MACROCEPHALY-CUTIS MARMORATA TELANGIECTATICA CONGENITA (MACROCEPHALY-CAPILLARY MALFORMATION)

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Introduction

This recently recognised entity (OMIM # 602501) (OMIM 2006) is characterised by the association of macrocephaly (megalencephaly), capillary malformation of the cutis marmorata telangectatica congenita type, cavernous haemangioma, asymmetric growth pattern, central nervous system malformations, and neurological abnormalities (Clayton-Smith et al. 1997, Gerritsen et al. 2000, Moore et al. 1997, Lapunzina et al. 2004). Despite extensive investigation of many of affected cases, no specific cause for the condition has yet been identified (Lapunzina et al. 2004).

In this chapter, we discuss the clinical findings, natural history, diagnostic criteria, and possible mode of inheritance of M-CMTC.

Recently, this entity has been renamed macrocephaly-capillary malformation (M-CM) (Conway et al. 2007, Toriello and Mulliken 2007) in line with the current terminology for vascular anomalies, hemangiomas and malformations (Enjorlas et al. 2007, Mulliken et al. 2006).

We chose to retain the original name throughout the text as this is still used in the current medical literature (Katugampola et al. 2008).

Historical perspective and eponyms

Although the association of macrocephaly, limb asymmetry, and capillary malformations was documented around 30 years ago, it was not until 1997 that Moore and co-workers (Moore et al. 1997) and Clayton-Smith and colleagues (Clayton-Smith et al. 1997) independently reported on 22 patients with common clinical findings and a similar facial gestalt. The main clinical features of these patients were overgrowth, macrocephaly and cutis marmorata telangiectatica congenita (M-CMTC) along with other associated anomalies. Subsequent communications pointed out that some patients reported by other authors might well have had this syndrome (Carcao et al. 1998, Stephan et al. 1975, Vogels et al. 1998, Wrobleski et al. 1988). A recent paper reported 6 additional cases, reviewed the literature and critically analysed the published evidence in order to further delineate the syndrome (Lapunzina et al. 2004). Since then, a further two patients have been described (Akcar et al. 2004, Dinleyici et al. 2004, Nyberg et al. 2005) bringing the total number of patients with M-CMTC described so far to 77 (Cohen et al. 2002).

Incidence and prevalence

Seventy-seven patients so far reported (Akcar et al. 2004, Dinleyici et al. 2004, Lapunzina et al. 2004, Nyberg et al. 2005). There is a slight preponderance of males but this is not statistically significant (M:F = 42:34).

Clinical manifestations

The main characteristics of M-CMTC are macrocephaly, pre and postnatal overgrowth, cutis marmorata, syndactyly, capillary malformation of the lip and/or philtrum, skin and joint laxity and develop-

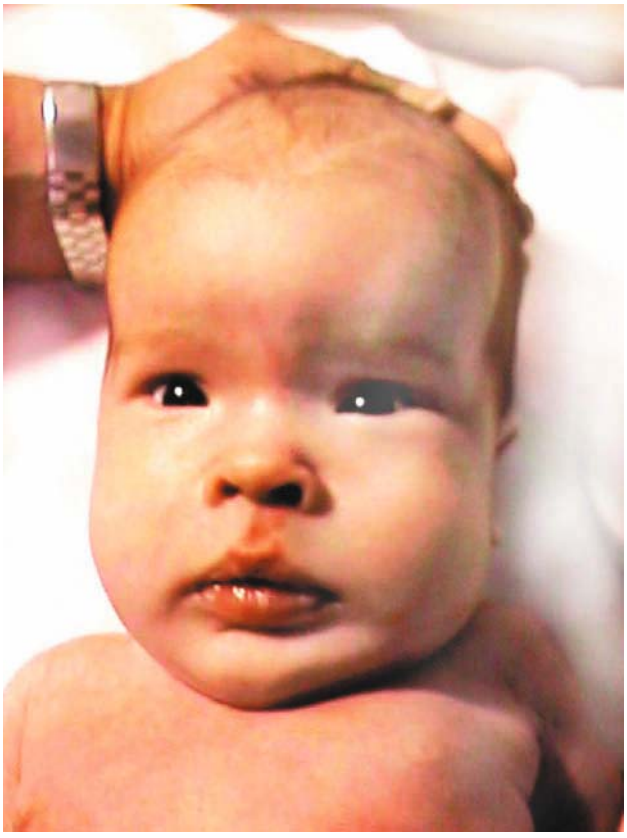

Fig. 1. Characteristic capillary malformation on the philtrum and the upper lips.

