Chapter 15
Cutis Marmorata Telangiectatica Congenita (Van Lohuizen's Syndrome)

Christos P. Panteliadis

Contents

Introduction

Cutis marmorata telangiectatica congenita (*CMTC*) is a rare, sporadic congenital disorder with local or generalized cutaneous vascular anomalies (slow-flow lesions) of unknown etiology. The disease was first described in 1922 by *van Lohuizen* [1], and in 1970, *Petrozzi* et al. reported the first case of CMTC in America [2]. CMTC has been referred in the literature under several different terms, including congenital generalized phlebectasia, nevus vascularis reticularis, congenital phlebectasia, congenital livedo reticularis, and van Lohuizen's syndrome [3]. Concerning the etiology, *Happle* suggested the concept of an autosomal lethal mutation surviving through mosaicism [4]. More recent studies identified *GNA11* mutations in skin biopsies from CMTC-affected skin areas, proposing a postzygotic mosaic condition. Further, autosomal recessive inherited homozygous mutations of the *ARL6IP6*

C. P. Panteliadis (✉)
Department of Paediatric Neurology and Developmental Neurology, Aristotle University of Thessaloniki, Thessaloniki, Greece
e-mail: cpanteliadis@hotmail.gr

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gene have been described in CMTC patients [5], the impact of which, however, is not clear.

CMTC usually presents at birth with persistent cutis marmorata, vascular telangiectasia, and, occasionally, ulcers [6, 7]. Ocular lacy capillary anomalies with prominent terminal bulbs observed in CMTC have not been described in other syndromes of vascular dysgenesis [8]. The ocular manifestations present at birth or during the first year of life. Other associated alterations include musculoskeletal and vascular abnormalities, cardiac defects, neurological defects, body asymmetry (difference in leg length), and anomalies of the gastrointestinal and genitourinary system [5].

Clinical Characteristics

Cutis marmorata telangiectatica congenita (*CMTC*) is a rare malformation characterized by persistent reticulated marbled erythema and tends to be associated with cutaneous atrophy, ulcerations, and body asymmetry. The vascular malformation comprises a network of capillary and venous-sized vessels, resulting in patchy bluish marbling, livedo-like discolorations of the skin that may involve large parts of the body. The discoloration may be enhanced in cold environment or become pale on palpation [9]. A recent case reported by *Khambati* et al. [10] exemplified the phenotype in a girl born with flat purple patches over the right leg and arm and small faded markings over the buttock and leg. The presence of a reticular erythema, generalized or localized in a specific area or limb, is pathognomonic of CMTC [11].

CMTC is classified as a simple vascular malformation and subclassified as a capillary malformation (*CM*) by the International Society for the Study of Vascular Anomalies (ISSVA). *Bui* et al. [5] reviewed 485 cases of CMTC, 206 (42.5%) of whom showed associated anomalies, 146 patients (30%) had no associated anomalies, and the remaining 133 patients (27.5%) did not have this information. The most frequent anomaly was body asymmetry (37.7%), which included asymmetry of the limbs, trunk, and face as a result of either hypertrophy or hypotrophy. The second most frequent associated alterations (10.1%) related to neurological defects, followed by ophthalmological complications in 9.9% of patients, half of which were congenital glaucoma. Furthermore, 5.2% had cardiovascular defects, 4.5% had Mongolian spots, 3.3% had dysmorphic features, 2.5% had genitourinary defects, and 1.0% had endocrinological defects.

The plethora of CMTC-associated alteration results in very diverse phenotypes of CMTC. The typical vascular alterations of CMTC may occur in combination with vascular streaks of the lips and philtrum, hemangioma, or port-wine stain or even in association with other vascular syndromes, like in a patient with Sturge-Weber syndrome, facial infantile hemangioma, and cutis marmorata telangiectatica congenita [12]. The affected cutaneous areas may develop cutaneous atrophy and ulcerations. The extracutaneous findings in 20–80% of cases include ocular and

neurological abnormalities [6, 13, 14]. The latter alterations comprise mental retardation, seizures, macrocephaly, cerebral atrophy, arteriovenous malformation of the brain, hydrocephalus, corpus callosum agenesis, hemispheric vascular anomaly, hearing impairment, microcephaly, and various occlusive vascular conditions like transient ischemic attack or porencephaly [5]. Malformations and dysmorphic features of the body seen in CMTC are syndactyly, renal hypoplasia, *Kartagener's* syndrome, micrognathia, hypertelorism, frontal bossing, low-set ears, club foot, and cleft palate among others [5].

Diagnosis

Kienast and Hoeger [13] published the diagnostic criteria for CMTC, which comprise three major criteria and five minor criteria, of which at least two have to be fulfilled. The major criteria are as follows:

- Congenital reticulate (marmorated) erythema
- Absence of varicosity (*venectasia*)
- Unresponsiveness to local warming

The minor criteria include the following:

- Fading of erythema within 2 years
- Telangiectasia
- Port-wine stain outside the area affected by CMTC
- Ulceration
- Atrophy

However, these diagnostic criteria have not been validated. According to *Lunge and Mahajan* [15], these criteria are sufficient for the diagnosis of CMTC. Diagnosis is based on clinical features that frequently are obvious even at birth [3, 16, 17].

Reticular erythema presenting at birth is a common finding in all reported cases and therefore was considered a major criterion for CMTC. Further, absence of venectasia in the affected region of cutis is a very important finding in differentiating CMTC from *Klippel-Trenaunay-Weber* syndrome (see Chap. 9).

Macrocephaly-cutis marmorata telangiectatica congenita is a recently recognized syndrome described mainly in the genetics literature. It denominates an association of the dermal vascular malformation with macrocephaly, dysmorphic facies, seizures, and body asymmetry affecting the face and limbs [18].

Another extremely rare variation comprises cutis marmorata telangiectatica congenita characteristics associated with hemiatrophy. Hemiatrophy refers to wasting or loss of tissue on one side of the body, possibly resulting from an intrauterine insult. In a recent report, *Leung* et al. [19] described two cases of this condition and found eight further cases in the literature using the key terms "cutis marmorata telangiectatica congenita" and "hemiatrophy."

Therapy

Therapy is mainly geared toward treating the symptoms of glaucoma, seizures, and bony defects.

Complete ophthalmologic evaluation, including measurement of intraocular pressure, gonioscopy, dilated fundus examination, and fluorescein angiography, is recommended in infants with suspected CMTC shortly after birth [3, 8]. Psychological support and physiotherapy prove invaluable to both the child and the family members. Follow-up examination includes continued screening for associated major and minor anomalies. The prognosis in uncomplicated cases is good.

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