Hereditary Hemorrhagic Telangiectasia
Neurovascular Phenotypes and Endovascular Treatment

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Abstract
Hereditary hemorrhagic telangiectasia (HHT) is inherited as an autosomal dominant trait with varying penetrance and expressivity. Some of the most devastating consequences of this disease result from cerebral vascular malformations that manifest themselves in either arteriovenous fistulae (AVF), small nidus-type arteriovenous malformations (AVM) or micro-AVMs with a nidus less than 1 cm in size. HHT displays an age-related penetrance of clinical manifestations: fistulae become symptomatic in early childhood, whereas AVMs are typically encountered in older children and young adults. Micro-AVMs in the HHT population did not bleed and were asymptomatic incidental findings in affected patients. Since members of the same family can present with completely different phenotypes of this disease, there seem to be no relationship between the type of mutation and the phenotype of the disease. There seem to be a continuum of vascular abnormalities (from large fistulous areas to small AVMs and micro-AVMs) associated with HHT, most likely being determined by the timing of the revealing event in relation to the maturity of the vessel. Presumably, the trigger of the quiescent genetical abnormality transforms a “dormant” disease into a morphologically and therefore clinically detectable one by impairing a specific vessel segment at a specific (more or less vulnerable) period of time. The nature of this triggering event is, however, yet unclear. Embolization employing superselective glue injection results in a high occlusion rate, esp. in AV fistulae. Since the natural history of neurovascular manifestations of HHT especially in children is associated with high morbidity and mortality, therapeutic intervention is mandatory. In most instances a morphological target can be identified; therefore, even partial and staged treatment can be performed. The endovascular approach employing glue as the embolizing agent represents a safe and efficient way to control the neurovascular phenotypes of HHT.

Key Words: Hereditary hemorrhagic telangiectasia · Rendu-Osler-Weber disease · Cerebral arteriovenous malformation · Cerebral arteriovenous fistula · Glue embolization

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Hereditäre hämorrhagische Teleangiektasie. Neurovaskuläre Manifestationen und endovaskuläre Therapie

Zusammenfassung
Die hereditäre hämorrhagische Teleangiektasie (HHT) ist eine autosomal dominant vererbte Erkrankung mit variabler Penetranz. Einige der klinisch bedeutsamsten Konsequenzen dieser Erkrankung erwachsen aus den neurovaskulären Manifestationen, bei denen man verschiedene Phänotypen nachweisen kann. Das Ziel dieser Arbeit ist es, die unterschiedlichen neurovaskulären Manifestationen der HHT zu typisieren und die therapeutischen Behandlungsoptionen darzulegen. Neurovaskuläre Manifestationen der HHT sind die spinalen arteriovenösen Fisteln (AVF), die zerebralen AVF, die „klassischen“ nidusförmigen glomerulären arteriovenösen Malformationen (AVMs) und die Mikro-AVMs (Nidus unter 1cm Größe, ohne verfrühte venöse Drainage). Während die Fisteln (sowohl spinal als auch zerebral) vor allem in der pädiatrischen Population symptomatisch wurden, wurden die glomerulären AVMs und Mikro-AVMs erst im späten Jugendalter und frühen Erwachsenenalter diagnostiziert. Die Phänotypologie der HHT ist variabel und scheint nicht mit der spezifischen Mutation

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Hereditary Hemorrhagic Telangiectasia (HHT) was first recognized in the 19th century as a familial disorder causing nosebleeds, gastrointestinal bleeding, and abnormal vascular structures. The combination of these clinical findings with iron deficiency anemia, characteristic telangiectasia on the lips, oral mucosa, and fingertips has become firmly established as a medical entity named Rendu-Weber-Osler disease or HHT. Yet this clinical scenario constitutes only one of the presentation patterns of HHT, and may not be evident in HHT patients who still have life threatening manifestations of disease. It is now recognized that, in addition to the above mentioned microscopic mucocutaneous telangiectasias derived from post capillary venules, HHT can also lead to the development of abnormal vascular structures at other sites. Arteriovenous malformations in the pulmonary, cerebral, and hepatic circulations account for some of the most devastating clinical complications of the disease.

HHT has been subject to under-reporting for many years. Recent careful epidemiological studies in France, Denmark, and Japan, however, reveal an incidence of one in 5–10,000 [1–3]. It is now estimated that at least 30% of HHT patients have pulmonary involvement [4], 30% hepatic involvement [5], and 10 to 20% cerebral involvement [6]. Therefore, this disease should and can not longer be regarded as a “rare” disease, and physicians dealing with patients suspected of having HHT should be aware of the possibly life-threatening clinical manifestations of HHT.

Pathophysiology
HHT is inherited as an autosomal dominant trait with varying penetrance and expressivity. Heterozygotes account almost exclusively for the patient population. Mutations in at least two genes, endoglin and activin receptor-like kinase (ALK) 1, have been shown to be responsible for HHT, with the disease subtypes designated HHT1 and HHT2, respectively [7–11]. Both, endoglin and ALK 1 play distinct roles in the transforming growth factor-beta (TGF-b) signaling pathway. The TGF-b superfamily of ligands are structurally related polypeptides that play roles in a number of different biological processes including cell cycle control, embryogenesis, growth, development, differentiation of several cell types, immunosuppression and embryonic patterning signaling [12]. Moreover, they are potent angiogenic factors and mediators of vascular remodeling as they control extracellular matrix production by endothelial cells, smooth muscle cells and pericytes [7]. Both, ALK 1 and endoglin are expressed primarily in endothelial cells [13], and both can bind TGF-b molecules to influence the process of angiogenesis. Endothelial cells lacking functioning endoglin or ALK 1 show an altered response to TGF-b and, therefore, form abnormal vessels and abnormal connections between vessels [7]. It has to be emphasized, that the target of the dysfunction in HHT are not the arteries, but the venules instead [10, 11].

The most likely determinating factor of the HHT phenotype is the maturity of the vessel and, to understand HHT, one has therefore to look at the role, endoglin and ALK 1 play in angiogenesis.

Angiogenesis can be viewed as two separate, but balanced phases: activation and resolution [12, 14]. During activation, a pro-angiogenic trigger results in increased permeability in the endothelial cell layer, degradation of the basement membrane, and formation of endothelial sprouts. Cell division behind this migrating front enables further invasion into this space. Lumen formation then proceeds from the proximal region of the sprout. During the resolution phase the above processes are terminated and the vessel maturation is completed. Termination involves a halt of endothelial cell proliferation and migration. The basement membrane which was degraded initially, is reconstructed around the new vessel, and the endothelial junctional complexes are reformed. The shift between the two phases is known as the angiogenic