An Unexpected Cause of Macrocephaly in a Child with Leukodystrophy

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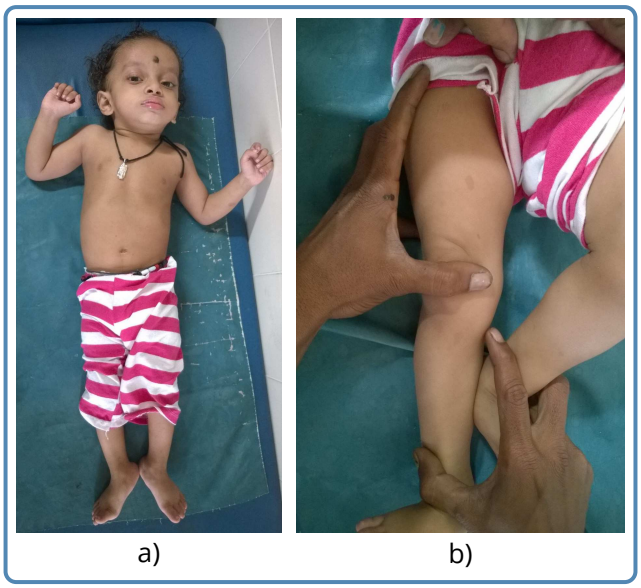
Abstract

Leukodystrophies are a heterogeneous group of genetic disorders predominantly involving the white matter of the brain, which are characterised by progressive psychomotor regression and abnormal neuroimaging findings. Macrocephaly is an important clinical finding which helps to considerably narrow down the differential diagnoses one has to consider in a patient with suspected leukodystrophy. However, macrocephaly may sometimes be a co-incidental finding or related to a co-existing condition in a patient. Here we describe one such patient with leukodystrophy and macrocephaly, wherein parental examination provided a vital clue to the diagnosis (father had Neurofibromatosis type I). This clinical report highlights the importance of a detailed family history and parental examination in clinical genetic evaluation. It also reiterates the fact that more than one genetic disease may exist in a family and the resultant phenotype of affected individuals in such families may be a combination of the individual disease manifestations.

Introduction

Leukodystrophies are a group of progressive genetic disorders characterised by abnormalities of the white matter, with or without involvement of the peripheral nervous system. Characteristic changes on MR imaging of the brain are essential for a diagnosis of leukodystrophy. Clinical approach to a case of leukodystrophy amalgamates various factors like age of onset, progression, involvement of peripheral nervous system and associated features like dysmorphism, ocular, dermatological and adrenal abnormalities along with characteristic neuroimaging findings. Macrocephaly is one such parameter which significantly narrows down the differentials one has to consider. Here, we describe an unusual cause of macrocephaly in a case of leukodystrophy, where in examination of the parents played a pivotal role in the diagnosis.



a) b)

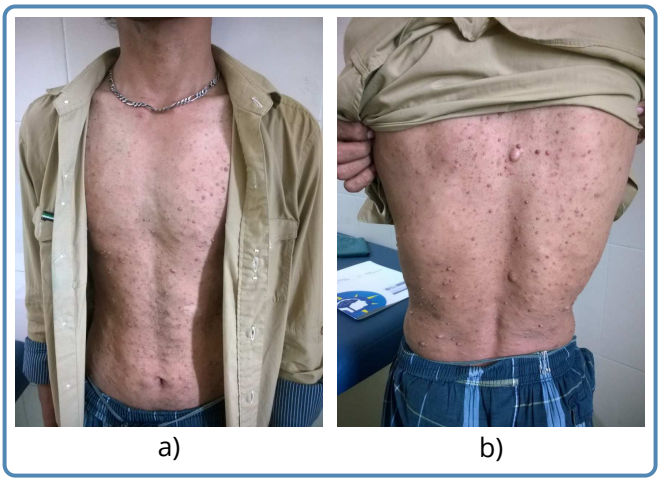
Figure 1 a). Photograph of the proband showing the macrocephaly and spasticity. b). Close-up of the proband's right lower limb showing the multiple café au lait macules.

Clinical Report

A 2-years-old male child was brought to the outpatient clinic of the Medical Genetics department with complaints of progressive loss of acquired milestones noted since about 13 months of age. The child was born to second degree consanguineous parents and was the first in birth order. He was born through a normal vaginal delivery after an uneventful antenatal period. There was history of admission to the neonatal intensive care unit on day 2 of life in view of respiratory distress for about 7 days. The child was breast-fed and had an apparently normal development till about 13 months of age which was followed by progressive loss of motor mile stones and subsequently of speech. There was no history of seizures, visual or hearing impairment. There was no history suggestive of any other systemic involvement.

