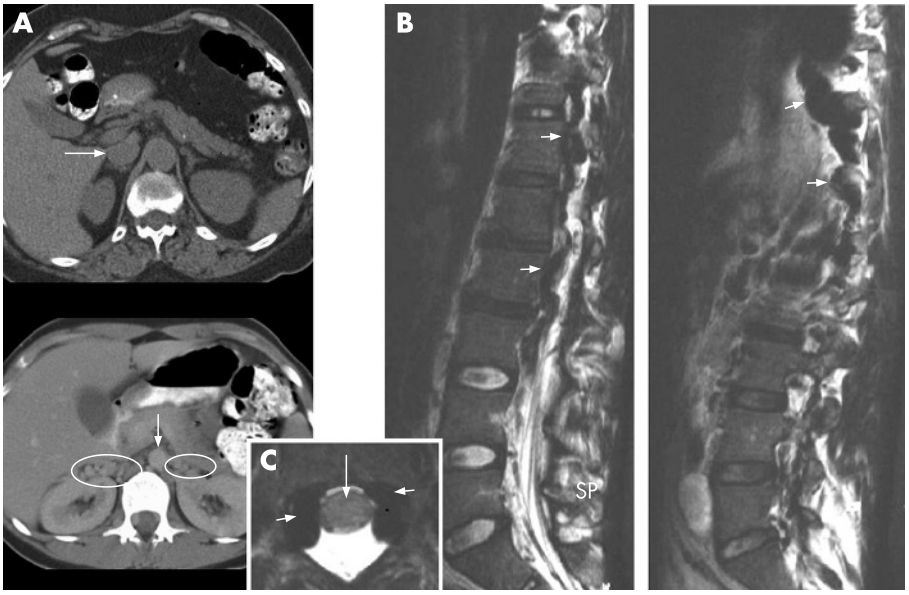

Figure 1 (A) Upper picture shows a transversal CT scan of the abdomen of a normal subject. Arrow indicates the vena cava inferior. Lower picture shows transversal CT scan of the abdomen of the index case. Arrow indicates the descending aorta. Note the absence of the vena cava inferior. Ovals are drawn around dilated and thrombosed intra-abdominal collateral renal and ovarian veins. (B) Sagittal T2 weighed MRI scan. Left picture shows a midsagittal view. Small arrows indicate dilated engorged internal vertebral venous plexus. Right picture shows a parasagittal view. Small arrows indicate dilated drainage vein into azygos. (C) Transversal T1 weighed MRI scan at the L1 level (patient is in the horizontal position, in this position there are no symptoms of cauda equina compression). Small arrows indicate enlarged veins, large arrow indicates the spinal cord.

longitudinal veins of the abdomen and chest in the case of obstruction of the IVC (eg, thrombosis, tumour compression, pregnancy) or IVCA. The clinical relevance of the VVS as a vehicle for metastases of tumours originating in the small intestine along the spine has already been pointed out by Batson in 1940.[3]

The increase in symptoms in the erect position, which occurred in our patient, is compatible with the observations of Théron and Moret.[4] They demonstrated that assuming an upright position is a prominent factor in directing blood flow through the VVS as an alternate route of cerebral venous return. In our patient, the IVVP was already engorged because of the IVCA and iliac vein thrombosis. In the upright position, venous return via the IVVP increases even more, thus inducing an increase in venous pressure in the cranial dural sinuses, which subsequently leads to increased intracranial venous pressure and headache.

Attention to pathology involving the VVS in the assessment of lumbar spine symptoms may improve diagnostic accuracy. For example, spinal epidural veins have been described that resembled prolapsed intervertebral discs on MRI, causing symptomatic nerve root compression. The correct diagnosis was only made during surgery. In this respect, Paksoy and Gormus[5] have described a series of 13 out of 9640 patients who had radicular symptoms due to IVC obstruction or occlusion causing dilatation of VVS vessels and nerve root compression. De Kruijk *et al* presented a patient with acute cauda equina compression syndrome caused by dilated anterior epidural veins secondary to thrombosis of the IVC.[6]

In conclusion, we have emphasised the neurological relevance of knowledge of the VVS, and have aimed to achieve more awareness of the VVS for clinicians who are involved in diagnostic imaging of the lower spine. In particular, our case history indicates the importance of appreciating soft tissue signals on MRI of the spinal area.

