J Neurol (2008) 255:77–88
DOI 10.1007/s00415-008-0675-3

ORIGINAL COMMUNICATION

Hereditary Systemic Angiopathy (HSA) with cerebral calcifications, retinopathy, progressive nephropathy, and hepatopathy

D. T. Winkler
P. Lyrer
A. Probst
D. Devys
T. Haufschild
S. Haller
N. Willi
M. J. Mihatsch
A. J. Steck
M. Tolnay

Received: 8 January 2007
Received in revised form: 14 May 2007
Accepted: 6 June 2007
Published online: 22 January 2008

D. T. Winkler, MD, PhD · P. Lyrer, MD · A. J. Steck, MD
Dept. of Neurology
University Hospital Basel
Petersgraben 4
4031 Basel, Switzerland

D. T. Winkler, MD, PhD · A. Probst, MD · M. J. Mihatsch, MD · M. Tolnay, MD
Dept. of Neuropathology
Institute of Pathology
University Hospital Basel
Petersgraben 4
4031 Basel, Switzerland

D. Devys, MD, PhD
Institut de Génétique et de Biologie Moléculaire et Cellulaire
CNRS/INSERM/ULP
B.P. 10142
67404 Illkirch Cedex
CU de Strasbourg, France

T. Haufschild, MD
University Eye Clinic
University Hospital Basel
Petersgraben 4
4031 Basel, Switzerland

S. Haller, MD
Dept. of Neuroradiology
Institute of Radiology
University Hospital Basel
Petersgraben 4
4031 Basel, Switzerland

N. Willi, MD
Cantonal Institute of Pathology
Mühlemattstrasse 22
4410 Liestal, Switzerland

M. Tolnay (✉)
Institute of Pathology
University Hospital Basel
Schönbeinstrasse 40
PO Box
4031 Basel, Switzerland
Tel.: +41-61/265-2896
Fax: +41-61/265-3194
E-Mail: mtolnay@uhbs.ch

Abstract Several hereditary conditions affecting cerebral, retinal and systemic microvessels have recently been described. They include CADASIL, CRV, and HERNS. We here report on a variant form of a hereditary systemic angiopathy (HSA) affecting two generations of a Caucasian family. Clinical symptoms of HSA appear in the mid-forties and are characterized by visual impairment, migraine-like headache, skin rash, epileptic seizures, progressive motor paresis and cognitive decline. Late symptoms include hepatic and renal failure. Retinal capillary microaneurysms and arteriolar tortuosity are associated with marked optic disc atrophy. Radiological hallmarks consist of multiple cerebral calcifications and tumor-like subcortical white matter lesions. Brain, peripheral nerve, muscle, kidney and colon biopsies have revealed a multi organ small vessel involvement with partly altered endothelium, perivascular inflammation and thrombotic microangiopathy.

No curative therapeutic options are known for hereditary cerebral vasculopathies. The use of cyclophosphamide, azathioprine and methotrexate was of no benefit in our cases of HSA. Early diagnosis of hereditary systemic angiopathies is important in order to prevent patients from repetitive invasive diagnostic measures and to avoid the use of inappropriate and potentially harmful drugs.

Key words angiopathy · vasculopathy · cerebral calcification · small vessel disease · HERNS · CRV · HVR · CADASIL

JON 2675

Abbreviations

HSA	hereditary systemic angiopathy
ADAMTS	a disintegrin-like and metalloproteinase with thrombospondin motifs
CADASIL	cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CARASIL	cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy
CRV	cerebroretinal vasculopathy
HERNS	hereditary endotheliopathy with retinopathy, nephropathy, and stroke
HIHRTL	hereditary infantile hemiparesis, retinal arteriolar tortuosity, and leukoencephalopathy
MELAS	mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes
vWF	von Willebrand factor

Introduction

Several hereditary small vessel diseases have recently been described. CADASIL is the prototypical example of a hereditary systemic small vessel disease and remains the only one which has been genetically characterized [9]. Other conditions with small vessel pathology include CARASIL [29], HERNS [7], CRV [5, 28], HVR [17, 23, 25], HIHRTL [27] and a recently described syndrome with leukoencephalopathy, cerebral calcifications, and cysts [10, 14]. HERNS, CRV and HRV have been linked to chromosome 3p21.1–3p21.3 [17] and may therefore have a common genetic origin. Interestingly, migraine-like headaches have been reported in most hereditary small vessel diseases, but little is known about the mechanisms underlying this association.

We here report on a three generations family in which affected members developed a variant form of a hereditary systemic angiopathy (HSA) with partly occluding sclerosis of brain microvessels, perivascular inflammation, cerebral calcifications and pseudotumoral brain lesions. The vessel pathology was compatible with a thrombotic microangiopathy and endotheliopathy, which was likely to be responsible for the elevation of vWF factor. The HSA we describe shares clinical and pathological features with other hereditary small vessel diseases such as HERNS, CRV and HVR but exhibits additional traits such as extensive cerebral calcification, perivascular inflammation and progressive hepatic and renal failure which sets it apart from previously reported families with hereditary small vessel disease.

Clinical, radiological, histopathological and genetic findings

Patients

Data have been collected from five members of a three generations Caucasian family. Three subjects of two generations have been analyzed in details (Fig. 1). They presented clinical evidence of a severe progressive CNS-disorder that was recognized as a hereditary syndrome. Clinical, radiological and histological data are summarized in Table 1. Informed consent was obtained from the subjects or next of kin for DNA samples collected and neuropathological studies performed.

Subject I/2 (see pedigree)

Only limited clinical data on this subject were obtained. The patient committed suicide at the age of 28 after a short history of mood-disorder, which led to psychiatric exploration. The patient's husband lived healthy up to the age of 70, at which he died from leukemia.

Patient II/1

K.B. 1924–1982, male. This toolmaker noted first minor visual disturbances at the age of 41. Ophthalmologic

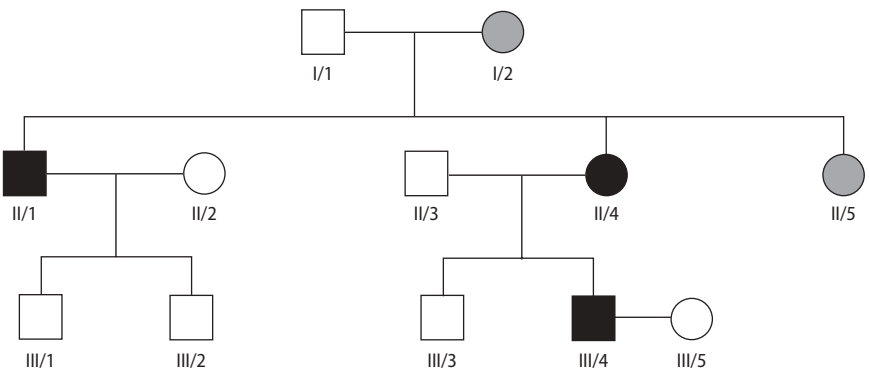

Fig. 1 Pedigree of the family. Black symbols indicate documented HSA with clinical, brain imaging and/or bioptic evidence of HSA in the 2nd generation and actual diagnostic work-up in the 3rd generation. Grey symbols indicate subjects with suspected HSA.