On examination, the child was found to have a relatively large head with sparse scalp hair and multiple cafe au lait spots (around 10 in number with some of the macules measuring >1cm) distributed over the trunk and all four limbs (Figure 1). No other obvious dysmorphic features were seen. His anthropometric measurements were as follows: head circumference – 49.5cm (97^{th} centile for age and sex), weight – 10 kg (3^{rd} centile), height – 79.5cm (-2 to -3 S.D below mean). Central nervous system examination revealed spasticity in all limbs, depressed deep tendon reflexes and up-going plantar reflexes suggesting a combination of pyramidal tract involvement with peripheral neuropathy. Cardiovascular system and abdominal evaluation was unremarkable. The child was accompanied by both the parents and parental examination revealed that the father of the child also had a relatively large head (head circumference - 58cm; +2.5 SD above mean) and dysmorphic features in the form of ocular hypertelorism and low set ears. A neurofibroma-like lesion seen on his chin prompted us to do a complete physical examination, which revealed multiple neurofibromas and cafe au lait spots distributed all over the trunk and all 4 limbs. The clinical features of the father were consistent with the diagnosis of Neurofibromatosis type 1 (Figure 2). As the child also had multiple cafe au lait spots, we could conclude that the child also had Neurofibromatosis type 1 in addition to a neurodegenerative condition. MRI brain of the child showed diffuse, symmetrical periventricular white matter hyperintensities in the T2 weighted images with sparing of subcortical U fibres.

Arylsulfatase A enzyme assay was done in the peripheral blood leukocytes and no enzyme activity (0 nmol/hr/mg) was detectable (reference range of the lab: 25-80 nmol/hr/mg). Pseudodeficiency of Arylsulfatase A was ruled out by testing for the p.N350S pseudodeficiency variant in the *ARSA* gene. Thus the child was diagnosed to have late infantile onset Metachromatic leukodystrophy along with Neurofibromatosis type 1. The family was appropriately counselled that the risk of recurrence of MLD in each of their subsequent offspring would be 25% and that of NF1 would be 50%.



a) b)

Figure 2 Close up of the trunk of the proband's father (a Front & b Back) showing the numerous café au lait spots and neurofibromas.

Discussion

Canavan disease, Alexander disease and Megalencephalic leukoencephalopathy with sub cortical cysts are the main diagnostic possibilities considered in the case of a young child presenting with a white matter neurodegenerative disease phenotype with macrocephaly [Vanderver et al., 2014]. Childhood ataxia with central nervous system hypomyelination (CACH) –megalencephaly, L2 Glutaric aciduria and GM2 gangliosidoses are other conditions associated with leucoencephalopathy and macrocephaly. The severe forms of Canavan disease and Alexander disease present in the early infantile period with macrocephaly and developmental regression. Elevated N-acetylaspartic acid (NAA) in urine and an NAA peak in Magnetic resonance spectroscopy (MRS) of the brain are suggestive of Canavan disease whereas, frontal

preponderance of cerebral white matter abnormalities which are otherwise extensive, altered signal intensities in the periventricualar region on T1 and T2 weighted imaging and abnormalities of the basal ganglia, thalami and brain stem strongly point towards the possibility of Alexander disease (van der Knapp et al, 2001). Megalencephalic leukoencephalopathy with sub cortical cysts, as the name suggests, has subcortical cysts on MRI with white matter abnormalities and usually has a much milder phenotype with slower progression.

The clinical and MR imaging findings of the above case were more consistent with the diagnosis of late infantile onset Metachromatic leukodystrophy (MLD), but the macrocephaly and cafe au lait spots were not clearly fitting in. MLD caused by deficiency of Arylsulfatase A activity is an autosomal recessive condition and is one of the commonest causes of progressive leukodystrophy (Austin et al., 1965; Von Figura et al., 2001). The late infantile onset form usually manifests after a period of normal development at around one year of age with progressive loss of acquired mile stones. Initial symptoms are usually in the form of clumsiness or frequent falls followed by a period of hypotonia which slowly progresses to limb spasticity and other pyramidal signs. Progressive deterioration of mental function occurs and peripheral nervous system is variably involved. Some reports of macrocephaly in MLD do exist, but head circumference is variable and more often than not macrocephaly is relative rather than being absolute (Kim et al, 1997; Kulkarni et al., 2005).

The clinching point in this scenario was the examination of the father which revealed features of Neurofibromatosis 1. The situation was slightly tricky as he was initially unwilling to share the details and allow for medical examination because of the stigma that is so often associated with such a disease. The fact that he was fully covered and had only a single neurofibroma on his chin did not help either. The diagnosis was evident once he was spoken to and examined in private in the absence of other family members. Neurofibromatosis type 1 is an autosomal dominant neurocutaneous disorder caused due to mutation in the *NF1* gene which is characterised by multiple cafe au lait spots, neurofibromas, axillary freckling, Lisch nodules and optic gliomas (Friedman et al., 1997). Neurofibromatosis 1 is often associated with macrocephaly (Clementi et al., 1999; Szudek et al., 2000) and the presence of multiple cafe au lait spots in the child along with a positive family history led us to believe that the child was affected with Neurofibromatosis 1 in addition to MLD.

It is not very often that one sees a patient with two different genetic disorders. The combination of an autosomal dominant and an autosomal recessive disease in a single patient has increased chances of occurrence when, as in our case, a person harbouring an autosomal dominant mutation marries consanguineously. In a country like ours, where consanguinity and inbreeding are common practices such situations might arise more frequently than when compared to other parts of the world where consanguinity is infrequent.

Our case serves as a gentle reminder in this era of next generation sequencing that "Trio analysis" is not just limited to analysis of novel/atypical molecular variants, but is indeed an integral part of genetic clinical evaluation, more so when there is an atypical or unexpected finding!

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