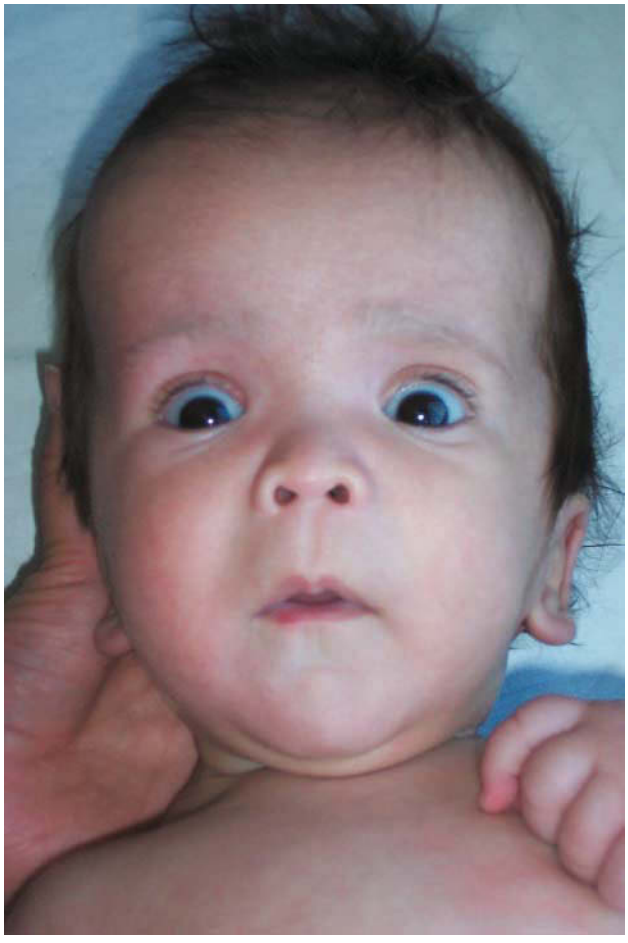

Fig. 2. Typical facial appearance of MCMTC demonstrating sunsetting" appearance of the eyes with frontal bossing, large forehead, and short nose, small chin and full lips.

mental delay (Figs. 1–6). In the following sections we discuss the clinical features by region.

Skin and connective tissue

The skin is affected in almost all patients with M-CMTC. Most of them have a combination of CMTC, nevus flammeus and flat or cavernous hemangiomas, usually most conspicuous in the limbs (Fig. 5). The capillary malformation on the philtrum and/or the upper lip is perhaps the most characteristic (Fig. 1) but some children have had a capillary malformation also of the back or buttocks. The generalised cutis marmorata tends to fade with time. One patients developed a mastocytoma-like nodule in the face (Giuliano et al. 2004). Deep vein thrombosis was observed in 2 cases.

The majority of patients have demonstrable increased skin laxity with or without thickening of the subcutaneous tissue. Pigmentary abnormalities (hyper or hypopigmentation, following the Blaschko lines) epidermal nevus and deep plantar and palmar creases have been observed in some patients (Baralle and Firth 2000). Hyperextensible joints, diastasis recti, umbilical hernia and inguinal hernia are additional findings suggesting a connective tissue component to the condition.

