Multiple coronary artery aneurysms in a child with neurofibromatosis type 1

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Abstract A number of frequently unrecognised vascular manifestations have been described in patients with neurofibromatosis type 1 (NF1), including involvement of the great vessels, cerebral, visceral and renal arteries. Rarely, changes in the coronary arteries have been reported in adults with NF1. We report on a 16-year-old boy affected by NF1 with dysmorphic features and three aneurysms in the mid-portion of the left descending coronary artery disclosed by chance during investigation for a malignant peripheral nerve sheath tumour. Molecular analysis detected a gross de novo deletion in the NF1 gene. The boy had had no previous cardiac symptoms but died suddenly after developing signs and symptoms suggestive of myocardial infarction.

Conclusion To the best of our knowledge, this represents the first report of multiple lesions in the coronary arteries in a child affected by neurofibromatosis type 1 with a known deletion of the neurofibromatosis type 1 gene.

Key words Neurofibromatosis type 1 · Coronary artery · Aneurysm · Vasculopathy · Childhood

Abbreviations NF1 neurofibromatosis type 1 · PNF plexiform neurofibroma

Introduction

Neurofibromatosis type 1 (NF1) (MIM 162200) is one of the commonest autosomal dominant diseases, with an estimate frequency of 1 per 2500–3000 births [9, 14, 25, 28]. It is an extremely variable and unpredictable disease. A number of frequently unrecognised vascular manifestations have been described in NF1 patients, including involvement of the great vessels and cerebral, visceral and renal arteries [9, 11, 14, 25]. Changes in the coronary arteries have been rarely reported in adults with NF1 [4, 9–15, 21, 25, 30].

We report on a 16-year-old boy with NF1 and dysmorphic features who had multiple coronary artery aneurysms and a gross de novo deletion in the NF1 gene. To the best of our knowledge, this represents the first report of multiple lesions in the coronary arteries in a child with NF1 and a known deletion of the NF1 gene [1, 5–12].

Case report

A 16-year-old boy was admitted to the neurofibromatosis clinic at our Department of Paediatrics for investigation of an enlarging
plexiform neurofibroma (PNF) localised over the left neck and left arm. The mass had been evident since the age of 1 year. He was diagnosed as having NF1 at age 5 years on the basis of the PNF, multiple café-au-lait spots, early axillary freckling and Lisch nodules of the left iris. There was no family history of NF1. Early developmental milestones were normal. At the time of diagnosis MRI of the brain revealed two small high signal lesions in the right basal ganglia and in the left cerebellar peduncle and no other brain abnormalities. At the same time a CT scan of the area involved with the PNF showed a large mass arising from and involving the entire left brachial plexus, the median nerve and the blood vessels of the neck. He was under no regular follow-up. He had been in normal school with extra help because of learning difficulties, attention deficit and hyperactivity.

On physical examination upon admission, he measured 175 cm in height (97th percentile) and 43 kg in weight (90th percentile). Head circumference was 56 cm (97th percentile). Numerous (ca. 30) café-au-lait spots (>1.5 cm) were noted over the body, and there was axillary, groin and neck freckling. There were dysmorphic features (Fig. 1) including coarse face with frontal bossing, flat nasal bridge, hypertelorism, large nose with anteverted nostrils, thick philtrum, large lips, prominent mid-face, micromastia, large and low-set ears and large hands and feet. There was a large, painful, subcutaneous swelling with ill-defined margins protruding from the left neck (Fig. 1) and left upper arm and multiple dermal and nodular neurofibromas over the trunk and limbs. There was mild scoliosis. The cardiovascular system was normal. On neurological examination there was poor gross and fine motor co-ordination and no other abnormalities. He was sociable. The remaining physical examination was unremarkable. Blood pressure was 100/60. Slit lamp examination revealed bilateral Lisch nodules of the iris. Fundi examination was normal. Full scale IQ was 85. An ECG showed a normal sinus rhythm and a rate of 78 beats/min. An MRI of the brain confirmed abnormalities. At the time of diagnosis developmental milestones were normal. At the time of diagnosis the patient was given small doses of acetylsalicylic acid (100 mg/day) to prevent cardiac complications. He underwent surgery and several fragments of the mass were excised to avoid further compression to prevent cardiac complications. He underwent surgery and several fragments of the mass were excised to avoid further compression to the trachea. Neuropathological examination revealed a highly malignant peripheral nerve sheath tumour. After transferral to the rehabilitation unit he did well over the next few months. Extensive studies showed no metastases and, therefore, he was enrolled in the appropriate oncology protocol [23]. After completing the first cycle of induction therapy with low doses of ifosfamide and etoposide his physical examination, laboratory analysis and ECG were unremarkable. On a regimen of acetylsalicylic acid and ramitidine he returned home where at bedtime he suddenly developed abdominal and chest pain, cough and dyspnoea, and later the same night died. No consent for autopsy was given.

**Methods**

Molecular analysis

DNA from the child and the family members had been extracted from peripheral blood leucocytes. The panel of markers used for analysis comprised 15 informative microsatellite markers of which 3 were extragenic; two markers (HHH202, UT172) being 5′ to the gene and one (C7) being 3′ to the gene. DNA was analysed by techniques published elsewhere [32, 33]. Investigation for informative markers revealed a maternally derived NF1 gene deletion spanning from intron 27 to intron 38. However marker data were insufficient to localise accurately the deletion breakpoint in the proband as the child was hemizygous/homozygous for all the markers tested distal to intron 38 and, therefore, the deletion was possibly much longer. Loss of heterozygosity was so far neither confirmed nor excluded in the specimens taken from the mediastinal mass.

**Discussion**

This patient had a severe NF1 phenotype and three large aneurysms in the anterior descending coronary artery. The aneurysms were not filled by thrombi and the size and flow were normal in the distal vessels. The remaining coronary arteries were normal. The mediastinal mass, not taking contrast, was shown to compress and deviate the left common carotid and left subclavian arteries. There were no anomalies in the remaining districts of the vascular tree.

As the coronary malformation was at that time asymptomatic, the patient was given small doses of acetylsalicylic acid (100 mg/day) to prevent cardiac complications. He underwent surgery and several fragments of the mass were excised to avoid further compression to the trachea. Neuropathological examination revealed a highly malignant peripheral nerve sheath tumour. After transferral to the rehabilitation unit he did well over the next few months. Extensive studies showed no metastases and, therefore, he was enrolled in the appropriate oncology protocol [23]. After completing the first cycle of induction therapy with low doses of ifosfamide and etoposide his physical examination, laboratory analysis and ECG were unremarkable. On a regimen of acetylsalicylic acid and ramitidine he returned home where at bedtime he suddenly developed abdominal and chest pain, cough and dyspnoea, and later the same night died. No consent for autopsy was given.