days. On one occasion after ingesting Cafegot, a preparation of ergotamine with caffeine, when aged 27, he experienced a myocardial infarct. Although we did not undertake a neurological examination at that time, magnetic resonance imaging (MRI) showed a small new lesion in the white matter of the left frontal lobe. Calcium channel antagonists, β adrenergic blockers, antidepressants, anticonvulsants, and aspirin had been used to prevent attacks. However, these drugs had a marginal effect, if any.

In August 2002, he first presented to us between attacks. Neurological examination revealed right handed clumsiness with a somewhat increased tone of the right arm. Pes cavus and equinovarus were also noticed. Electrocardiography supported the history of a previous myocardial infarct. Laboratory studies—including coagulation profile, fibrinogen level, protein C and S levels, screening for collagen diseases, anticardiolipin antibody, and homocysteine—did not show any cardiovascular risk factors. Cerebrospinal fluid was normal (0/3 cells/mm³, protein 27 mg/dL, glucose 65 mg/dL, IgG index 0.52). Genetic screening was carried out after obtaining informed consent, and was negative for mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), myoclonic epilepsy associated with ragged-red fibres (MERRF), voltage sensitive P/Q-type calcium channel mutation, and NOTCH3 mutation. Pattern reversal visual evoked potentials were normal. Our first MRI examination (28 February 2003) revealed only the above mentioned old lesion in the left brain (fig 1A) with normal MRA findings (data not shown). Disorders of the peripheral nervous system were not detected clinically or electrophysiologically. Disorders of language, agnosia, or apraxia were never noticed. Drugs selected from propranolol, arotinolol, nifedipine, diltiazem, isosorbide, nicorandil, nisoldipine, diazepam, phenytoin, valproate, and aspirin were used for prevention. Each was taken for at least three months. However, no clear beneficial effect was observed.

Repeated MRI did not yield any findings until 22 August 2003, when left eye pain and decreased vision started and developed into a right hemiparesis. Emergent MRA showed disappearance of the left ICA, indicating absence or little flow in the ICA (fig 1B). However, no new lesion was found in the brain parenchyma (data not shown). The symptoms resolved six days later. The left ICA was of normal appearance on follow up MRA in September 2003 (fig 1C). Narrowing of the right ICA was also confirmed as decreased intensity of vascular image on 17 October 2003, on the first day of the attack. Stenosis appeared to start a little distal to the carotid bifurcation in the petrous segment (fig 1, panels D and E). Subsequent SPECT revealed decreased blood supply in the right brain (fig 1, panels F and G). The symptoms disappeared by 23 October 2003.

We concluded that the transient hemiparesis resulted from ICA vasospasm. To reverse ICA vasoconstriction at an early stage, we undertook a stellate ganglion block by the standard anterior paratracheal approach at the C6 transverse process, and he immediately recovered. Vasodilatation was successfully demonstrated by CCDS (fig 1, panels G and H). Although a single application of stellate ganglion block was able to ameliorate the vasospasm, further blocks to the affected side were carried out on three consecutive

days to thoroughly suppress sympathetic activity. Sadly, a preventive effect on ICA vasospasm was not observed and the frequency of the attacks was unchanged.

Comment

We describe a patient with repeated ICA vasospasm of unknown origin. Because of the consanguinity of his parents and the Friedreich's foot seen in various genetic neurological disorders,¹ genetic screening was undertaken, but a gene disorder was not identified.

We initially diagnosed him as having hemiplegic migraine because migraine manifesting aura alone is well documented, and narrowing of the large or small arteries during a migrainous attack has been reported.² However, vasodilatation or hyperperfusion seen after the aura in migrainous attacks³ was not observed even when MRA, CCDS, and SPECT were done on several occasions from the time of onset to just after the attacks ended. Worsening on standing indicated that insufficient blood supply rather than cortical spreading depression was the primary cause of his hemiparesis. The affected side was not fixed, in contrast to familial hemiplegic migraine caused by a genetic disorder of the voltage sensitive P/Q-type calcium channel.³ As multiple sclerosis can produce a transient neurological deficit, it should be ruled out. However, normal cerebrospinal fluid and visual evoked potential findings and lack of demyelination on MRI did not support multiple sclerosis as a diagnosis.

We used stellate ganglion block to reverse ICA vasoconstriction by blocking sympathetic activity.⁴ The favourable effect observed confirmed that the neurological deficit resulted from ICA spasm. Hypersensitivity of the ICAs to neuropeptide Y and noradrenaline may be related to vasospasm.