Table 1 Overview on clinical and radiological findings in our HSA patients

Patient	II/1	II/4	III/4
Age at onset	± 40	± 40	± 35
Initial symptoms	visual impairment	migraine, psychiatric disturbances	chronic diarrhea, migraine
Age at death	58	48	44
Migraine	Ø	+++	++
Epileptic seizures	Ø	+++	+++
Progressive motor paresis	++	++	++
Cognitive decline and psychiatric disturbances	+++	+++	+
Cerebral calcifications	+++	+	+++
Subcortical infarcts	+	+	+
Retinopathy	++	+	++
Myopathy	Ø	Ø	++
Hepatopathy	–	++	+++
Nephropathy	–	+	++
Enteropathy	Ø	–	++

– = absent; Ø = not reported; + = present; ++ = moderate finding; +++ prominent sign

investigation at the age of 52 documented a central scotoma on the left and marked atrophy of optic discs. Fluorescein angiography revealed multiple capillary aneurysms and increased tortuosity of the vessels in the posterior pole of both eyes. At the age of 54, mild memory deficits, diffuse weakness of both legs and impaired balance were noted. Neurological examination at the age of 56 showed left central facial palsy, mild weakness of the left arm, brisk tendon reflexes on the left (3+) and stooped posture as he walked. Multiple cerebral calcifications were seen on CT scan and were attributed to a progressive encephalopathy of unknown vascular origin. Cerebrospinal fluid cell count and protein level were normal. One year later, the patient presented confused and required permanent supervision at home. Meanwhile bilateral loss of vision with pale optic discs had occurred. Left side muscle tone was increased and his gait was slow and uncoordinated. He died at the age of 58. Autopsy was not performed.

Patient II/4

L.H. 1929–1978, female. Chronic progressive headache at the beginning of her 5th decade of life was followed by mental decline, emotional lability and major depressive episodes. She was admitted to a psychiatric clinic because of stupor at the age of 48. First generalized epileptic seizures occurred one month later. Aphasia, apraxia, partial optic atrophy in the right eye and motor hemiparesis on her right side were noted in our neurological clinic. A fronto-parietal solid tumor-like lesion was biopsied and glucocorticosteroids were given to reduce the cerebral edema. This was followed by an almost complete recovery of the hemiparesis and a clinically stable period of a few months. Thereafter, seizure incidence increased and her clinical condition deteriorated with severe aphasia, partial gaze palsy to the right, right central facial palsy and worsening of her right spastic hemiparesis. Laboratory findings furthermore revealed a progressive cholestatic hepatopathy. The patient died nine months after her first admission to the hospital from a hypovolemic shock after an episode of melena. No autopsy was performed.

Subject II/5

Limited data were available on this subject. According to family members, this woman was hospitalized in a psychiatric institution due to a mental disorder. Thereafter, contact with her relatives was lost.

Patient III/4

P.H. 1960–2005, male. This salesman suffered from chronic migraine-like headaches since his late 30's. Episodic oral aphtous lesions and chronic severe diarrhea occurred. The presence of anti-gliadin antibodies suggested celiac disease, which was supported by the findings of a duodenal biopsy. Strict diet nevertheless remained without clinical improvement. Mild muscular weakness was known since childhood. At the age of 39, the patient presented with a progressive weakness of his left leg with a paresis of the left peroneal and tibial muscles. Electromyography showed myopathic changes and an ischemic forearm exercise test revealed slightly increased lactate levels. One year later, the patient complained about numbness in the territory of the ophthalmic and maxillary branches of the right trigeminal nerve. Brain MRI revealed multiple bihemispheric white

matter lesions. CSF was normal. Soon thereafter, the patient experienced a sudden loss of vision of the right eye. Ophthalmologic examination stated a pale left papilla and marked reduction of blood flow in the inferotemporal region as a result of vascular occlusion. Fluorescein angiography revealed reduced perfusion in the temporal half of the macula (Fig. 2). Shunt vessels and slight leakage were seen in the late phase. Few months later, a severe attack of headaches was followed by a sensorymotor left hemiparesis. Cranial CT showed a tumor-like fronto-temporal mass on the right side and multiple small subcortical calcifications. Parathormone levels were normal. Stereotactic brain biopsy revealed a severe fibrosis of small vessels with perivascular inflammation. Biventricular cardiopathy with decreased cardiac output progressive hepatopathy, intestinal malabsorption with persistent, therapy-refractory diarrhea and an intermittent pleural effusion were diagnosed. A renal biopsy was taken due to chronic renal failure. Liver enzymes (alanine aminotransferase, aspartate aminotransferase, gamma-glutamyltransferase, alkaline phosphatase) and plasma creatinine were progressively increasing. Negative titers were measured for rheumatoid factors, antineutrophil cytoplasmic antibodies, anti-DNS-antibodies, anti-extractable nuclear antigens antibodies (Sm, RNP, SSA, SSB, Scl-70, Jo-1, histones, centromere), anti-cardiolipin-IgM and -IgG. Nevertheless, a connective tissue disease with multi-organ involvement was suspected. The patient underwent immunosuppressive treatment with steroids and cyclophosphamide, which after two months was replaced by azathioprine. Because of continuous deterioration, immunoglobulins were given intravenously, followed by methotrexate administration over 8 months.

At the age of 42, serial partial motor epileptic seizures and secondarily generalized seizures occurred. Treatment with phenytoin and levetiracetam was started. Both, total protein (819mg/l) and albumin (548mg/l) levels were elevated in CSF and 2 specific bands were detectable, but no pleocytosis. CSF PCR was negative for JC-virus, BK-polyoma virus, CMV, HSV and toxoplasma gondii.

Analysis of the coagulation system revealed a massive increase of von Willebrand factor (vWF, 500 %), factor VIII (200 %) and slightly elevated D-dimers. The activity of the vWF-cleaving protease ADAMTS 13 was within normal range. There were no protease inhibitory antibodies detected. Under low molecular heparin treatment, clinical course became transiently stabilized for almost one year. Neuropsychological examination showed moderate cognitive deficits. Episodes of depression and agitation were reported. Then, general condition deteriorated, mainly due to the progressive protein-losing enteropathy. Hepatic insufficiency was associated with ascites and portal hypertension. Due to a persistent subileus, the patient was fed parenterally for several months before he died at the age of 44 from bronchopneumonia. A brain autopsy was performed.

Neuroimaging studies

Patient II/1

Axial non-enhanced (Fig. 3 A) and enhanced CCT sections at the age of 56 showed bilateral, multiple and nodular calcifications. Approximately 50 calcifications were found in the frontal, parietal and temporal lobes and in the basal ganglia, pons and cerebellum. Their size varied from a few millimetres up to 2 cm.

Patient II/4

EMI scan at the age of 48 revealed an oval-shaped contrast enhancing lesion in the left frontoparietal region. The lesion was surrounded by an extensive perifocal edema causing slight midline shifting to the right.