Craniofacial anomalies

The facial features and craniofacial anomalies seen in these patients are striking and give rise to a dis-

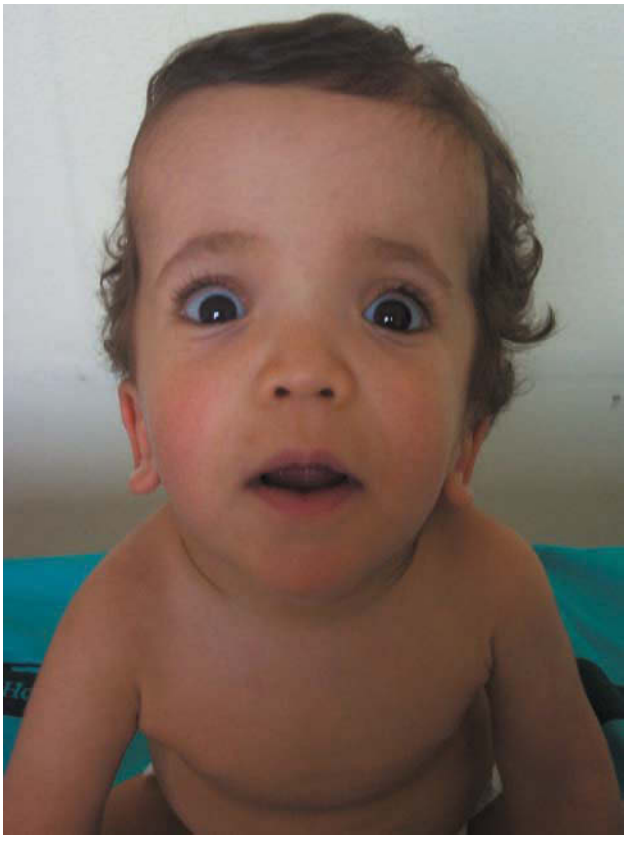

Fig. 3. Note the prominent supraorbital ridges associated to facial asymmetry.

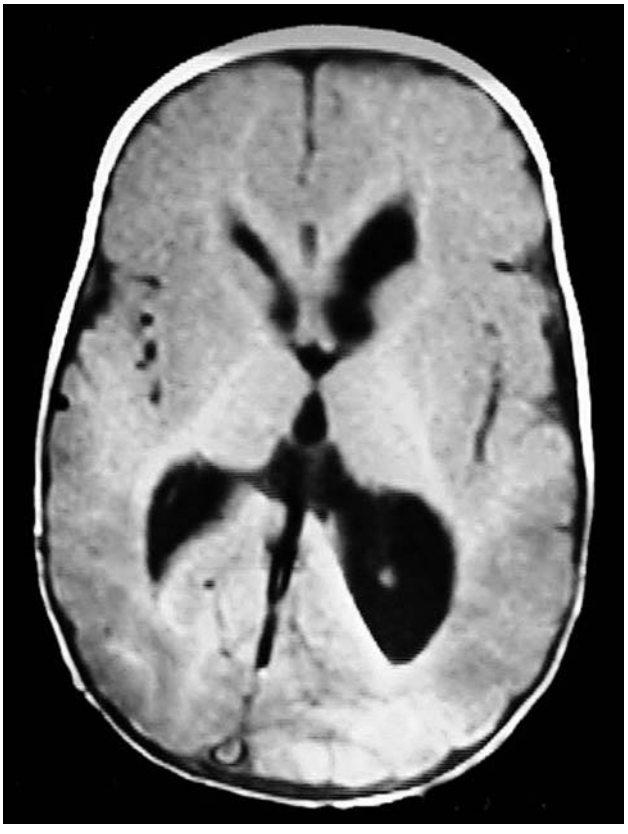

Fig. 4. Axial T1-weighted MR image of the brain demonstrating left hemimegalencephaly with dilated ventricular horns.

