Cardiac failure associated with McCune–Albright syndrome

Introduction

McCune–Albright syndrome is a rare genetic condition characterized by fibrous dysplasia of bone, skin pigmentation and endocrine dysfunction. A female infant presented with cardiac failure and left ventricular hypertrophy secondary to systemic hypertension and Cushing's syndrome resulting from this syndrome. Cardiac failure secondary to McCune–Albright syndrome has not been described before. There was complete long-term resolution of the cardiac hypertrophy and cardiac failure with beta-blocker therapy.

Discussion

McCune–Albright syndrome is a rare disease so reliable prevalence figures are not available. Dumitrescu and Collins (2008) estimated prevalence to be anywhere between 1/100 000 and 1/1 000 000. The disease occurs as a result of a random genetic mutation. It is not inherited from parents. In affected individuals this random mutation is present in only some of the body's cells. As a result the clinical symptoms and physical characteristics associated with this disorder vary greatly from case to case and depend upon the cell type and tissues that are affected by the mutation.

The main defect is a post-zygotic mutation of the gene GNAS1 which is involved in G-protein signalling (Olsen, 1998; Davies et al, 2001; Diaz et al, 2007; Dumitrescu and Collins, 2008). This defect results in the constitutive activation of the subunit of the Gs protein leading to overproduction of cAMP (Olsen, 1998; Davies et al, 2001; Diaz et al, 2007). Diagnosis of McCune–Albright syndrome is usually established on clinical grounds.

McCune–Albright syndrome onset occurs in early childhood and the age of onset tends to be earlier in females than in males. Lifespan in affected individuals is relatively normal, although there are reports of sudden death in people with severe forms of the disease (Dumitrescu and Collins, 2008).

McCune–Albright syndrome was originally defined by fibrous dysplasia of bone, café-au-lait skin pigmentation which may be present from birth and endocrine dysfunction often with precocious puberty (Albright et al, 1937). It has now been recognized that other endocrine conditions can be associated with this condition including hyperthyroidism, growth hormone excess leading to acromegaly, renal phosphate wasting with or without rickets or osteomalacia, and Cushing's syndrome (Albright et al, 1937; Kirk et al, 1999; Davies et al, 2001; Dumitrescu and Collins, 2008).

The fibrous dysplasia aspect of the disease is not rare and is reported to account for up to 7% of all benign bone tumours (Dumitrescu and Collins, 2008). Fibrous dysplasia is where an individual develops areas of abnormal scar-like tissue in his/her bones. This may often occur in more than one bone. Replacement of bone with fibrous tissue may lead to fractures, uneven growth and deformity. These tend to affect one side of the body. When lesions occur in the bones of the skull and jaw it can result in uneven growth of the face. Asymmetry may also occur in the

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Case Report

A female infant presented at 6 weeks of age with tachypnoea, failure to thrive and cyanotic episodes. At 10 weeks of age she was admitted to hospital with increasing respiratory distress. Initial investigations revealed a respiratory infection and she showed early improvement on antibiotic treatment. However, she later deteriorated with increasing breathlessness and new signs of cardiac failure.

Physical examination revealed an irritable infant with cushingoid facies (*Figure 1*). There was generalized hypotonia, wasting of the lower limbs and a large pigmented naevus was present over the left side of the face. Her weight and head circumference were well below the third centile for age. There was evidence of heart failure with a respiratory rate of 100/min and hepatomegaly. She had hypertension with a blood pressure of 110/70 mmHg (>95th centile for age).

Initial echocardiography at 6 weeks of age showed a hyperdynamic circulation with a hypertrophied left ventricle. Repeat echocardiography 4 weeks later showed severe left ventricular hypertrophy that was greater in the interventricular septum than the posterior wall (septal thickness 10 mm >95th centile). There was cavity obliteration during systole with mild sub-aortic narrowing related to apposition of the mitral valve to the ventricular septum.

The findings were consistent with heart failure secondary to hypertrophic cardiomyopathy or hypertension. Propranolol 3 mg three times daily was commenced with rapid resolution of the signs of cardiac failure and resolution of the left ventricular hypertrophy over a 6-month period. Medication was stopped and long-term follow up over a 12-year period has shown normal function with no recurrence of the ventricular hypertrophy

Renal ultrasonography showed bilateral nephrocalcinosis, and skeletal survey revealed radiolucent and sclerotic areas, consistent with fibrous dysplasia. Serum cortisol levels were elevated at 266 nmol/litre and showed loss of diurnal variation and failure of suppression with both low- and high-dose dexamethasone. However, complete clinical resolution of her Cushing's syndrome had occurred by 6 months of age, without any treatment.