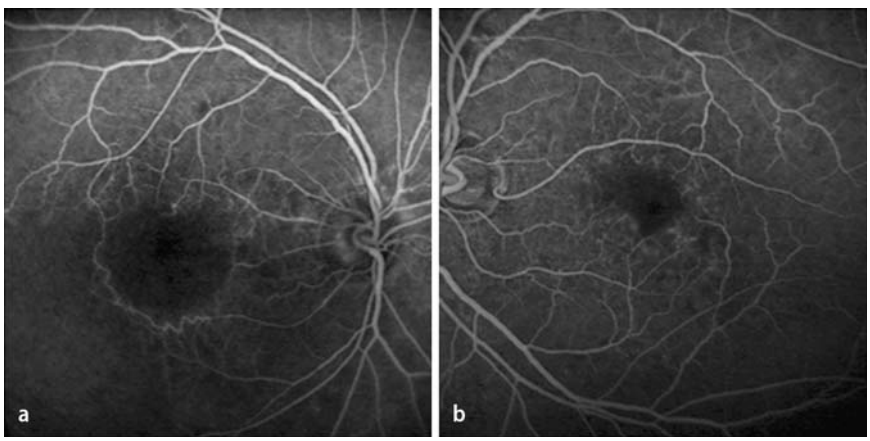

Fig. 2 Fluorescein angiography of subject III/4 at the age of 42. Right eye with marked reduction of flow in the inferotemporal region as a result of a vascular occlusion three years earlier (**A**). Shunt vessels surrounding the increased avascular zone of the fovea. Left eye with increased central avascular zone. Both sides lack signs of a vasculitis (**B**).

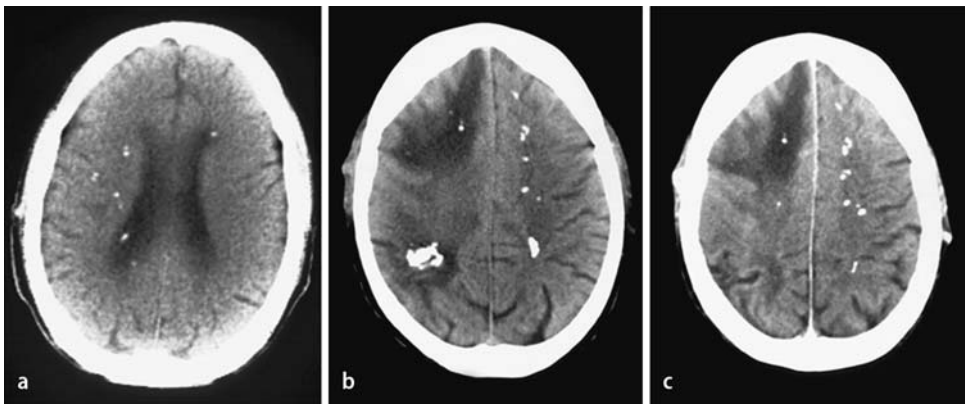

Fig. 3 An axial non-enhanced CT scan of patient II/1 (**A**) shows multiple nodular calcifications spread in both hemispheres. Similar findings are seen in a native axial CT scan of patient III/4 presenting multiple nodular cerebral calcification foci (**B**). Note the right frontal hypodense white matter lesion consistent with focal edema causing a mild mass effect to the left hemisphere. This tumor-like lesion is lacking focal enhancement of contrast media (**C**).

Patient III/4

Axial non-enhanced (Fig. 3 B) and enhanced (Fig. 3 C) CCT sections showed bilateral, multiple and nodular calcfications at the age of 42, similar to the findings in subject II/1. There was marked edema in the right frontal lobe with mild mass-effect.

The size of the edematous lesions exhibited a characteristic fluctuating time-course, as illustrated by serial MR imaging. The first axial TSE T2w image at the age of 39 (Fig. 4 A) revealed mild temporo-occipital intracranial edema but no relevant mass-effect. One year later, there was a massive progression of edema with now marked mass-effect and midline-shift towards the left (Fig. 4 B). In the centre of the edematous region, there was a relatively hypodense area surrounded by ring-enhancement in CE T1w images.

Three years after the first scan, at the age of 42 (Fig. 4 C), the right temporo-occipital edema and the mass-effect had almost completely resolved. However, there was a new frontal right edema with moderate mass-effect. Again, there was in its centre an irregularly shaped, rim enhancing lesion in the CE T1w scan (Fig. 4 D).

Histopathological studies

Biopsies were taken from the brain, skin and liver of patients II/4 and III/4 and from kidney, peripheral nerve, skeletal muscle, duodenum and colon of patient III/4. Brain autopsy was performed from patient III/4.

Brain biopsies (II/4 and III/4) and brain autopsy (III/4)

Brain biopsies taken from the white matter of the left (II/4, at the age of 48) and right (III/4, at the age of 39 and 42) frontal lobes revealed multiple, often confluent, foci of coagulation necrosis (Fig. 5 A). In other parts of the biopsy there were subnecrotic areas of subtotal ischemia with reactive astrocytic gliosis. Some small calcifications were present within necrotic foci. A quite prominent feature was the presence of perivascular inflammation, consisting of B- and T-lymphocytes, histiocytes and plasma cells (Fig. 5 B). Features of a vasculitis, however, were not observed. Occasionally sparse lymphocytic inflammation was present in non-necrotic brain tissue in addition to edema, reactive astrogliosis and microvessel proliferation (Fig. 5 C). Necrosis and ischemic brain tissue changes were associated with a variety of vasculopathic changes involving mainly small arteries and veins. Fibrinoid necrosis of vessel walls with extravasation of fibrinoid material into adjacent brain tissue and occasional thrombosis of small vessels were found in both necrotic and non-necrotic tissue (Fig. 5 D). A hallmark feature consisted of markedly thickened, fibrotic and sclerotic small vessel walls with an often severe narrowing of the lumen (Fig. 5 E, F). There was no PAS-positive granular material in the vessel wall. In many microvessels endothelial cells appeared enlarged with hyperchromatic nuclei and prominent nucleoli (Fig. 5 G). Material reprocessed for electron microscopy did not allow for detailed analysis. There was a prominent thickening of the intimal layer in small arteries and a thickening of the capillary basement membrane. In none of the vessels there was deposition of granular osmiophilic material (GOMs). Brain autopsy of patient III/4 revealed multiple, partly cystic and largely calcified, old necrotic lesions in the white matter of the right frontoparietal ($8 \times 4.5 \times 3$ cm) (Fig. 5 H, I), right temporoparietal ($2 \times 1.5 \times 1$ cm) and right and left parietooccipital lobes ($2 \times 1 \times 1$ cm). Similar, but smaller lesions (about 5 mm in diameter) were also present in the cerebellar white matter while no such changes could be found in the brainstem. Autopsy further confirmed the small vessel pathology (Fig. 5 I) already obtained by earlier brain biopsies, however, perivascular inflammatory changes were absent.