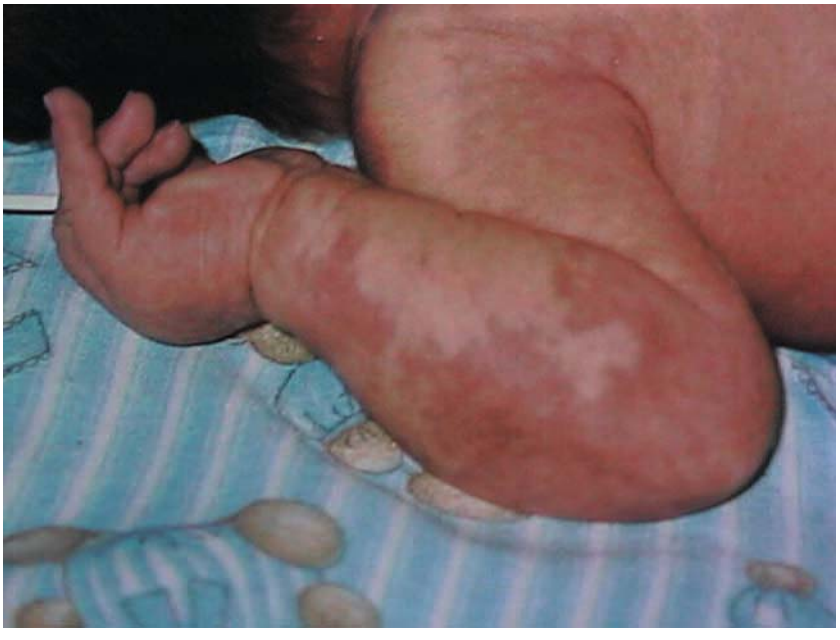

Fig. 5. Combination of CMTC, nevus flammeus and flat haemangioma in the right upper limb.

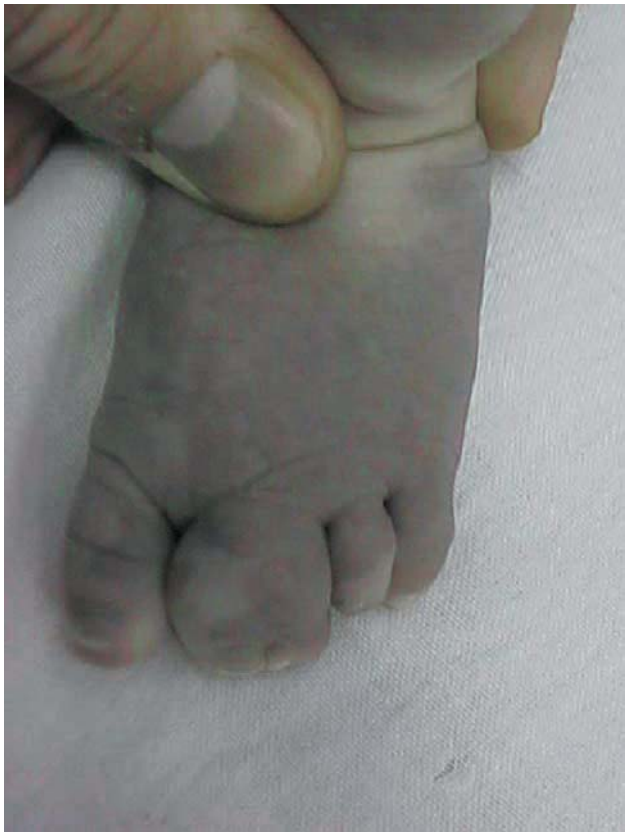

Fig. 6. Syndactyly of the 2nd–3rd toes.

tinctive facial *"gestalt"* (Figs. 1–3). Macrocephaly, present at birth and progressive in nature has been present in more than 95% of cases of M-CMTC (Lapunzina et al. 2004). The increased occipitofrontal circumference (OFC) is often independent of the presence of hydrocephalus and the head size may continue to increase in size disproportionately even after shunting. Frontal bossing, large forehead, short nose, small chin, full lips and thick gums are usually present. A characteristic finding is a mid-facial capillary malformation, found mostly on the philtrum and/or upper lip (Fig. 1). This finding is a useful diagnostic feature. The cheeks may be full and fleshy and sometimes with patchy reddish areas of skin. Most patients have deep-set eyes with prominent supraorbital ridges. A "sun-setting" appearance of the eyes may be present along with ptosis of the eyelids and facial asymmetry (Figs. 2 and 3). Along with the latter there may also be asymmetric gingival hyperplasia. Macroglossia and craniosynostosis are infrequent findings (Moore et al. 2004, Vogels et al. 1998).