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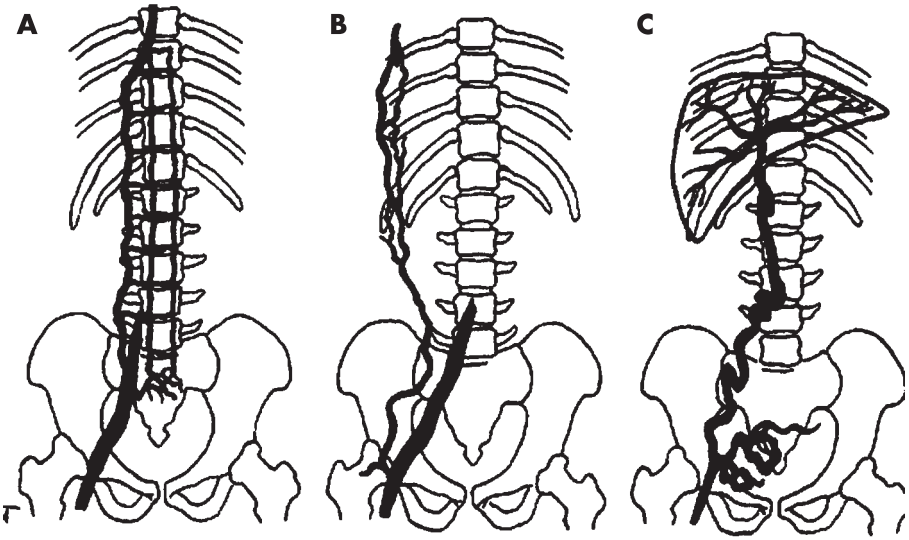

Figure 2 Diagram showing the three main collateral pathways in obstruction or agenesis of the vena cava inferior. (A) Vertebrolumbar pathway. (B) Anterior abdominal wall pathway. (C) Transumbilical portocaval pathway. Adapted from Gorenstein and colleagues.[1]

Hydrocephalus induced chorea

Chorea can result from many causes, and the diagnostic workup can be challenging. Although often accompanied by other extrapyramidal symptoms, hydrocephalus has not been mentioned as a possible cause of chorea to date. Here we report an unusual case of

chorea secondary to normal pressure hydrocephalus, which clearly improved after shunt placement. Hydrocephalus may cause extrapyramidal symptoms, which are most likely a result of pressure on tracts of the nigrostriatal pathway or the cortico-striato-pallido-thalamo-cortical circuit. Apparently, hydrocephalus induced pressure may occasionally also compromise the caudate nucleus which lies immediately adjacent to the enlarged ventricles, resulting in chorea. We suggest that clinicians should be more alert to hydrocephalus as a rare but reversible cause of chorea.

Normal pressure hydrocephalus (NPH) typically presents with the triad of cognitive deterioration, abnormal gait and urinary incontinence. Additional akinetic or tremulous movements may result from both idiopathic and secondary NPH. In contrast, hyperkinetic movements other than tremor have not been reported to result from hydrocephalus. When present, such hyperkinetic movements in NPH were exclusively observed secondary to causes not related to the hydrocephalus.[1] Indeed, secondary chorea has been described to result from a variety of causes, but not from hydrocephalus.[2]

Here we report a case of NPH induced chorea, which completely resolved after shunt placement. We will briefly discuss the pathophysiological mechanisms underlying movement disorders in hydrocephalus.

Case report

A 76-year-old woman presented with urinary incontinence and gradually increasing cognitive impairment, particularly a disturbed short term memory and spatiotemporal orientation. She later developed abundant involuntary movements of all extremities, which after 4 weeks eventually resulted in loss of ambulation. Her medical history revealed rheumatoid arthritis and mild cognitive impairment as a result of a small ischaemic stroke in the right cerebellum 1 year earlier, after which she had recovered to independent functioning and had been able to drive a car. She had not used dopaminergic medication, neuroleptics, antiemetics or any other drug known to induce chorea.[2] Her family history was negative for Huntington's disease and other choreas.

Neurological examination showed marked cognitive impairment, notably impaired visuospatial orientation, attention and working memory. There were clear choreatic movements of her head and all extremities, which markedly interfered with walking. Balance was also disturbed. The presence of a possible concomitant cerebellar ataxia could not be ascertained because of prominent bradykinesia. Systemic signs of autoimmune disease were absent; erythrocyte sedimentation rate was 42 mm, which is consistent with her history of rheumatoid arthritis.