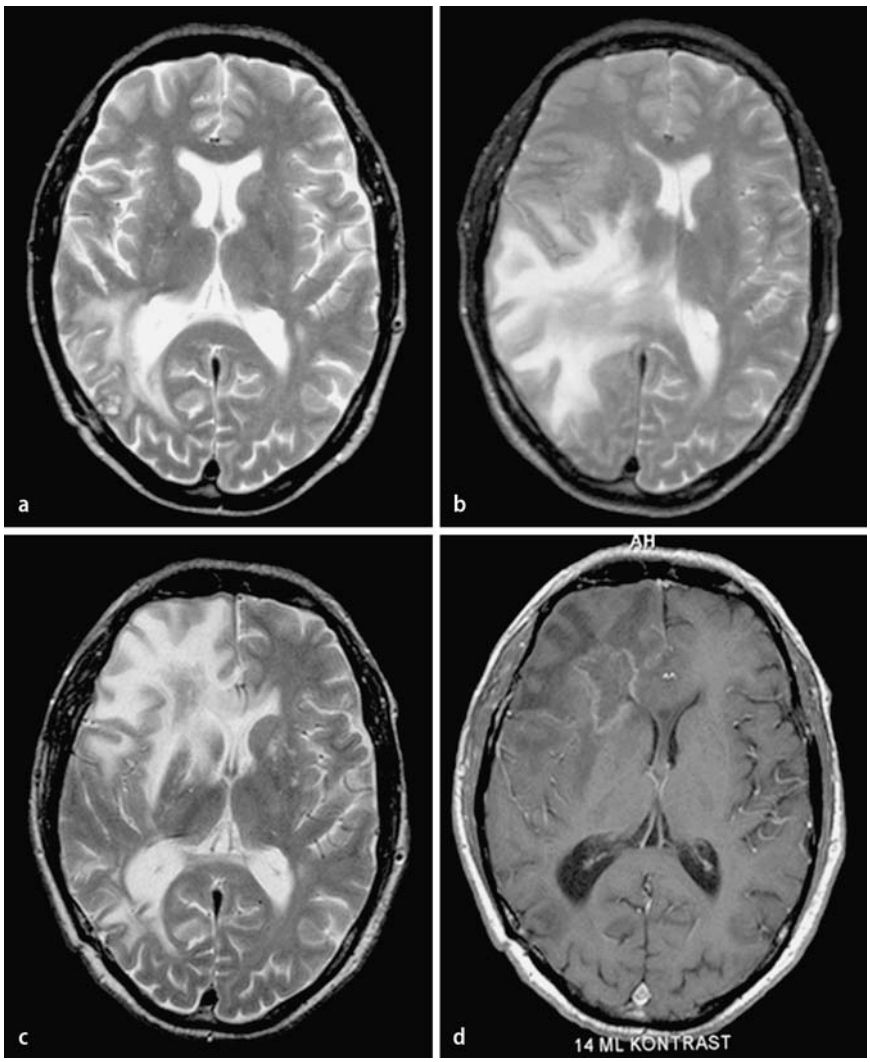

Fig. 4 Serial MRIs of patient III/4, illustrating the characteristic disease progression in phases (**A–D**). At the age of 39, a hyperintense signal-alteration right temporo-occipital adjacent to the right lateral ventricle is seen in an axial TSE T2w image (**A**). Note, that the lesion, which is compatible with perifocal edema, spares the grey matter and lacks relevant mass-effect at this time point. An equivalent slice at the age of 40 reveals massive progression of the right temporo-occipital edema with mass-effect and midline-shift to the left hand side (**B**). Again, the cortex is relatively spared. The further course at the age of 42 reveals almost complete resolution of the temporo-occipital right edema (**C**). However, a new frontal right lesion with extensive perifocal edema has developed. In an axial SE T1w scan post Gadolinium (**D**), this subcortical lesion exhibits irregularly shaped rim enhancement. The surrounding hypointense signal alteration, corresponding to the T2w hyperintense edema, is again sparing the cortical layers.

Skeletal muscle and peripheral nerve biopsies (III/4)

A striking feature in a biopsy taken from the left peroneal muscle was the presence of many muscle fascicles that showed a centrofascicular atrophy associated with hypertrophy of the adjacent perifascicular muscle fibres (Fig. 6 A). Since there were many, mainly arterial, small vessels with a thickened fibrotic wall (Fig. 6 B) that resulted in a severe narrowing of the lumen, we interpreted centrofascicular changes to be most likely due to ischemia. Inflammatory changes were not observed, and there were no ragged red fibres. In a sural nerve biopsy there was loss of myelinated nerve fibres and axonal breakdown with signs of segmentation myelin sheat ellipsoides (Fig. 6 C). As in the brain and skeletal muscle, there were small vessels with an obliterated lumen due to fibrous thickening of the vessel wall (Fig. 6 D).

Colon and duodenal biopsy (III/4)

A colon biopsy performed at the age of 42 showed disorganisation of the crypts and fibrosis of the lamina propria. In the mucosa and submucosa there were many small vessels with hyalin thickening of their walls. The lumen was either dilated, narrowed or even totally obliterated (Fig. 7 A). Duodenal biopsy at the age of 35 showed discrete mononuclear inflammatory infiltrates in the lamina propria and slight atrophy of villi. The vessels, however, were reported to be normal.

Renal biopsy (III/4)

The small renal biopsy contained cortex and medulla. The latter was unchanged. In the cortex there were six glomeruli which showed severe collapse lesions. The small arteries exhibited severe intimal fibrosis with a