Growth

More than 95% of the patients have had prenatal overgrowth with a high birth weight and increased OFC. Length was normal or just slightly increased in the majority of children. In view of the neonatal macrosomia this syndrome is included in the nosology of the overgrowth syndromes (Cohen et al. 2002). Postnatal overgrowth may occur but is less common and with age the weight and height tend to normalise or even fall below the normal centiles for age and sex (Moore et al. 1997). Postnatal failure to thrive was reported in a small number of cases (Moore et al. 2004, Reardon et al. 1996).

Asymmetric growth in the form of hemihyperplasia/hemihypertrophy or unilateral overgrowth of the face, thorax and/or limbs is commonly observed (Table 1).

Central nervous system and performance

Brain imaging by MRI or CT scans demonstrated that hydrocephalus with or without hemimegalencephaly is very frequent in M-CMCT (Fig. 4). White matter anomalies demonstrated by MRI have been recorded in ~12% of children (consisting in white matter irregularities with increased signal on T2-weighted images) (Conway et al. 2008). Cortical dysgenesis, a thickened, hyposplastic or agenetic corpus callosum, enlarged cerebellum, Chiari type I malformation, loss of normal sulcation, pachygyria, polymycrogyria and abnormal myelinisation with prominent Virchow-Robin spaces have all been observed (Akcar et al. 2004, Carcao et al. 1998, Conway et al. 2008, Franceschini et al. 2000, Garavelli et al. 2005, Vogels et al. 1998, Reardon et al. 1996). A distinctive feature in more than 50% of patients in one study (Conway et al. 2008) was cerebellar tonsillar herniation (which was acquired in some cases) associated with rapid brain growth and progressive

Table 1. Summary of Findings in 77 cases[#] of Macrocephaly-Cutis Marmorata Telangiectatica Congenita (modified from Lapunzina 2005)

Very frequent (>77%)	
Macrocephaly	75/77
Cutis marmorata telangiectatica	72/77
Asymmetry of the head, face or body	66/77
Overgrowth/high birth weight	60/77
Hemangioma of the lip and/or philtrum	60/77

Frequent (25–77%)	
Developmental delay[a]	49/77
Syndactyly of the 2nd–3rd toes	48/77
Hydrocephalus	48/77
High forehead/frontal bossing	42/77
Joint laxity/hypermobility	42/77
Hypotonia	36/77
Hemimegalencephaly	28/77
Hypereslatic skin	25/77
Thick subcutaneous tissue	25/77

Less frequent (<25%)	
Dolichocephaly	15/77
Polyhydramnios	15/77
Polydactyly	16/77
True hypertelorism	12/77
White matter anomalies	11/77
Syndactyly 3rd–4th fingers	11/77
Internal A-V malformation	10/77
Seizures	8/77
Pigmentary abnormalities	8/77
Venous aneurysms/thromboses	7/77
Gap between 1st and 2nd toes	9/77
Small palpebral fissures	9/77
Failure to thrive	6/77
Chiari-type malformation	6/77
Hypoglycaemia	5/77
Stridor	5/77
Thick gums	5/77
Arrhythmia/sudden death	4/77
Ptosis of eyelids	4/77
Tumours*	4/77
Cardiac malformation	5/77
Umbilical hernia	3/77
Deep plantar creases	4/77
Pectus carinatum	2/77
Intestinal lymphangiectasia	2/77
Epidermal nevus	2/77
Macroglossia	2/77
Hip dysplasia	2/77
Macrodactyly	2/77
Hip dysplasia	2/77
Single umbilical artery	1/77
Hydronephrosis	1/77
Mesenteric anomalies	1/77
Atrophic abdominal aorta	1/77

Females 34 cases; Males 42 cases; 1 case gender not reported.

