condition. In 1997, the workers from Mexico postulated that localised activation of endothelial cells by an abnormal population of platelets, with ensuing release of fibroblast growth factors, might play a central role in the pathogenesis of the acropachy.[6] More recently, the same doctors have found increased plasma levels of vascular endothelial growth factor in five patients with primary hypertrophic osteoarthropathy. Thus, this cytokine may be implicated in the pathogenesis of this condition.[7]

Our first two siblings, with clubbing of the fingers, hyperhydrosis, delayed closure of the skull fontanels, and both with a patent arterial duct, are almost identical to the cases reported by Martinez-Lavin and colleagues.[2] Digital clubbing persisted in both our children after surgical ligation of the duct, and even after the sympathectomies. To date, neither of these children have periostitis of the tibias and fibulas. Of additional interest is the ventricular septal defect found in the third sibling, that underwent spontaneous closure. This patient did not have clubbed fingers. Whatever the genetic defect in this syndrome, which was not obvious on standard chromosomal analysis, there appears to be variable expressivity in our patients. If further cases and families are found, it might be possible to map the syndrome to a specific chromosome, or there may be a detectable mutation, comparable with that of the NKX2.5 gene that has recently been described by Benson and colleagues.[8] Another hand-heart syndrome, the Char syndrome, is an inherited disorder with patency of the arterial duct that maps to chromosome 6p12-p21.[9] This is further evidence to support the contention that our patients may have a chromosomal defect, which may be detectable using sophisticated techniques.

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