Vascular malformations are defined as developmental anomalies, probably caused by dysregulation in signalling that regulates proper formation of the vascular tree. They consist of abnormal vessel channels lined with quiescent endothelium [1]. There are hereditary vascular malformation syndromes caused by single gene mutations and congenital sporadic variants (Table I). The latter are generally considered to be the consequence of mutations that can only survive in a mosaic context and can be accompanied by growth disturbances of soft or skeletal tissue. The abnormalities can vary widely in extent and severity giving rise to diagnostic and classification problems, which in turn complicates scientific communication and research. Many authors have attempted to create order in this apparent chaos, some by proposing a classification based strictly on anatomical/histological or functional terms and map the extent of the disease, rather than name it according to the eponymous classification.

**Key words:** Klippel-Trenaunay syndrome, Sturge-Weber syndrome, Vascular malformations, Mosaicism, Lethal gene theory

**Case report**

A 28 year old woman of Dutch descent with mild psychomotor retardation was referred to our department because of a non-healing ulcer on the medial side of her left ankle. It had existed for almost a year. Furthermore we noticed that the patient had widespread congenital capillary malformations on her face. At birth her family noticed that she had several areas of redness of the skin. No further data are available regarding her birth. She first came to medical attention at age 6 years for asymmetric development of the legs. She underwent an epiphysiodesis of the left tibia and fibula at the age of 12 years, and an osteotomy of the proximal part of the left tibia 2 years later. Short complex partial seizures occurred at the age of 6 years and seizures were successfully treated with valproate. A leptomeningeal dysplasia at the level of the right occipital lobe was...
diagnosed at the age of 8 years old. A skull radiograph made at that age revealed gyrated (“tram-line”) intracranial calcification in the parieto-occipital region (Fig. 1d). A CT-scan made at the age of 12 years revealed cortical atrophy of the right parieto-occipital region and slightly dilated ventricles. A cerebral MRI, made at the age of 29 years, showed cortical atrophy in the right parieto-occipital region with leptomeningeal dysplasia and an ipsilateral enlarged choroidal plexus; the right sinus transversus and sinus sigmoides were hypoplastic (Fig. 2). Glaucoma of the right eye occurred at the age of 11 years. Laser treatment has diminished the extent and redness of the capillary malformation over the face (Figs. 1b-c). The family history was unremarkable. A physical examination at the time of referral showed capillary malformations with telangiectasias over the left leg and buttocks as well as the back, chest and face. We noticed heterochromia of the irises and soft tissue hypertrophy of her lower lip (Figs. 1a-c). A clean sharply demarcated ulcer was present on the left medial malleolus. A varicose vein, probably a persistent marginal vein, was present on the lateral side of the left leg. There were no clinical signs of deep venous insufficiency. The left leg was longer than the right leg by 2 cm and had a larger circumference. Apart from a small left sided visual field defect, neurological examination revealed no obvious defects.

Discussion

The patient we describe above has a complex congenital syndrome of vascular malformations with several internal abnormalities of the brain combined with bone and soft tissue hypertrophy of one leg. According to the eponymous classification, this patient would meet the criteria for Klippel-Trenaunay syndrome as well as for the Sturge-Weber syndrome [4]. The use of eponymous classifications is of little use for complex abnormalities such as the one described here. Indeed, this case, and several others in the literature, show abnormalities not limited to a single region. Therefore such eponymous classification becomes untenable, and should be replaced by a description that does justice to the complexity of the disease phenotypes.

Table I. Classification of vascular malformations based on anatomical/histological and hereditary criteria [1, 2].

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>*Cerebral cavernous malformation. (capillary venous malformation)</td>
<td>isolated. Cutaneous (arterio)venous malformation *Non-cutaneous vascular malformations without associated symptoms</td>
<td>Proteus syndrome: *Partial gigantism of hand/or feet *Hemihypertrophy, macrocephaly *Subcutaneous nodular vascular malformations.</td>
</tr>
<tr>
<td>*Venous malformation</td>
<td>-associated/combined with tissue abnormalities. Vascular malformations with soft tissue hyper/hypotrophy and bone abnormalities.</td>
<td></td>
</tr>
<tr>
<td>*Glomuvenous malformation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Hereditary hemorrhagic telangiectasia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Congenital lymphedema</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Lymphedema praecox</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Lymphedema with diastichi.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In 1987, Happle postulated a concept for the genetic basis of sporadic congenital abnormalities with capillary malformations [13, 14]. The phenomenon that one organism is composed of two or more genetically different cell populations derived from a genetically homogeneous zygote is called mosaicism [15]. These sporadic congenital abnormalities share a few striking characteristics. First, they are, with rare exceptions, not hereditary; second, the skin lesions are distributed over the body in a mosaic pattern and may follow the lines of Blaschko; third, the extent of the disorder varies on a per case basis; Fourth, only part of the body is affected; finally, women and men are affected equally [13, 14].

The “lethal gene” theory can explain the overlap and complexity of these phenotypes. During embryogenesis, a lethal autosomal mutation can occur in a genetically homogeneous zygote. This lethal mutation is usually followed by death of the zygote [16]. However, cells carrying a lethal mutation can survive in the proximity of normal cells. The phenotype and extent of the anomalies is dependent on the moment of mutation in embryogenesis and where the mutated cells end up [13-15].

In Table I we classify vascular malformations according to the Mulliken classification with some additions referring to clinical characteristics. The differential diagnosis comprises other congenital disorders with vascular malformations, such as Proteus and Mafucci/Ollier syndrome. These entities are regarded as a spectrum of complex vascular (capillary, venous, arterial, lymphatic anomalies and combinations) anomalies with a great variability of symptoms, which sometimes complicate differential diagnosis. Therefore it is of utmost importance to carefully map the symptoms and their extent, in patients suffering from vascular malformations [17]. Furthermore this case illustrates the necessity of a careful follow-up of these vascular malformations by a multidisciplinary team in order to prevent complications.

In conclusion, this case shows that a classification scheme based on a rigid subdivision of the body in single areas with subsequent assignment to an eponymous category does not further contribute to more insight into the pathophysiology. The lethal gene theory and the influence
Figure 1a-d. Figure 1a shows the back and legs of the patient. The capillary malformations follow the lines of Blaschko in a mosaic pattern. Figure 1b shows capillary malformations at the age of 6 years over the face and trunk. Also note heterochromia of the irises. Figure 1c shows that at the age of 29 years heterochromia of the irises is more pronounced. Furthermore the patient developed hypertrophy of the lower lip. As a result of laser therapy the capillary malformations over the face are less widespread. The skull radiograph in figure 1D shows gyrated intracranial calcifications in the parieto-occipital region.
of mosaicism can better explain the overlap and diversity of these congenital vascular syndromes.

References