[#]Including the cases of Ringrose et al. (1965); 4 cases of Stephan et al. (1975); 1 case of Meyer (1979); 2 of López-Herce Cid et al. (1985); 1 of Wroblewski et al. (1988); 2 of Cristaldi et al. (1995); 1 of Barnicoat et al. (1996); 1 of Reardon et al. (1996); 9 of Clayton-Smith et al. (1997); 13 of Moore et al. (1997); 1 of Carcao et al. (1998); 4 of Vogels et al. (1998); 1 of Berbel Tornero et al. (1999); 1 of Moffit et al. (1999); 1 of Thong et al. (1999); 1 of Baralle and Firth (2000); 2 of Franceschini et al. (2000); 1 of Gerritsen et al. (2000); 5 of Robertson et al. (2000); 1 of Howells et al. (2000); 1 of Bottani et al. (2000); 3 of Yano and Watanabe (2001); 1 of Schwartz et al. (2002); 1 of Mégarbané et al. (2003); 1 of Stoll (2003), 7 cases of Giuliano et al. (2003), 6 of Lapunzina et al. (2004); 1 of Nyberg et al. (2005); and 1 of Dinleyici et al. (2004) and Akcar et al. (2004) (both the same case).

[a]Some patients did not reach the age for evaluation.

growing of the posterior fossa during infancy. Other findings have been ventriculomegaly, bifrontal extraaxial fluid collections, and cavum septi pellucidum and vergae. Focal CNS infarcts and ischaemic changes have occasionally been reported (Giuliano et al. 2004). Conway et al. (2008) postulated that this constellation of unusual brain features suggests a dynamic process of mechanical compromise in the posterior fossa, perhaps initiated by a rapidly growing cerebellum, which leads to congestion of the venous drainage, compromised cerebrospinal fluid reabsorption, increased posterior fossa pressure and acquired tonsillar herniation.

All degrees of developmental delay have been observed in M-CMTC, with a predominance of moderate to severe retardation (Robertson et al. 2000). This retardation seems to be related not only to brain anatomic anomalies (increased size of cerebral ventricles, hemimegalencephaly, white matter abnormalities, etc) but also to probable CNS cortical dysplasia as developmental delay may be present in the absence of significant structural malformations of the brain. Ventriculo-peritoneal shunts were inserted in about half of the patients but these had little influence on the macrocephaly, suggesting a true megalencephaly (Moore et al. 1997, Vogels et al. 1998). Hypotonia, anisocoria, esotropia, facial nerve palsy, optic atrophy and brain arteriovenous malformation were observed in several patients. Seizures have occurred in a few patients but are not a common finding (Lapunzina et al. 2004).

Limbs

The hands are usually large and broad with a "fleshy" appearance. Some patients may have polydactyly (postaxial) and syndactyly of the fingers (Fig. 6) (Clayton-Smith et al. 1997, Franceschini et al. 2000, Moore et al. 1997). Macrodactyly was observed in one case.

Cutaneous syndactyly of the second and third toes, usually up to the distal phalanx is very frequent (Fig. 6). There is often a wide space between the first and second toes. One patient had bilateral oligodactyly with absent fifth toes (Giuliano et al. 2003). Hypoplastic toenails were observed sporadically. In some patients the nails are flattened and have an appearance similar to that seen when there has been oedema in utero.

A degree of body disproportion and asymmetry has been observed in a high percentage of cases, with or without vascular compromise of the involved region (Table 1). Joints may be hyperelastic with a tendency to subluxation in some occasions. Hip dysplasia was reported in a small number of cases.

Thorax and abdomen

Complex cardiac malformations were described in two cases (Clayton-Smith et al. 1997, Giuliano et al. 2003), a ventricular septal defect (VSD) in another and a dilated aortic root in further children (Moore et al. 1997, Nyberg et al. 2005). Akcar et al. (2004), reported a child with an atrial septal defect and a giant atrial septal aneurysm, and Giuliano et al. (2003) reported a further patient with an atrial septal defect (ASD). Cardiac arrhythmias such as atrial flutter or supraventricular tachycardia have been observed and are often life-threatening situations requiring intervention. (Clayton-Smith et al. 1997, Giuliano et al. 2003, Yano and Watanabe 2001). Mesenteric angina was reported by Howells et al. (Howells et al. 2000), and intestinal lymphangiectasia and atrophic abdominal aorta by others (Megarbané et al. 2003, Thong et al. 1999). Unlike other overgrowth syndromes, enlargement of the liver, spleen or kidneys are not often seen.