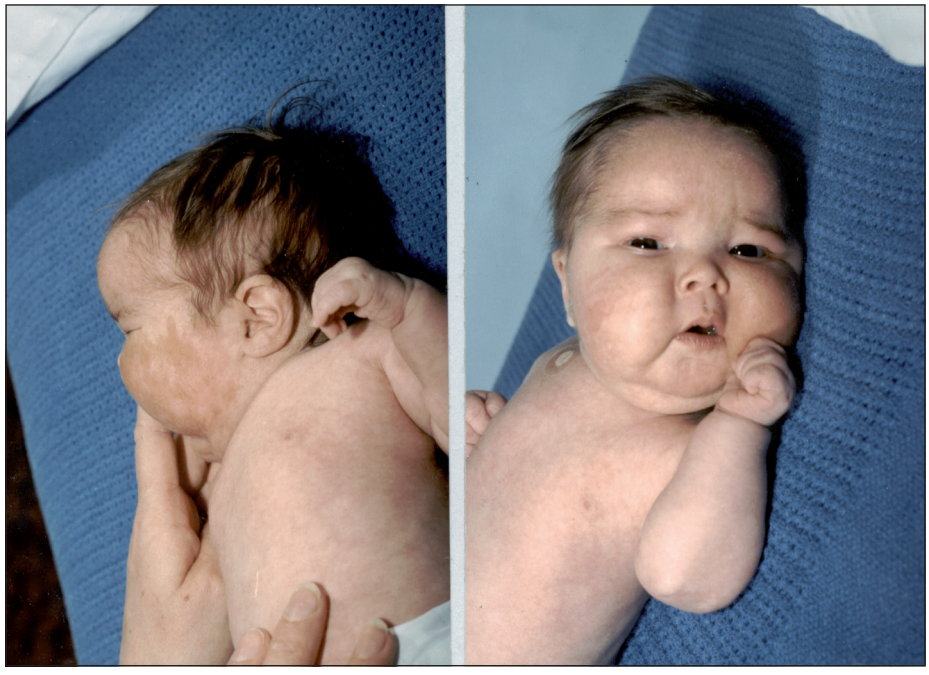

Figure 1. Photograph of infant on presentation at 10 weeks of age demonstrating pigmentation on left cheek and cushingoid appearance.

long bones; uneven growth of leg bones may cause pain and limping. Affected individuals can present with pathological fractures.

The areas most commonly involved are the proximal femur and skull base (Dumitrescu and Collins, 2008). Around 90% of the total body skeletal disease burden is usually established by the age of 15 years. Abnormal curvature of the spine (scoliosis) may also occur. Hart et al (2007) reported that lesions in the craniofacial region were established earliest, with 90% of the lesions present by 3.4 years of age. With regards to extremities, 90% of lesions were present by 13.7 years, and in the axial skeleton, 90% of lesions were present by 15.5 years. The appearance of new lesions later in life is very uncommon.

The range of severity of the disorder and presentation is very broad. Some children are diagnosed in infancy with obvious bony involvement and increased hormone production by one or more of the affected endocrine glands, while others show no evidence of bone, skin or endocrine malfunction in childhood and may enter puberty without any complications. There is no known hormonal or medical treatment for controlling this aspect of bone disease although surgery can help correct some fractures and deformities.

Girls with McCune–Albright syndrome usually reach puberty early. These girls usually have menstrual bleeding by 2 years of age, many years before secondary sex characteristics such as breast enlargement and pubic hair are seen. This early onset of menstruation is believed to be caused by excess oestrogen and can be accompanied by loss of adult height potential. Less commonly, boys with McCune–Albright syndrome may also experience early puberty. Other manifestations of McCune–Albright syndrome probably occur equally in both sexes.

McCune–Albright syndrome is a multisystem disorder in which cardiac complications have not been described previously.

Conclusions

The authors believe that this is the first report of a child presenting with McCune–Albright syndrome and cardiac failure. There were echocardiographic features consistent with hypertrophic cardiomyopathy although these features are likely to be related to hypertension and/or to the high cortisol levels (Kirk et al, 1999; Davies et al, 2001). Treatment with a beta-blocker controlled the cardiac failure and lead to complete resolution of the hypertrophy. There has been no recurrence of the hypertrophy during the adolescent growth spurt, making it unlikely that she has a primary myocardial disorder. **BJHM**

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LEARNING POINTS

- McCune–Albright syndrome is not inherited – it is caused by a mutation to the DNA that occurs in the womb while the baby is developing. This mutation is not passed on to any of the person's children.
- McCune–Albright syndrome is caused by mutations in the GNAS1 gene. The abnormal gene is present in a fraction, but not all, of the patient's cells (mosaicism).
- Cardiac failure can develop in patients with McCune–Albright syndrome related to high cortisol levels and systemic hypertension.