Cerebral arteriopathy in neurofibromatosis type 1

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INTRODUCTION

Neurofibromatosis type 1 (NF1) is a common neurocutaneous syndrome with an incidence of 1 in 2,500–3,000.¹ It is either autosomal dominant or due to spontaneous gene mutation, progressive, heterogenous condition with highly variable phenotypic expression. It is diagnosed when at least two of seven criteria are present as per National Institutes of Health (NIH) consensus statement.² They are (1) café-au-lait (CAL) spots, (2) intertriginous freckling, (3) Lisch nodules, (4) neurofibromas, (5) optic pathway gliomas, (6) distinctive bony lesions, and (7) a first degree family relative with NF1 meeting the above criteria. The hallmark of the disease is the presence of CAL spots present in almost 100% of patients. Children with NF1 are susceptible to neurological complications ranging from seizures, behavioural disorders, to hydrocephalus. Cerebral arteriopathy is being increasingly recognised as an underreported manifestation in NF1.³ We present a child who presented with headache and features of cerebral arteriopathy on neuroimaging and discuss its therapeutic implications.

CASE REPORT

Our patient, a 10-year-old boy born of third degree consanguineous parentage, full-term with normal antenatal record (Figure 1), had history of seizures at eight months of age. Seizures were generalised tonic with posturing, stiffening of limbs with uprolling of eyeballs. Seizures continued for 15 minutes and were terminated by anticonvulsants followed by sleep. Seizures recurred at 18 months and three years of age. He was on anticonvulsants till five years of age. He had constant headaches since four years of age, lasting couple of hours with twice weekly frequency over forehead and vertex, throbbing, with worsening after exertion, meals, and on hearing loud sounds. There was associated emesis and sour eructations. Headaches were relieved at rest, on taking analgesics and have

diminished following initiation of topiramate and flunarizine over six months. He had breathlessness on accustomed exertion for two years. There is no history of orthopnoea or paroxysmal nocturnal dyspnoea.

He had history of black to brownish hyperpigmented spots of varying sizes present all over the body since birth with increase in size and number since infancy. There was a family history of similar spots in younger sister, father, and paternal grandmother. He was scholastically poor.

Examination revealed a tall obese child with stature >95th percentile and weight >97th percentile for age, respectively. He had a head circumference of 55.5 cm (near upper limit of normalcy) and BP of 106/66 mmHg (normal). His sexual maturity ratio (SMR) is 1 (prepubertal).

He had multiple (nine) CAL spots all over the trunk and extremities measuring >5 mm in size with one on the back covering area over lower scapula measuring >16 cm in size (Figure 2). There was diffuse circumferential hyperpigmentation of the skin around the neck. He had bilateral axillary freckling.

Ophthalmological evaluation including slit lamp was normal. There was no evident focal neurological deficit. There were no subcutaneous nodules or bony abnormalities.

Figure 1 Family tree.
CAL: café-au-lait.

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Figure 2 Back of the patient showing one large café-au-lait spot on the left-hand side and another café-au-lait spot on the left arm, medial aspect.

Investigations showed Hb 9.2 g% with microcytic hypochromic anaemia. Stool for occult blood was negative; Blood chemistry including liver and renal functions, sugar, and HbA_{1c} were within normal limits. Thyroid studies were normal.

Magnetic resonance angiogram dated 29 September 2010 (Figure 3) showed attenuated irregular lumen of right M1 middle cerebral artery (MCA), right anterior cerebral artery (ACA) and attenuated bilateral P1 posterior cerebral artery (PCA) with multiple collaterals in interpeduncular fossa with prominent postcommunicating arteries.

Intelligence quotient (IQ) assessment showed an IQ of 108 with normal psychometry. The echocardiography was normal. Renal angiography, chest radiograph, high resolution computed tomography of chest, and pulmonary angiography were normal. The abdominal ultrasonography showed nodular lesions in liver with normal echotexture. Spirometry showed >15% exercise induced reduction forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) with normal ratio. Proteinase 3-antineutrophil cytoplasmic antibody (ANCA), myeloperoxidase (MPO)-ANCA, anti-nuclear antibody (ANA) and lupus erythematosus (LE) cell done to exclude vasculitis were negative. Levels of IgG, IgM, IgA were within normal limits.

DISCUSSION

Presence of CAL macules with axillary freckling and first degree relatives with NF1 fulfilled three of the seven cardinal diagnostic criteria for NF1 in our patient.¹ These criteria have been shown to be highly sensitive and specific in adults with NF1⁴ and up to 97% children with NF1 have been reported to meet the criteria by eight years of age.¹ The presence of CAL lesions in female sibling, father, and paternal grandmother is consistent with the autosomal dominant nature of this disorder.

The patient fulfilled the revised International Headache Society (IHS) diagnostic criteria for migraine without aura.⁵ Children with NF1 have proneness for headache with as many 34% of headaches among them being migrainous.⁶ Our patient's

Figure 3 Magnetic resonance angiography showing left VA, right MCA and right ACA stenosis.

ACA: anterior cerebral artery, ICA: internal carotid artery, MCA: middle cerebral artery, MF: magnetic field, RHA: right hepatic artery, PCA: posterior cerebral artery, VA: vertebral artery.

good response to topiramate and flunarizine is also indicative of the same. The cause of breathlessness could not be specifically ascertained.

The tests for systemic vasculitis were all negative with erythrocyte sedimentation rate (ESR) being normal. The cerebral vascular lesions could be attributed to NF1, as cerebral arteriopathy; it is being documented with increasing prevalence in case series of NF1, incidence ranging from 2.5% to 6%.^{3,7,8} It is frequently asymptomatic with majority of patients not having focal deficits as a result of their cerebral arteriopathy.^{3,7,8} In the short duration of our observation of the patient, there has been no radiologic progression of the disease or any focal neurologic symptoms caused by ischaemic symptoms. Progression of stenosis in a minority of patients have been documented in some literatures.^{3,7} Though concurrent optic glioma with arteriopathy has been reported to be common by Rea et al,³ our patient did not have any such feature.

Neurofibromatosis type 1 results from mutations in the NF1 tumour-suppressor gene in the long arm of chromosome 17 encoding neurofibromin, a regulatory protein that inhibits activity of Ras signalling pathway.⁹ Lack of inhibitory regulation of the Ras signalling pathway leads to excessive smooth muscle cell proliferation. Presence of increased concentrations of activated monocytes and pro-inflammatory cytokines in patients with NF1 and mice studies suggest chronic inflammation as an important contributor of NF1 arteriopathy.⁹ Detection of an arteriopathy mandates institution of other antiplatelet medication to prevent stroke.³

The microcytic hypochromic anaemia could be nutritional in the absence of upper gastrointestinal (UGI) endoscopy findings. The learning disability in our patient is a well-documented finding seen in 60% NF1 patients.¹ The association of anaemia with possible gastrointestinal lesions complicates management because of the manifest need to give antiplatelet agents for cerebral arteriopathy. There is a likelihood of stroke in our patient justifying the need for clopidogrel due to intolerance to aspirin use. Hence it is mandatory to follow-up the patient in a systematic way periodically to ensure optimum care.

CONFLICTS OF INTEREST

None identified.

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