M-CMTC and Tumours

A total of four patients with M-CMTC have developed tumours (acute leukemia, meningioma, Wilms tumour and retinoblastoma) (Lapunzina et al. 2004, Moore et al. 1997, Schwartz et al. 2002). The boy with retinoblastoma reported by Schwartz et al. (2002) did not have the typical characteristics of M-CMTC however and might be an atypical case. One patient was found to have a frontal perifalcine mass resembling a meningioma at age 5 years in one study (Conway et al. 2008). Although the number of patients with M-CMTC currently reported is low and the types of neoplasia seen so far are heteroge-

neous, the putative 5–6% tumour risk appears to be similar to other overgrowth syndromes (Cohen 1989, Lapunzina 2005, Lapunzina et al. 1998). Thus it has been recommended that patients with this syndrome should have regular screening for tumours (Lapunzina 2005) and this will be discussed in more detail below.

Pathogenesis and molecular genetics

The cause of M-CMTC is not known. All cases reported to date have been sporadic. There is a slight preponderance of males but this is not statistically significant (M:F = 42:34). No affected parents or siblings have been observed but increased paternal age has been noted in several cases. All these data would seem to support an autosomal dominant pattern of inheritance with the condition arising due to a new dominant mutation. The parents of patient 4 of Vogels et al. (1998) were consanguineous (second cousins) with otherwise unremarkable family history and the parents of the patient of Berbel Tornero et al. (1999) were first cousins of Gypsy ancestry (an ethnic group with a high degree of consanguinity). Clayton-Smith et al. (1997) suggested that some of the clinical findings of this disorder such as patchy vascular markings of the skin, asymmetry, and occasional pigmented skin lesions which follow Blaschko's lines might be due to somatic mosaicism. Chromosome anomalies have been observed in three patients with M-CMTC; mosaicism in skin fibroblasts (diploidy/tetraploidy; 92, XXXY [2]/46, XY [17]) in one patient was reported by Bottani et al. (2000). Skin fibroblast chromosomes from other patients failed to confirm any similar alteration (Lapunzina et al. 2004). The other chromosome abnormalities were a 16q deletion in a girl (Cristaldi et al. 1995) and recently, an apparently balanced translocation 2:17 (p11; p13) (Stoll 2003). Although the latter may be significant the t(2; 17) could be purely coincidental or due to culture artefact. Data of the 16q deletion in the report by Cristaldi et al. (1995) is scant and unfortunately no breakpoint on 16q is given and molecular studies were not done. Thus, a cryptic balanced translocation was not excluded and the significance of this finding remains unclear. The cause of M-CMTC thus remains elusive but will probably be elucidated as further patients are described (Lapunzina et al. 2004).

Diagnosis and diagnostic criteria

Diagnosis must be based on clinical findings as no molecular defect has been defined so far. The clinical findings observed in the majority of patients are listed in Table 1. Major and minor criteria of M-CMTC were set forth by Franceschini et al. (2000) who suggested that the diagnosis could be made in the presence of: a) macrocephaly and at least two other findings such as b) cutis marmorata, overgrowth, capillary malformation, syndactyly or asymmetry. Other groups have proposed similar criteria (Baralle and Firth 2000, Yano and Watanabe 2001), suggesting that the diagnosis should be sustained on the presence of macrocephaly and at least two of the following findings: overgrowth, cutis marmorata, capillary malformation, polydactyly/syndactyly and asymmetry. Robertson et al. (2000) have laid down more stringent criteria. They suggested as major criteria the presence of: congenital macrocephaly and CMTC and in addition at least 4 of the following findings: neonatal hypotonia, developmental delay, connective tissue defect, frontal bossing, midline facial nevus flammeus, cutaneous toe syndactyly, segmental overgrowth and hydrocephalus. With a condition such as M-CMTC where the spectrum of problems is broad, more stringent criteria might exclude milder cases which could provide useful clues to the aetiology of the condition. On the other hand, the less stringent criteria may not be restrictive enough. Only when the underlying genetic basis is identified will it be possible to validate the different sets of diagnostic criteria suggested.