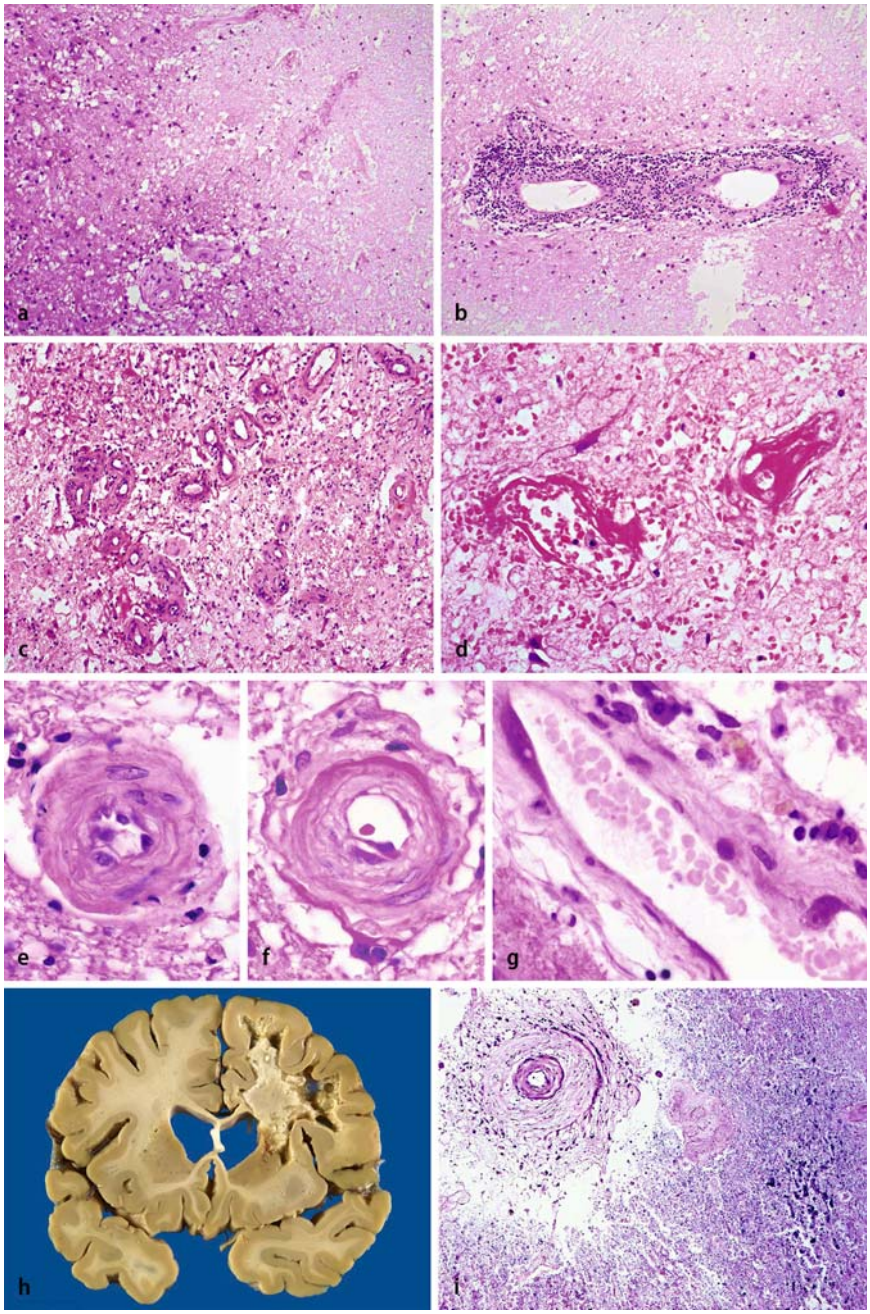

Fig. 5 Brain biopsies from patient II/4 (**A–C**) and III/4 (**D–G**) and brain autopsy from patient III/4 (**H, I**). Coagulation necrosis is apparent in the white matter (**A**). Some vessels are surrounded by prominent perivascular inflammation (**B**). Edema, astrocytic gliosis and proliferation of microvessels with thickened vessel walls (**C**). Fibrinoid necrosis of vessel walls. A microthrombus is observed in the small vessel to the right (**D**). (**D**). White matter vessels with markedly thickened, fibrotic and sclerotic vessel wall (**E, F**) are sometimes associated with adventitial fibrosis (**F**). Activated endothelial cells in microvessels are characterised by enlarged endothelial cells with hyperchromatic nuclei and prominent nucleoli (**G**). Old, partly cystic and calcified necrosis in the right frontoparietal white matter (**H**). White matter vessel with obliterated lumen in the vicinity of a mostly calcified necrosis (**I**). H&E stain. A, B, I x150; C, D, x200; E, F x400; G x630.

significant narrowing of the vessel lumens (Fig. 7 B). The arterioles exhibited severe narrowing of the vascular lumen due to prominent protein deposits in the vessel walls, partly in the subendothelium, partly in the media (Fig. 7 C). In the tubulo-interstitial space a striped pattern of fibrosis with tubular atrophy without significant inflammation was present. Immunofluorescent microscopy revealed medium severe unspecific deposits of IgM, C3c and C5b-9 in the arterioles and minor unspecific deposits of IgM, IgA, C3c, C4, C5b-9 and C1q in glomeruli. Electron microscopy showed a massive thickening of the intimal layer in small arteries due to matrix accumulation and minor myofibroblast proliferation with a severe narrowing of the vessel lumen. In glomerular capillaries, prominent thickening of the peripheral basement membranes – especially of the lamina rara interna – was present without any osmiophilic deposits (Fig. 7 D). GOMs were found to be absent in all vessels investigated. On the basis of the light, immunohistological as well as the electron microscopic findings, the diagnosis of thrombotic microangiopathy was made.

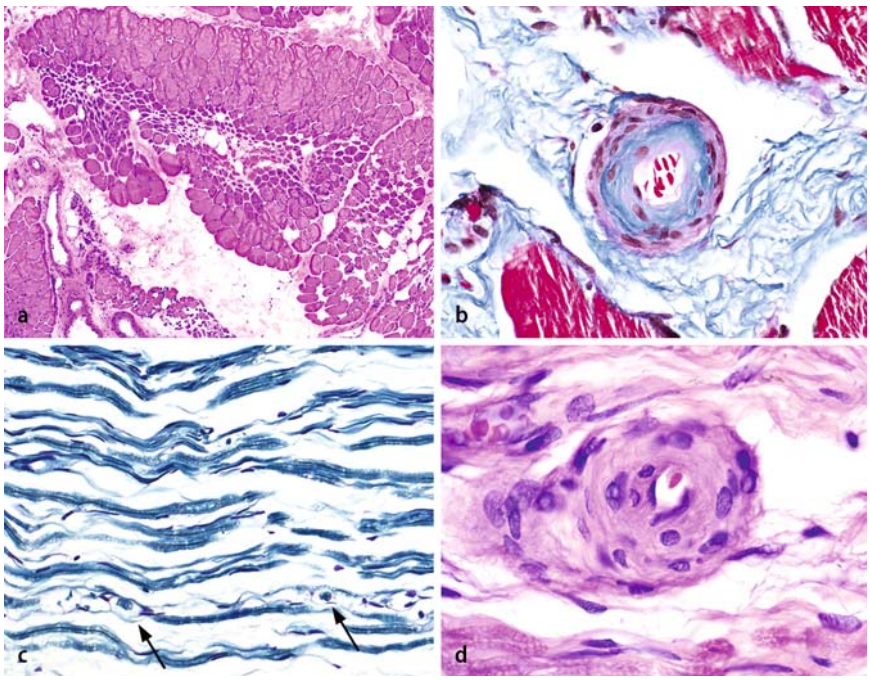

Fig. 6 Peroneal muscle (**A, B**) and sural nerve biopsy (**C, D**) from patient III/4. A striking feature of the peroneal muscle is the presence of centrofascicular atrophy while there is hypertrophy of adjacent perifascicular muscle fibres (**A**). A small endomysial artery shows a markedly thickened and sclerotic vessel wall (**B**). Loss of myelinated fibres is observed in the sural nerve biopsy. Breakdown and segmentation into ellipsoids of the myelin sheath (arrows) indicates ongoing axonal degeneration (**C**). Abnormally thickened vessel wall with obliteration of the lumen is seen in a small epineural artery (**D**). A, D: H&E stain; B: Masson-Trichrom stain; C: Holmes-Luxol stain. A x100; B x280; D x400; C x200.

