Case Reports

Megalencephaly-capillary malformation syndrome: a report of two cases

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Introduction

Megalencephaly capillary malformation syndrome (MCAP) is a rare overgrowth syndrome characterized by unique somatic and neuroimaging abnormalities[1]. We report 2 distinct cases of MCAP syndrome who presented to us with macrocephaly and typical cutaneous manifestations. This has been reported due to its rarity and to highlight the importance of recognizing the varied spectrum of malformations and abnormalities in brain imaging associated with this syndrome.

Case report:

Case 1: A 6-month old boy, born to non-consanguineous parents, presented with increasing head size for the last 2 months. Birth history was normal and neonatal period uneventful. There were no seizures or paucity of limb movements. His developmental milestones were normal. The weight was 5kg (<3rd centile), length was 65cm (10th centile) and occipito-frontal circumference (OFC) was 47.5cm (>+2SD) suggesting macrocephaly. Sun setting sign was present with prominent scalp veins. He had capillary haemangioma over occiput (Figure 1) with generalized skin laxity.

There was bilateral syndactyly involving 2nd and 3rd toes. Fundus was normal. Neurological examination revealed hypotonia with normal deep tendon reflexes. Examination of other systems was normal. Baseline haematological, biochemical and thyroid function tests were normal. Magnetic resonance imaging (MRI) of brain revealed hydrocephalus with inferior herniation of cerebellar tonsils suggesting Chiari type 1 malformation (Figure 2).

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Cardiology evaluation revealed a normal electrocardiogram (ECG) with tiny patent foramen ovale detected on 2D echocardiogram. Decompressive surgery was advised by the neurosurgeon if symptoms of decompensation appear.

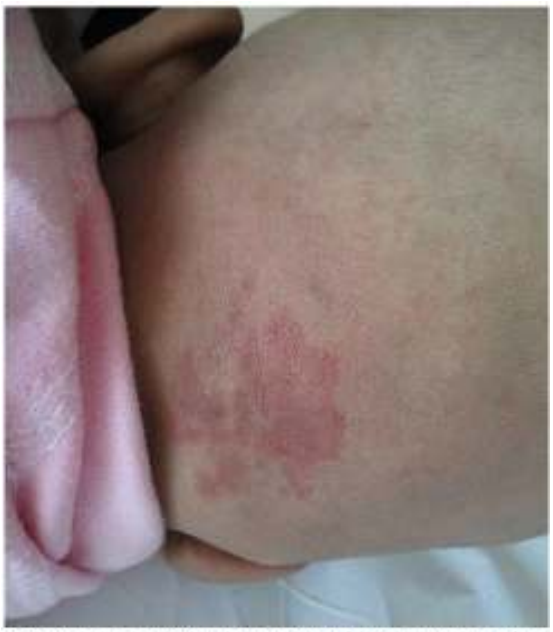

Figure 1: ***Capillary haemangioma over occiput***

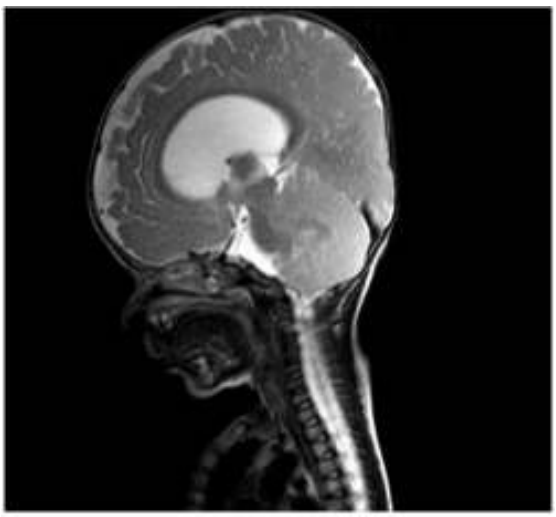

Figure 2: ***Magnetic resonance imaging of brain***

Case 2: A 1 year 5 month old girl born out of a 3rd degree consanguineous marriage presented with failure to thrive and macrocephaly noticed at 3 months of age. Her birth history was unremarkable. There was delay in motor milestones. Examination showed a length of 67cm (<3rd centile), a weight of 6.5kg (<3rd centile) and an OFC of 49 cm suggesting macrocephaly. Midline strawberry haemangioma was present over the sternum with postaxial polydactyly of right foot (Figure 3).

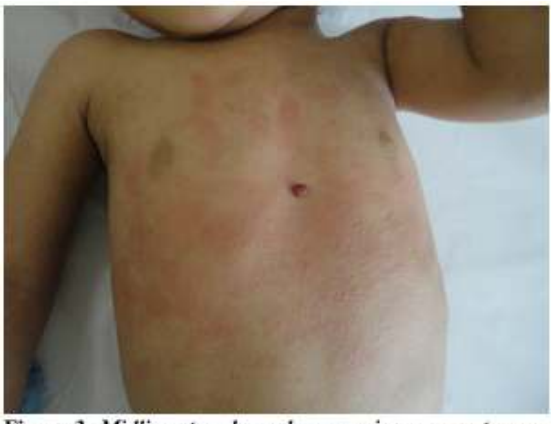

Figure 3: ***Midline strawberry haemangioma over sternum***

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There was generalized hypotonia with preserved deep tendon reflexes. Baseline blood investigations were normal. MRI of brain revealed hydrocephalus with asymmetry of lateral ventricles suggestive of hemimegalencephaly. ECG, 2D echocardiogram and abdominal ultrasonography were normal. Ventriculo-peritoneal shunt was placed by the neurosurgeon. Physiotherapy exercises were taught to parents.