Abnormalities have been identified prenatally in several patients when macrocephaly, macrosomia, limb asymmetry, hemimegalencephaly, polyhydramnios, ascitis and/or pleural effusions were observed (Moore et al. 1997, Nyberg et al. 2005, Robrtson et al. 2000, Vogels et al. 1998) Elevated maternal serum alpha fetoprotein was observed one one occasion (Robertson et al. 2000). It is difficult to make a

firm diagnosis of M-CMTC prenatally, however, as the characteristic skin signs, one of the diagnostic hallmarks of the condition, cannot be visualised.

Differential diagnosis

Differential diagnosis includes other disorders with overgrowth/macrocephaly (Barnicoat et al. 1996, Cohen et al. 2002, Lopez-Herce Cid et al. 1985, Meyer 1979, Mofitt et al. 1999, Ringrose et al. 1965) such as Beckwith Wiedemann syndrome, Simpson Golabi Behmel syndrome, Sotos syndrome, Perlman syndrome, Proteus syndrome, Costello syndrome and Bannayan–Zonana syndrome. Disorders with skin vascular malformations and asymmetry such as Klippel–Trenaunay, Parkes Weber must also be considered. M-CMTC may be easily diagnosed when the full phenotype, characteristic features and typical *gestalt* are present.

Prognosis and follow-up

Long-term prognosis is usually determined by the neurological (Giuliano et al. 2003) and cardiac mani-

Table 2. Management Plan For A Child With M-CMTC

Age	Problem	Health Check/Investigation
At Birth	Macrocephaly/overgrowth	Plot baseline growth parameters
	Structural heart defects	Echocardiogram
	Cardiac arrhythmia	ECG
	Internal vascular malformations	Abdominal ultrasound scan Brain imaging
	Hip dysplasia	Ultrasound scan hips
0–12 months Paediatric follow-up at monthly intervals for first three months, then three monthly	Ventriculomegaly	Plot OFC monthly Monthly neuro examination Refer neurosurgeon if excessive increase or signs of raised intracranial pressure
	Predisposition to malignancy	3 monthly abdominal ultrasound examination
	Ophthalmological	Formal ophthalmological examination
	General	Monitor growth and development with physiotherapy/occupational therapy referral as appropriate Regular vision and hearing checks
Early childhood	Predisposition to malignancy	3 monthly abdominal ultrasound scans until age 5
	General	Six monthly paediatric assessment with abdominal and neuro examinations Offer genetic referral
	Developmental problems	Formal developmental assessment at 12 months. Early intervention programme
	Hemihypertrophy	Refer to orthopaedic surgeon if significant leg length discrepancy
5–10 years	General	Monitor growth and development 6–12 monthly Regular vision and hearing checks
	Developmental problems	Pre-school assessment of special educational needs
10 years plus	General	Annual health check with general examination
	Developmental problems	Review educational needs on a regular basis

festations. There is almost always some degree of mental impairment, ranging from mild to severe. About half of the patients need a ventricular shunt for treatment of hydrocephalus. Some children can attend normal school, but in general almost all of them will need support and a special educational program. An ECG, together with neurological and cardiac evaluations are recommended for all patients with M-CMTC due to the fact that some patients have had life-threatening arrhythmias. It is not clear whether or not these children need to enter a tumour surveillance program. It has been suggested recently that regular physical examination, abdominal and renal ultrasound and AFP analysis should be carried out (Lapunzina 2005). This recommendation is empirical and more patients need to be followed up for a longer period of time before it can be validated. Table 2 summarises the management plan for a child with M-CMTC.

It is clear from the patients reported so far that there is a great deal of variability between patients with M-CMTC. This should be borne in mind when discussing the diagnosis with the parents, emphasising that perhaps the best guide to determining the prognosis for an individual child, after ruling out any significant medical complications, is observation of the child's progress during the first years of life.

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