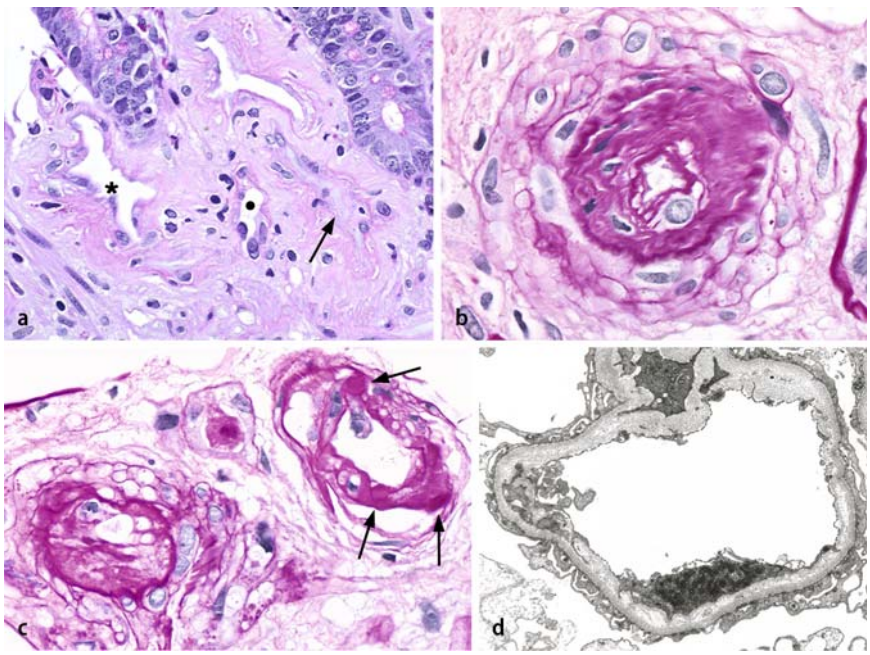

Fig. 7 Colon (**A**) and renal biopsy (**B–D**) of patient III/4. Small vessels of the colon mucosa show hyalin thickening of their walls (**A**). Some vessels appear dilated (asteriks), others of reduced diameter (black dot) or totally obliterated (arrow). A small artery of the renal cortex exhibits a severe intimal fibrosis with significant narrowing of its lumen (**B**). Prearteriole with thickening of its vessel wall (left) and an arteriole that shows a severe narrowing of its lumen due to protein deposition in the subendothelium and the media (arrows) (**C**). By electron microscopy glomerular capillaries exhibit thickening of the peripheral basement membranes (**D**). A: H&E stain; B, C: PAS stain. A x400; B, C x630; D x7300.

Liver biopsies (II/4 and III/4)

Liver biopsies of both patients showed foci of hepatic fibrosis and a dilatation of periportal sinusoids. There were few, most likely reactive inflammatory cells consisting of B- and T-lymphocytes and some plasma cells. These changes were interpreted to be compatible with an obstruction of vascular outflow.

Skin biopsies (II/4 and III/4)

A skin biopsy taken from the left elbow (II/4) revealed epidermal parakeratotic changes, mild unspecific inflammation and some ectatic small vessels exhibiting enlarged endothelial cells. A skin biopsy taken from patient III/4 revealed subepidermal lymphocytic and neutrophilic infiltration, which was considered compatible

with herpetiform dermatitis of Duhring. Skin vessels were found to be unchanged.

Genetic studies

Chromosomal analysis of patient III/4 showed a normal 46 XY karyotype without signs of major structural defects.

Genetic analysis of mitochondrial DNA was performed on tissue samples obtained from a muscle biopsy in patient III/4 as published previously [11]. In brief, deletion or duplication of the mitochondrial genome were excluded by Southern blotting. No point mutations have been found at the positions 3243 (MELAS), 3271 (MELAS), 8344 (MERRF) and 8356 (MELAS/MERRF) by a combined PCR and RT-PCR approach.

Screening for polyglutamine proteins was performed as described [26] and did not reveal elevated levels of polyglutamine containing proteins, when supernatant from homogenized lymphoblastoid cell lines of patient III/4 was analyzed by Western blotting using the polyglutamine sensitive antibody 1C2.

Discussion

We report on a Caucasian family affected by a variant form of a hereditary systemic angiopathy (HSA). Multiple cerebral calcifications on brain CT and MRI scans were found to be associated with a sclerosing and necrotizing vasculopathy of small and medium-sized cerebral vessels. Clinical hallmarks were (a) chronic migraine and (b) retinopathy, early in the course of the disease, followed by (c) motor paresis, (d) severe intractable seizures, (e) cognitive decline, (f) chronic liver sclerosis with progressive hepatic dysfunction and (g) nephrosclerosis with renal dysfunction and chronic anemia. Polyneuropathy, myopathy, cardiopathy and gastrointestinal symptoms with chronic diarrhea and malabsorption were prominent in one patient (see Table 1).

In all subjects, diagnosis of HSA was delayed and a broad work up for differential diagnosis was performed. Diagnostic difficulties originated from the stepwise progressive nature of the disease as well as from the unfamiliar radiological and pathological findings. Initial brain imaging studies suggested recurrent edematous inflammatory or tumoral brain lesions rather than a vasculopathy. This led to multiple brain biopsies in two of the subjects. Several cerebral lesions were of large size and altered their shape rapidly. Some lesions diminished their size spontaneously, others in response to steroid treatment. Differential diagnosis was broad and ranged from tuberous sclerosis, early in the course of the disease, to rheumatological disorders, when multiple organs became involved, up to rare hereditary conditions (see Table 2) [19].

In our patients, progressive occlusion of arterial retinal vessels leads to ischemic retinopathy with subsequent optic disc atrophy and formation of capillary aneurysms and shunts. These findings are reminiscent of the retinal pathology reported in subjects suffering from HRV [25]. Interestingly, in contrast to HSA, disease penetrance seems to be very low in HRV since only 6,9 % of all HRV family members present retinopathy, while retinopathy is present in all our affected HSA patients. Vascular retinopathy was also reported in a French family [6] and in CRV [28], where it may occur together with focal cerebral calcifications [15, 16]. Compared to HSA, these syndromes are less systemic in nature, although hepatic involvement has been suspected in two CRV patients [22, 28]. A combination of prominent retinopathy and systemic vasculopathy (HERNS) has been reported in a Chinese family [7]. In contrast to HSA, neither cerebral calcifications nor recurrent seizures have been reported in HERNS patients. Furthermore, the clinical symptoms in HERNS patients neither include prominent liver and gastrointestinal dysfunction nor myopathy or cardiopathy [7, 21]. An autosomal recessive cerebroretinal vasculopathy with cerebral calcifications has recently been reported in a German sister pair [15, 16, 20]. This disorder, however, differs from HSA by the juvenile onset, the presence of microcephaly and the absence of systemic disease manifestations.

Pathology and mechanisms of disease progression

The histopathological findings in brain tissue of HSA patients share similarities with brain lesions reported in CRV [5, 28] and in HERNS [7]. In all these syndromes there is coagulation necrosis reminiscent of delayed radiation-induced brain tissue damage. Moreover, the vasculopathic changes are quite comparable, both at the level of light and transmission electron microscopy (e.g., thickened and/or multilayered basement membranes) [7], while perivascular inflammation seems to be an inconsistent finding among the different syndromes. Brain autopsy in one of our patients revealed large confluent cerebral white matter calcifications. Histologically, calcifications have not been reported in HERNS [7]. In contrast, a true calcinosis characterised by calcified arteriolar vessel walls and "encrusted" neural cells, has been described in a French family by Rambaud et al. [18].