A cerebral MRI scan demonstrated a tumour in the left cerebellopontine angle, compatible with a vestibular schwannoma, which was accompanied by enlargement of the lateral ventricles and a patent aqueduct (fig 1). The tumour was otherwise without symptoms. The right cerebellum showed signs of ischaemic stroke from an earlier occurrence. There was mild atrophy of the caudate nucleus, but no signs of lacunar stroke in the basal ganglia or subthalamic nucleus.

A ventriculo-peritoneal drain with a medium pressure valve was placed, and CSF pressure was normal (18 cm H_2O). Ventricular CSF showed increased protein (1.8 g/l). Glucose, cell count and cytological examination were normal. As the vestibular schwannoma was not symptomatic, no further treatment was initiated. Within weeks after the ventriculo-peritoneal drain placement, cognitive function improved to premorbid levels with normal short term memory and spatio-temporal orientation. The choreatic movements disappeared completely. A repeat MRI showed improvement of the hydrocephalus. The patient was able to live independently again. Three year radiological follow-up revealed no increase in the vestibular schwannoma, and 5 year clinical follow-up disclosed no recurrent chorea.

Discussion

We have presented a patient with chorea that was most likely secondary to idiopathic NPH. A causal relationship between chorea and hydrocephalus was suggested by various factors. Firstly, the chorea resolved completely shortly after shunt placement. Secondly, there was no recurrence of the chorea over time, with a maximal follow-up of 5 years. Thirdly, other main causes of secondary chorea in elderly people were excluded, such as lacunar stroke in the basal ganglia or subthalamic nucleus and use of medications which are known to cause chorea. There were no systemic signs of autoimmune disorders at presentation or during follow-up, and the mildly elevated erythrocyte sedimentation rate (42 mm) was consistent with a prior history of rheumatic arthritis. This disease course—with an isolated ''bout'' of chorea that remitted shortly after shunting of NPH and that never recurred—is difficult to reconcile with a second concurrent disease, certainly when this was an autoimmune disease that was left untreated. We considered Sydenham's chorea as this may resolve spontaneously without treatment, but this disorder usually presents at 5–20 years of age. Rare episodes of Sydenham's chorea at older ages have been described, but such patients typically had several childhood episodes of Sydenham's chorea.[3] We also considered Huntington's disease, but this was deemed unlikely because of the disease course, with complete remission shortly after shunting and the negative family history. Furthermore, the patient died 5 years later after a myocardial infarction without any signs of recurrent chorea.

Hydrocephalus induced movement disorders typically include tremor, rigidity, loss of postural reflexes, bradykinesia, a higher level ''frontal'' gait disorder and bradyphrenia.[1] Signs of midbrain dysfunction, including Parinaud syndrome, may be present in cases of aqueduct stenosis. Hyperkinetic movement disorders have been described in hydrocephalus, but these were exclusively secondary to causes unrelated to hydrocephalus itself, such as the use of phenytoin or basal ganglia infarction. Huntington's disease has been associated with NPH in three cases, and with obstructive hydrocephalus in one case.[4 5] These four patients had a positive family history of involuntary movements. Clinical improvement occurred after shunting in all patients, but the choreatic movements never disappeared fully, as was the case in our patient. Hydrocephalus might have disclosed a subclinical disposition of Huntington's chorea in these cases.

Hydrocephalus causes extrapyramidal symptoms, most likely due to local pressure on tracts of the nigrostriatal pathway or the cortico-striato-pallido-thalamo-cortical circuit. Parts of these pathways lie in close proximity to the ventricular system and may be subjected to volume effects or ischaemic changes secondary to ventriculomegaly, resulting in a hypokinetic rigid syndrome or tremor. Apparently, hydrocephalus induced pressure may occasionally also compromise the caudate nucleus which lies immediately adjacent to the enlarged ventricles, in this case resulting in chorea. Perhaps some of the cognitive impairment in this patient also resulted from caudate function.

Why such focal caudate nucleus involvement is not seen more frequently in hydrocephalus remains unclear. Perhaps chorea is under recognised as a sign of hydrocephalus (eg, because more severe bradykinesia distracts the clinician's attention from the more subtle signs of chorea). We suggest that clinicians should be more alert to hydrocephalus as a rare but reversible aetiology in chorea.