Spontaneous vasospasm as a cause of ischaemic attacks should be carefully considered using neuroimaging techniques such as MRA and CCDS. As successful prevention of ICA vasospasm by treatment with a calcium channel antagonist has been reported,⁵ and as stellate ganglion block was able to ameliorate the vasoconstriction in our case, evidence of the presence of vasospasm may change the treatment and management of patients with ischaemic attacks.

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Adult onset leucoencephalopathy with brain stem and spinal cord involvement and normal lactate

Leucoencephalopathy with brain stem and spinal cord involvement and raised lactate (LBSL) is a white matter disease that has recently been described based on typical magnetic resonance imaging (MRI) findings.^{1,2} These include widespread, homogeneous or inhomogeneous white matter abnormalities, corpus callosum involvement, and selective involvement of certain brain stem and spinal cord tracts. Increased white matter lactate levels are usually found on magnetic resonance spectroscopy (MRS). Clinically, the condition is characterised by a childhood onset slowly progressive course. Here we report two patients who presented with adult onset LBSL and normal lactate on MRS.

Case report

A 23 year old woman and her 25 year old brother were referred to our department because of a slowly progressive gait disorder. At the age of 20 (in the female patient) and 23 years (in the male patient), the siblings had first noted an unsteady gait, stiffness in both legs, and bilateral clumsiness. They had both had normal development, and their former medical history was unremarkable. They had achieved unsupported walking at ages of 14 months (female patient) and 15 months (male patient). Both had been examined during early adolescence, with normal neurological findings. They were the only affected members in their family, and their parents were non-consanguineous.

Neurological examination on admission revealed mild spastic tetraparesis (affecting the legs more than the arms), generalised ataxia, saccadic smooth pursuit, saccadic dysmetria, and horizontal, gaze evoked nystagmus. Both patients had hyperreflexia, and plantar reflexes were extensor. Sensory testing was remarkable for a distal symmetrical decrease in position and vibration sense. Neuropsychological testing (Wechsler Memory Scale Revised, Rey-Osterrieth Complex Figure Test, logical reasoning, dual task paradigm, Multiple Choice Vocabulary Test B) revealed that they were of average intelligence and did not show signs of cognitive decline. The following laboratory investigations

Figure 1 Cerebral and spinal magnetic resonance imaging (MRI) of the female patient ((A) fluid attenuated inversion recovery images; (B) T1 weighted images; (C) to (G) T2 weighted images). (A) "Spotty" signal changes were observed within the white matter sparing the U fibres (arrow). (B) T1 weighted imaging revealed hypointensities corresponding to the hyperintense T2 lesions (arrow). (C) The signal changes were also seen in the deep white matter, especially the posterior limb of the internal capsule (arrow). (D) Besides the supratentorial white matter changes (arrowhead), white matter abnormalities were also observed infratentorially (white arrow, superior cerebellar peduncle; black arrow, inferior cerebellar peduncle). (E)–(F) MRI of the brain stem revealed selective involvement of the intraparenchymal trajectories of the trigeminal nerves ((E), white arrow), medial lemniscus ((E), black arrow), superior cerebellar peduncle ((E), white arrowhead), mesencephalic trigeminal tract ((E), black arrowhead), inferior cerebellar peduncle ((F), black arrow), and pontine trigeminal tract ((F), white arrow). (G) MRI of the spinal cord revealed white matter abnormalities within the dorsal columns (white arrow) and the corticospinal tracts (black arrow). (H) Single voxel MR spectroscopy of the affected white matter revealed decreased *N*-acetylaspartate (NAA) and increased choline levels (Cho), but no lactate increase.