The finding of activated endothelial cells (e.g., enlarged endothelial cells with hyperchromatic nuclei and prominent nucleoli) in many microvessels of the brain, as well as the presence of thrombotic microangiopathy in the renal biopsy suggests that an endothelial damage might be an important factor causing HSA. One conse-

Table 2 Differential diagnosis of HSA

Disease	Similarities with the presented HSA family	Differences from the presented HSA family
Aicardi-Goutieres syndrome (1)	– encephalopathy with cerebral calcifications	– early onset – no systemic findings
CADASIL (9)	– autosomal-dominant inheritance – stroke like episodes – gastrointestinal involvement	– no hepato- and nephrosclerosis
CRV (28)	– autosomal dominant inheritance – retinopathy – vasculopathy – cerebral calcifications	– no systemic findings
Epilepsy with bilateral occipital calcifications (3)	– anti-gliadin antibodies – cerebral calcifications – encephalopathy	– no systemic findings – not hereditary – histology not compatible with Coeliac disease
HERNS (7)	– hereditary retinopathy – vasculopathy – cerebral calcifications – nephropathy	– no cerebral calcifications – no prominent hepato-gastrointestinal involvement – no myopathy – seizures not prominent
HRV (25)	– hereditary retinopathy – vasculopathy	– no systemic findings – low disease penetrance
Leukoencephalopathy, cerebral calcifications, and cysts (14)	– encephalopathy – cerebral calcifications	– early onset – no systemic findings
MELAS (4)	– myopathy – encephalopathy – stroke like episodes	– no cerebral calcifications – ragged red fibers
Rambaud's syndrome (18)	– protein losing enteropathy	– facial dysmorphy – only female patients reported
Sjögren syndrome	– positive Schirmer test – oral aphtosis – tubular proteinuria – myopathy – portal hepatic sclerosis – partial steroid response	– SS-A, SS-B positive – histology
Susac syndrome (24)	– encephalopathy – retinopathy – vasculopathy – partial steroid response	– self-limited
Tuberous sclerosis	– cerebral calcifications – encephalopathy – seizures – autosomal-dominant inheritance	– no hepato- and nephrosclerosis – presence of skin hamartoma – no retinopathy

quence might be capillary and arteriolar dysfunction, which in turn leads to slow progressive systemic multiorgan failure. In line with the hypothesis of primary endothelial damage, we measured increased levels of von Willebrand factor (vWF) and factor VIII, while ADAMTS 13 protease dysfunction could be excluded as a causative factor for vWF elevation.

Interestingly, HSA seems to progress in stages as it happens in other thrombotic microangiopathies, like the thrombocytopenic purpura [13]. Hypothetically, a critical vascular injury may lead to an activation of the coagulation cascade with subsequent microthrombosis and systemic microinfarctions.

Genetic knowledge about vasculopathies is limited and only a few hereditary cerebrovascular syndromes such as CADASIL [8] and hereditary hemorrhagic telangiectasia [12] have been genetically identified. Due to common clinical features, a common genetic origin has been considered for CRV, HRV and HERNS, and recently all these syndromes have been linked to the same locus on chromosome 3p21 [17]. Interestingly, the Aicardi-Goutieres syndrome, a further disease with progressive leukoencephalopathy, has been located to 3p21 [2], a region to which also the polyglutamine disease spinocerebellar ataxia 7 has been linked. We screened for polyglutamine proteins in one patient. Although we did not find polyglutamine proteins in our screen, we cannot exclude the possibility of a poly-repeat phenomenon other than glutamine-repeats as the causative defect in HSA.

Treatment of HSA and cerebral vasculopathies

So far no treatment for cerebral vasculopathies is known. Nevertheless, in all our patients, long-term use of low dose steroids proved helpful to control brain edema surrounding cerebral lesions. Acute cerebral mass lesions responded to steroid pulse therapy.

Assuming a role for microthrombi in the pathogenesis of HSA, the use of antiplatelet agents can be tried. Low molecular heparin therapy led to stabilization of the course of the disease over about one year in one of our patients. Successful use of aspirin and pentoxifylline has previously been reported in a patient suffering from CRV [28].

In contrast, cyclophosphamide, azathioprin and methotrexate worsened the pre-existing hepatic dysfunction without beneficial effects on overall disease progression in our patients. The use of immunosuppressants also was not favorable in CRV [28] and should be discouraged due to its side-effects. Early recognition of HSA and other hereditary vasculopathies is thus of particular importance to protect patients from harmful and inappropriate drug treatment.

In summary, diagnosis of HSA can be suspected in the presence of a clinical constellation with migraine-like headache, motor paresis, recurrent epileptic seizures, in combination with cerebral calcifications visible in CT-scans, retinal aneurysms in fluorescein angiography and a biopsy of an affected organ revealing angiopathic changes including activated endothelial cells and microthrombi. It is important to note that HSA is not responsive to immunosuppressants that have the potential to provoke additional damage to liver and kidneys. Administration of low molecular heparin can be tried to minimize the formation of microthrombi. When cerebral mass lesions provoke midline shift, steroid application has been shown to reduce the edema. Future work will help to elucidate the pathogenic mechanisms responsible for the endothelial damage in HSA.

Acknowledgement We wish to thank Prof. Dr. G. Spagnoli, University of Basel, for establishing lymphoblast cell culture lines. We thank Dr. L.J. Trecjokas, PhD, MD, consultant neurologist, Santa Monica, CA, USA, for his help by providing clinical and radiological data. We further acknowledge Prof. Dr. E.W. Radue, Dept. of Neuroradiology, Prof. Dr. A. Tyndall, Dept. of Rheumatology, Prof. Dr. G. Marbet, Dept. of Hematology, University of Basel, for discussion. We also thank Prof. Dr. B. Lämmle, University of Bern, for measuring ADAMTS 13 protease activity.