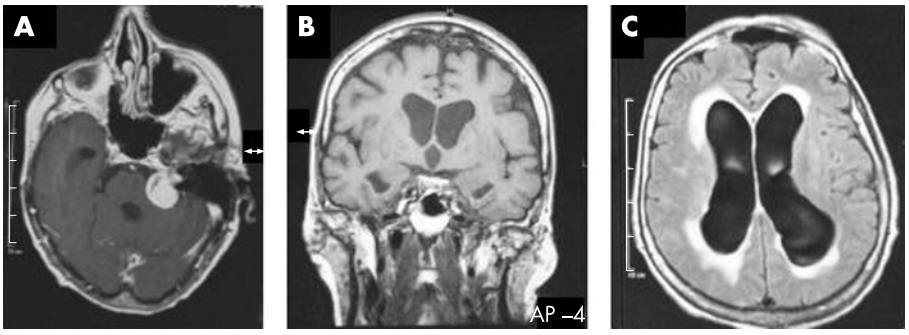

Figure 1 (A) T1 weighted MRI scan demonstrated a tumour in the left cerebellopontine angle, compatible with a vestibular schwannoma which was accompanied by enlargement of the ventricles adjacent to the caudate nucleus. The aqueduct is patent (B). Fluid attenuated inversion recovery series showed periventricular effusion (C).

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A novel founder mutation in the *MFN2* gene associated with variable Charcot–Marie–Tooth type 2 phenotype in two families from Southern Italy

Charcot–Marie–Tooth (CMT) disease is the most common hereditary neuropathy. CMT falls into two main forms: the demyelinating CMT type 1 with decreased nerve conduction velocities and the axonal CMT type 2. CMT2 is further subtyped by linkage analysis into >10 loci, with eight genes identified.

Recently, mutations in the mitochondrial fusion protein 2 (*MFN2*) gene were reported in families with CMT2A[1] and additional mutations have been detected in other studies, bringing to 42 the total number of different *MFN2* mutations described thus far.[2–4]

In the current study, we report a novel *MFN2* mutation shared by two apparently unrelated CMT2 families originating from the same area in Southern Italy.

Vertical transmission and male-to-male inheritance were documented in both families, indicating that CMT2 segregates as an autosomal dominant trait. In family 1, 14 affected individuals were identified in four generations (three deceased before the study). After giving informed consent, eight affected individuals and 12 unaffected family members were examined by neurologists and enrolled in the genetic study. All affected individuals showed bilateral pes cavus, lower extremity wasting and steppage gait; only two of eight affected family members (IV-6, IV-7) complained of leg pain. Electrophysiological examination revealed decreased compound motor action potential (CMAP) and sensory action potential (SAP) amplitudes and mildly slowed motor and sensory nerve conductions that were consistent with axonal neuropathy. Age at onset was very variable and ranged from the first decade (IV-6 and IV-7) to the fifth decade (III-5 and III-7). Generally, the affected subjects belonging to the last generation showed an early onset that appeared to correlate with a faster progression of the disease and a more severe phenotype.

In family 2, six subjects with CMT2 were reported in three generations. Two (mother and son) signed the informed consent to be enrolled in the clinical and genetic study.

The proband (indicated by an arrow in fig 1) noticed pes cavus and walking difficulties at age 10 years. On examination at age 33 years, he showed bilateral pes cavus, steppage gait, distal muscle weakness and wasting (mild in the upper limbs and moderate in the lower limbs), reduced to absent deep tendon reflexes and mild sensory loss in both feet. He also had postural upper limb tremor. Nerve conduction studies showed reduced amplitudes of CMAPs and SAPs; nerve conduction velocities were preserved in the upper limbs and mildly slowed in the lower limbs. His mother showed a less severe phenotype. On examination at age 61 years, she had slight pes cavus and mild steppage gait; wasting and weakness in distal muscle was minor in the upper limbs but clear in the lower limbs, ankle jerks were absent and there was foot sensory loss. On nerve conduction studies, CMAP and SAP amplitudes were slightly decreased to normal in the upper limbs and reduced in the lower limbs; nerve conduction velocities were mildly decreased only in the lower limbs.

Mutational screening of the *MFN2* gene was performed by denaturing high performance liquid chromatography (Transgenomic WAVE system).

In the index cases of both families, denaturing high performance liquid chromatography analysis, followed by direct sequencing of the PCR product of exon 11, revealed a heterozygous C>T transition at position 1148 (c.1148C>T) leading to the p.A383V amino acid substitution. Analysis of the other family members confirmed the presence of the mutation in all CMT2 affected subjects and in two unaffected subjects of family 1 (III-10 and IV-13). Neurological and EMG examinations of these subjects, 70 years and 36 years old, respectively, revealed no clinical signs or symptoms or any electrophysiological motor or sensory nerve impairment. The possibility of a common polymorphism was excluded as the mutation was not detected in 440 control chromosomes.