were normal: routine blood chemistry, ammonia, creatine kinase, vitamins E and B-12, folic acid, thyroid function, antinuclear antibodies, lactate, pyruvate, very long chain fatty acids, phytanic acid, copper, caeruloplasmin, lysosomal enzymes (arylsulphatase-A, galactocerebrosidase, β -galactosidase, hexosaminidase-A), and routine cerebrospinal fluid indices (including lactate). Central motor and somatosensory evoked potentials were delayed. Sensory and motor nerve conduction velocities were normal. MRI (1.5 Tesla) of the brain revealed a non-enhancing, inhomogeneous ("spotty") appearance, that was hypointense on T1 weighted and hyperintense on T2 weighted images. Most signal changes were seen within the deep and periventricular cerebral white matter (fig 1, panels A to C), completely sparing the U fibres. The signal changes were also observed in the posterior limb of the internal capsule (fig 1C) and in the posterior part of the corpus callosum. Infratentorial changes were seen in the cerebellar white matter, pyramidal tracts, medial lemniscus, superior and inferior cerebellar peduncles, and in the intraparenchymal trajectories of the trigeminal nerves (fig 1, panels D to F). On spinal MRI, abnormalities were detected in the dorsal columns and lateral corticospinal tracts (fig 1G). Repeated MRS with short (STEAM, TR = 1500 ms, TE = 20 ms) and long (PRESS, TR = 1500 ms, TE = 135 ms) echo time of the affected white matter revealed mildly decreased *N*-acetylaspartate and increased choline levels, but normal lactate levels (fig 1H). The patients were started on a low dose of baclofen and have

shown a moderate improvement in spasticity over time.

Comment

The two patients reported here presented with slowly progressive pyramidal and cerebellar signs and a mild concomitant dorsal column dysfunction. MRI revealed "spotty" cerebral white matter changes, abnormality of the pyramidal and sensory tracts over their entire length, and a remarkably selective involvement of cerebellar and trigeminal tracts. As in the majority of all reported cases,^{1–3} no cognitive decline was detectable by standard neuropsychological testing. Thus these patients have the clinical characteristics and distinct MRI pattern of LBSL,^{1,2} which is different from those seen in all other known leucoencephalopathies.³ However, despite repeated examinations and the full blown disease pattern on MRI in our patients, we did not detect increased lactate levels on MRS and in serum and cerebrospinal fluid, although we detected decreased *N*-acetylaspartate and increased choline levels, as previously described for LBSL.¹

Besides the MRI changes, increased lactate on MRS has been considered the only consistently abnormal finding among all indices tested.⁴ Moreover, in most patients described to date, motor deterioration started relatively early (5 ± 4 years), with some patients showing delayed development from birth onwards.^{1,2} Our cases show that LBSL may begin in adulthood in some instances,

and that increased lactate levels on MRS may be missing even at advanced disease stages. Furthermore, as we report here the third pair of affected siblings with LBSL, an autosomal recessive mode of inheritance becomes increasingly likely. With 20 patients now reported since the first description of the disorder,¹ LBSL seems to comprise a relatively large subgroup among patients with leucoencephalopathy of unknown origin. Moreover, cases with late onset and atypical findings on MRI and MRS may become increasingly known, as clinicians become aware of this novel disease entity, and a more appropriate name may be coined once the underlying genetic abnormality and the full clinical spectrum have been identified.

These cases may help to better define the clinical spectrum of this novel disease. Moreover, our findings suggest that until a critical number of informative families has been collected for a genetic linkage study and genetic testing ultimately becomes available, the diagnosis of LBSL is based on the suggestive MRI findings and the exclusion of other leucoencephalopathies by a complete metabolic screen.

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The *LRK2* gene in Parkinson's disease: mutation screening in patients from Germany

Since the identification in 2004 of mutations within the leucine-rich repeat kinase 2 (*LRK2*) gene in patients with autosomal, dominantly inherited Parkinson's disease, this gene has been the focus of research on Parkinson's disease.¹ Mutations in the *LRK2* gene and especially the common mutation G2019S may account for 1–2% of familial and 3–6% of sporadic cases of Parkinson's disease, including those of early and late onset.² The *LRK2* gene is situated on chromosome 12p11.2–q13.1 and encodes a large protein named dardarin. Dardarin contains several functional domains, including a leucine-rich repeat domain, WD40, renin-angiotensin system/guanosine triphosphatases and kinase domains. The presence of the leucine-rich repeat and WD40 domains suggests a role in protein–protein interaction. In addition, function was demonstrated kinase for dardarin *in vitro*.³

Some questions remain about the growing demand of DNA diagnostics and genetic counselling in Parkinson's disease. Which subpopulation of patients with Parkinson's disease harbours the highest risk of mutations in the *LRK2* gene? What is the frequency and penetrance of different *LRK2* mutations? Nine exons (exons 19, 24, 25, 29, 31, 34, 35, 38 and 41) of the *LRK2* gene were screened for sequence variations in a cohort of 120 patients (mean age at onset 56.3 years). The cohort was recruited in Germany and consisted of 10 (8%) patients with early-onset (age at onset <45 years) and 110 (92%) patients with late-onset Parkinson's disease. Approximately 25.8% of the patients had a family history of Parkinson's disease. Screening was carried

out by PCR, denaturing high-performance liquid chromatography and direct DNA sequencing. The ethics committee of Ruhr-University Bochum, Bochum, Germany, approved this study. More detailed information and primer sequences are available from the authors upon request.