References

1. Aicardi J, Goutieres F (1984) A progressive familial encephalopathy in infancy with calcifications of the basal ganglia and chronic cerebrospinal fluid lymphocytosis. Ann Neurol 15(1):49–54
2. Crow YJ, Jackson AP, Roberts E, van Beusekom E, Barth P, Corry P, Ferrie CD, Hamel BC, Jayatunga R, Karbani G, Kalmanchey R, Kelemen A, King M, Kumar R, Livingstone J, Massey R, McWilliam R, Meager A, Rittey C, Stephenson JB, Tolmie JL, Verrips A, Voit T, van Bokhoven H, Brunner HG, Woods CG (2000) Aicardi-Goutieres syndrome displays genetic heterogeneity with one locus (AGS1) on chromosome 3p21. Am J Hum Genet 67(1):213–221
3. Gobbi G, Bouquet F, Greco L, Lambertini A, Tassinari CA, Ventura A, Zaniboni MG (1992) Coeliac disease, epilepsy, and cerebral calcifications. The Italian Working Group on Coeliac Disease and Epilepsy. Lancet 340(8817):439–443
4. Goto Y, Nonaka I, Horai S (1990) A mutation in the tRNA(Leu)(UUR) gene associated with the MELAS subgroup of mitochondrial encephalomyopathies. Nature 348(6302):651–653
5. Grand MG, Kaine J, Fulling K, Atkinson J, Dowton SB, Farber M, Craver J, Rice K (1988) Cerebroretinal vasculopathy. A new hereditary syndrome. Ophthalmology 95(5):649–659
6. Gutmann DH, Fischbeck KH, Sergott RC (1989) Hereditary retinal vasculopathy with cerebral white matter lesions. Am J Med Genet 34(2):217–220
7. Jen J, Cohen AH, Yue Q, Stout JT, Vinters HV, Nelson S, Baloh RW (1997) Hereditary endotheliopathy with retinopathy, nephropathy, and stroke (HERNS). Neurology 49(5):1322–1330
8. Joutel A, Bousser MG, Biousse V, Labauge P, Chabriat H, Nibbio A, Maciazek J, Meyer B, Bach MA, Weissenbach J, et al. (1993) A gene for familial hemiplegic migraine maps to chromosome 19. Nat Genet 5(1):40–45
9. Joutel A, Corpechot C, Ducros A, Vahedi K, Chabriat H, Mouton P, Alamowitch S, Domenga V, Cecillion M, Marechal E, Maciazek J, Vayssiere C, Cruaud C, Cabanis EA, Ruchoux MM, Weissenbach J, Bach JF, Bousser MG, Tournier-Lasserve E (1996) Notch3 mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia. Nature 383(6602):707–710
10. Labrune P, Lacroix C, Goutieres F, de Laveaucoupet J, Chevalier P, Zerah M, Husson B, Landrieu P (1996) Extensive brain calcifications, leukodystrophy, and formation of parenchymal cysts: a new progressive disorder due to diffuse cerebral microangiopathy. Neurology 46(5):1297–1301
11. Magistris MR, Kohler A, Pizzolato G, Morris MA, Baroffio A, Bernheim L, Bader CR (1998) Needle muscle biopsy in the investigation of neuromuscular disorders. Muscle Nerve 21(2):194–200
12. McAllister KA, Grogg KM, Johnson DW, Gallione CJ, Baldwin MA, Jackson CE, Helmbold EA, Markel DS, McKinnon WC, Murrell J, et al. (1994) Endoglin, a TGF-beta binding protein of endothelial cells, is the gene for hereditary haemorrhagic telangiectasia type 1. Nat Genet 8(4):345–351
13. Moake JL (2002) Thrombotic microangiopathies. N Engl J Med 347(8):589–600
14. Nagae-Poetscher LM, Bibat G, Philippart M, Rosemberg S, Fatemi A, Lacerda MT, Costa MO, Kok F, Costa Leite C, Horska A, Barker PB, Naidu S (2004) Leukoencephalopathy, cerebral calcifications, and cysts: new observations. Neurology 62(7):1206–1209

15. Niedermayer I, Graf N, Schmidbauer J, Reiche W (2000) Cerebroretinal vasculopathy mimicking a brain tumor. Neurology 54(9):1878–1879
16. Niedermayer I, Reiche W, Graf N, Mestres P, Feiden W (2000) Cerebroretinal vasculopathy and leukoencephalopathy mimicking a brain tumor. Report of two early-onset cases with Fanconi's anemia-like phenotypes suggesting an autosomal-recessive inheritance pattern. Clin Neuropathol 19(6):285–295
17. Ophoff RA, DeYoung J, Service SK, Joosse M, Caffo NA, Sandkuijl LA, Terwindt GM, Haan J, van den Maagdenberg AM, Jen J, Baloh RW, Barilla-LaBarca ML, Saccone NL, Atkinson JP, Ferrari MD, Freimer NB, Frants RR (2001) Hereditary vascular retinopathy, cerebroretinal vasculopathy, and hereditary endotheliopathy with retinopathy, nephropathy, and stroke map to a single locus on chromosome 3p21.1–p21.3. Am J Hum Genet 69(2):447–453
18. Rambaud JC, Galian A, Touchard G, Morel-Maroger L, Mikol J, Van Effenterre G, Leclerc JP, Le Charpentier Y, Haut J, Matuchansky C, et al. (1986) Digestive tract and renal small vessel hyalinosis, idiopathic nonarteriosclerotic intracerebral calcifications, retinal ischemic syndrome, and phenotypic abnormalities. A new familial syndrome. Gastroenterology 90(4):930–938
19. Razvi SS, Bone I (2006) Single gene disorders causing ischaemic stroke. J Neurol 253(6):685–700
20. Schmidbauer JM, Voges M, Kasmann-Kellner B, Graf N, Henn W, Ruprecht KW (2000) Hereditary occlusive cerebroretinal vasculopathy in two sisters. Klin Monatsbl Augenheilkd 217(4):246–251
21. Seifried C, Sitzer M, Jen J, Auburger G (2005) HERNS. A rare, hereditary, multisystemic disease with cerebral microangiopathy. Nervenarzt 76(10): 1191–1192, 1194–1195
22. Siveke JT, Schmid H (2003) Evidence for systemic manifestations in cerebroretinal vasculopathy. Am J Med Genet 123A(3):309
23. Storimans CW, Van Schooneveld MJ, Oosterhuis JA, Bos PJ (1991) A new autosomal dominant vascular retinopathy syndrome. Eur J Ophthalmol 1(2):73–78
24. Susac JO, Hardman JM, Selhorst JB (1979) Microangiopathy of the brain and retina. Neurology 29(3):313–316
25. Terwindt GM, Haan J, Ophoff RA, Groenen SM, Storimans CW, Lanser JB, Roos RA, Bleeker-Wagemakers EM, Frants RR, Ferrari MD (1998) Clinical and genetic analysis of a large Dutch family with autosomal dominant vascular retinopathy, migraine and Raynaud's phenomenon. Brain 121(Pt 2):303–316
26. Trottier Y, Lutz Y, Stevanin G, Imbert G, Devys D, Cancel G, Saudou F, Weber C, David G, Tora L, et al. (1995) Polyglutamine expansion as a pathological epitope in Huntington's disease and four dominant cerebellar ataxias. Nature 378(6555):403–406
27. Vahedi K, Massin P, Guichard JP, Miocque S, Polivka M, Goutieres F, Dress D, Chapon F, Ruchoux MM, Riant F, Joutel A, Gaudric A, Bousser MG, Tournier-Lasserve E (2003) Hereditary infantile hemiparesis, retinal arteriolar tortuosity, and leukoencephalopathy. Neurology 60(1):57–63
28. Weil S, Reifenberger G, Dudel C, Yousry TA, Schriever S, Noachtar S (1999) Cerebroretinal vasculopathy mimicking a brain tumor: a case of a rare hereditary syndrome. Neurology 53(3):629–631
29. Yanagawa S, Ito N, Arima K, Ikeda S (2002) Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy. Neurology 58(5):817–820