The presence of the same mutations in unrelated cases may be ascribed to two different events, namely a founder effect or the presence of a mutational hot spot. In order to explore these hypotheses, seven polymorphic markers (three intragenic and four close to *MFN2*) have been analysed on chromosome 1p36.22. In family 1, an at risk haplotype segregates in all of the affected subjects. Interestingly, the affected subjects of family 2 share the same at risk alleles for six out of seven markers (fig 1) thus indicating that our finding is more likely the result of a founder effect rather than a mutational hot spot. In addition, the fact that both families originate from the same geographic area supports the hypothesis that the mutation may have been inherited from a common ancestor.

In common with previously reported *MFN2* mutations, CMT2 phenotype associated with

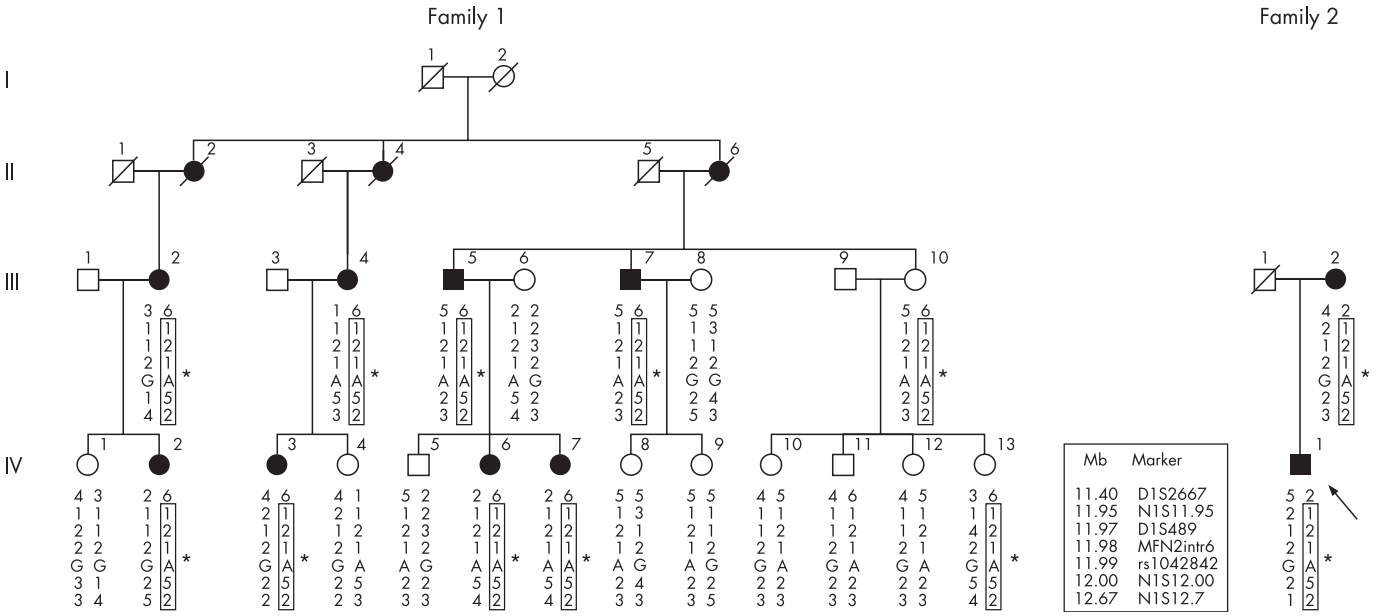

Figure 1 Pedigrees of the CMT2A families. Markers D1S489, MFN2intr6 and SNP rs1042842 are located, respectively, in intron 2, intron 6 and exon 19 of MFN2, whereas D1S2667, N1S11.95, N1S12.00 and N1S12.7 map in the immediate vicinity of the gene. Markers N1S11.95, MFN2intr6 and N1S12.7 are microsatellite sequences starting respectively at positions 11954818, 11981194 and 12006003 of the chromosome 1 assembly (UCSC hg18, NCBI Build 36.1). Boxes indicate the at risk haplotype cosegregating with the p.A383V (*) mutation in both families.