Several common exonic (G1624G, K1637K, S1647T) exchanges and intronic single-nucleotide polymorphisms (Ivs33-31T>C, Ivs34+32A>G, Ivs34-51A>T, Ivs35+23T>A, Ivs38+35G>A) were identified. Of three (2.5%) patients who carried mutations in heterozygous state, two harboured the common mutation G2019S (age at onset 30 and 44 years) and one patient showed a novel mutation A1151T (age at onset 55 years).

To optimise future genetic testing and counselling, we aimed at identifying patient phenotypes with the highest risk for mutations in the *LRK2* gene in Germany. The patients represent a cohort with sporadic and familial, early-onset and late-onset Parkinson's disease. In our study, three (2.5%) patients carried *LRK2* mutations (G2019S, A1151T). This frequency may even be an underestimation of *LRK2* mutations, because our screening was limited to 9 of the 51 exons of the gene. In all, 6.7% of the patients with a family history of Parkinson's disease and 1.1% of the patients with sporadic Parkinson's disease are mutation carriers. Patients with early-onset Parkinson's disease may have the highest risk for mutation in the *LRK2* gene: 2 of the 10 patients with early-onset Parkinson's disease but only 1 of the 110 patients with late-onset Parkinson's disease harbour a mutation. Further investigations with larger cohorts are needed to verify the observed tendencies.

The novel mutation A1151T was identified in a patient with late-onset Parkinson's disease (onset at 55 years). The patient's mother died at the age of 68 years and her father at the age of 30 years. Thus it remains unclear whether the mutation is fully penetrant or has appeared de novo and whether the parents died before manifestation of the disease. The mutation was not observed in 336 ethnically but not age-matched control chromosomes of senior healthy blood donors from Germany. The A1151T mutation is located within the leucine-rich repeat domain (fig 1). Although the pathogenicity is not yet confirmed, conservation of the A1151 residue lends some support to the hypothesis that the A1151T exchange may be causally related to Parkinson's disease. Onset of the disease in this patient occurred at the age of 55 years,

with resting tremor in the left hand and akinesia. After a disease duration of 10 years, the patient has distinct on-off fluctuation and mild cognitive impairment.

Two patients carried the common G2019S mutation in heterozygous state. The mutation was not observed in 336 ethnically matched control chromosomes of senior healthy blood donors from Germany. To date, the mutation has been found in only one of more than 4000 healthy controls of different ethnic backgrounds.⁴ One mutation carrier of German origin has typical, asymmetric, levodopa-responsive early-onset Parkinson's disease (age at onset 44 years). He reported that his father had tremors. DNA and neurological examination of the patient's father were impossible. The other mutation carrier from Belarus had early-onset Parkinson's disease (age at onset 30 years) dominated by akinesia and rigors. Besides the early manifestation of the disease, no other atypical features were observed. In her great grandmother, Parkinson's disease, with tremor and manifestation in her 70s, has been reported. Her mother is also a mutation carrier in heterozygous state, but remains asymptomatic (clinical examination) at 68 years. The question arises whether the mutation is incompletely penetrant or whether the manifestation is age dependent. Discordant findings in monozygotic twins favour the hypotheses of environmental modifiers.⁵ Taken together, our findings support the hypothesis of a complex interplay between genetic and environmental factors in the pathogenesis of Parkinson's disease. The hypothesis of incomplete penetrance is supported by an unaffected 89-year-old with a G2019S mutation.⁴

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Figure 1 Structure of the leucine-rich repeat kinase 2 protein and functional domains: leucine-rich repeat (LRR), renin-angiotensin system in complex (ROC) proteins, C-terminal domain of ROC (COR), mitogen-activated protein kinase kinase kinase (MAPKKK) and WD40 repeats (WD40). The position of the novel mutation A1151T (exon 25) in the LRR domain and the conservation of the alanine residue among several other vertebrate species are seen.