Table 1 shows the characteristic features of other overgrowth syndromes

Table 1: ***Characteristic features of other overgrowth syndromes***

Disorder	Characteristic feature
CLOVES syndrome	Congenital lipomatous overgrowth mainly truncal area, vascular malformations overlying the truncal overgrowth, musculoskeletal manifestations such as scoliosis, knee dislocation, chondromalacia patellae, renal agenesis, neurological abnormalities like neural tube defects, rarely megalencephaly and PMG
Fibro-adipose hyperplasia	Overgrowth involving visceral or muscular tissues, lipomatous infiltration of muscles, progressive skeletal overgrowth, rarely vascular malformation
Megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome	Clinical manifestations similar to MCAP syndrome. Distinguished by the absence of cutaneous vascular malformations
Klippel-Trenaunay syndrome	Asymmetric tissue hypertrophy with extensive cutaneous capillary malformations and venous varicosities often combined with visceral vascular malformations
Bannayan Riley Ruvalcaba syndrome	Megalencephaly with truncal lipomatous overgrowth, intestinal polyposis and pigmented lesions over penis
Proteus syndrome	Asymmetric skeletal overgrowth, cerebriform connective tissue naevi and epidermal naevi

Discussion

This disorder was named megalencephaly-cutis marmorata telangiectatica congenita (MCMTC) by Moore et al in 1997[1]. The term cutis marmorata telangiectatica congenita was replaced with capillary malformation and the nomenclature changed to macrocephaly-capillary malformation syndrome (MCM)[2]. Subsequently, the term macrocephaly was replaced with megalencephaly to reflect increased brain size and the nomenclature changed to megalencephaly capillary malformation syndrome (MCAP) by Mirzaa et al in 2012[3]. Further, these disorders were subdivided based on brain imaging findings into megalencephaly-capillary malformation (MCAP) and megalencephaly-polydactyly-polymicrogyria-hydrocephalus (MPPH) syndromes[3]. Mutations in the *PIK3CA* gene are thought to cause MCAP[4]. PIK3CA associated segmental overgrowth phenotypes include those related to brain (MCAP syndrome and hemimegalencephaly) and those with segmental body overgrowth (CLOVES syndrome and fibro-adipose hyperplasia)[4,5].

Anomalies associated with MCAP include primary megalencephaly or hemimegalencephaly, prenatal

overgrowth, brain and body asymmetry, cutaneous vascular malformations, cortical brain malformations notably polymicrogyria, digital anomalies consisting of syndactyly with or without postaxial polydactyly and connective tissue dysplasia involving the skin, subcutaneous tissue and joints[5,6]. The classic features of MCAP include OFC >2SD above mean, segmental or generalized overgrowth, single or generalized capillary malformation and generalized hypotonia. Megalencephaly in MCAP is usually congenital and progressive but a few cases may have a normal head size at birth with macrocephaly being noted in later infancy[5,7,8].

Secondary to megalencephaly features noted on brain imaging include ventriculomegaly, thickened corpus callosum and cerebellar tonsillar ectopia. The other important finding in brain imaging is cortical dysgenesis in the form of polymicrogyria (PMG)[8]. Perisylvian PMG is the most common form responsible for seizures, motor or intellectual disability[9,10]. The commonest form of vascular malformation is mid-facial or generalized extensive capillary haemangioma. Other vascular malformations reported are venous malformations, visceral malformations and vascular rings[2,6]. Somatic overgrowth is a main feature MCAP. Macrosomia is noted at birth in most children but failure to thrive may be seen in a few due to growth hormone deficiency. Asymmetric growth leading to limb hypertrophy/limb length discrepancy is also reported[11]. Connective tissue dysplasia in the form of ligamentous laxity, joint hypermobility and skin hyper-elasticity may be present. Other features of MCAP include cardiac septal defects, arrhythmias and occurrence of benign (haemangioma and angiomyolipoma) and malignant tumours (Wilms tumour and leukemia) in some cases[12].

MCAP should be differentiated from the PIK3CA associated segmental overgrowth syndromes as well as other disorders presenting with macrocephaly and somatic overgrowth[4,5] (Table 1). The diagnosis of MCAP is confirmed by detecting PIK3CA pathogenic variant allele by sequence analysis of DNA derived from skin or saliva. Genetic diagnosis was not performed in this study due to financial constraints.

Management is mainly supportive in the form of physiotherapy and occupational therapy for hypotonia. Early neurosurgical referral is warranted in the presence of rapidly enlarging OFC with symptoms and signs of raised intracranial tension and symptomatic tonsillar ectopia.

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