PostScript

LETTERS

Chronic meningitis and thalamic involvement in a woman: Fabry disease expanding phenotype

Fabry disease (FD, OMIM 301 500) is a lysosomal storage disorder caused by an X-linked inborn error of glycosphingolipid catabolism, resulting from deficient activity of α-galactosidase A. It leads to accumulation of globotriaosylceramide (Gb_3) in various organs. Manifestations of FD occur mostly in affected hemizygous males but also in heterozygous (carrier) females.[1 2]

Neurological complications in FD include CNS involvement, acroparesthesia, peripheral neuropathy, cranial nerve palsies with predominant VIIIth nerve involvement, and autonomic dysfunction.

Because a specific treatment has recently emerged, the diagnosis of FD may have a strong practical impact. Yet, enzyme replacement therapy has no proven efficacy on CNS Fabry manifestations.

We report on a woman who suffered from chronic meningitis which revealed heterozygous FD.

Case report

A 25-year-old woman was referred because of headache. Since the age of 12 years, the patient had complained of recurrent episodes of paresthesia in her four limbs, over 7–15 days, and sometimes leading to syncope. Headache started in November 2003, lasting 2–3 h everyday. In March 2004, the patient was hospitalised because her headache was unusually severe. At physical examination, hypoesthesia was affecting the left part of the body with respect to the face. C reactive protein blood level was 4.7 mg/dl (normal <1). CSF analysis showed 8 elements/μl. Brain and cervical medulla MRI was normal.

Throbbing headache recurred in October 2004. Body temperature was 38.5°C. She complained of sicca syndrome. There was persistent hypoesthesia of the left part of the body. Numerous telangiectasia were disclosed on the trunk. C reactive protein level was 2.7 mg/dl. Creatinine blood level was normal.

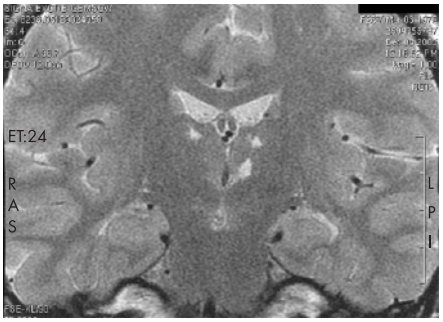

Figure 1 Brain MRI. T2 weighted coronal section shows bithalamic small infarcts, as fluid T2 hyperintensities, of the dorsolateral and left centromedial nuclei.

Microalbuminuria was slightly elevated at 44 mg/dl (normal <15). A second lumbar puncture was then performed showing 76 elements/μl with lymphocytes (44%) and granulocytes (43%). Testing for infectious agents and serum autoantibodies was negative.

Audiogram found a bilateral sensorineural hearing loss of 20 dB on 1000–8000 Hz frequencies. Ultrasound study of the extracranial and intracranial supra-aortic arteries was normal. Brain MRI was considered normal. Total body CT scan, bronchoalveolar lavage, and bronchial and salivary gland biopsy specimen analysis were normal.

Taking into consideration chronic meningitis and the fact that the patient originated from an area endemic for tuberculosis, antituberculous treatment was started in October 2004. In May 2005, the patient was hospitalised again. CSF analysis showed 31 elements/μl with 72% of lymphocytes and 14% of granulocytes. A third brain MRI disclosed an abnormal signal in both thalami (fig 1). Past familial history was then more thoroughly addressed. Her younger sister had also suffered from recurrent pain in the four limbs in her adolescence. Their father had been on haemodialysis since the age of 42 years and died at 47 years, with no further data on the cause of renal disease or death.

FD was considered. Cornea verticillata was disclosed on a slit lamp ophthalmological examination. Globotriaosylceramide dosage in urine was highly elevated at 41.2 nmol/mmol of creatinine (n<6). The leucocyte specific activity of alpha-galactosidase A was decreased at 54 nmol/h/mg of protein (n in controls = 95). Analysis of the gene encoding alpha-galactosidase A found a deletion (c123delC) in exon 1.

The patient was then treated with acetylsalicylic acid 250 mg/day, gabapentine 300 mg three times a day and paroxetine 20 mg/day. Enzyme replacement therapy for FD was begun in October 2005. In June 2006, after 9 months of enzyme replacement therapy, there was no improvement in CSF analysis (40 elements/μl with 50% of lymphocytes and 37% of granulocytes) and the patient suffered from definite intracranial hypertension (recurrent headache, blurred vision, bilateral papilloedema, high CSF pressure with unchanged MRI). Intracranial hypertension resolved completely and CSF analysis improved (9 elements/μl) after 2 weeks of high dose steroid treatment.

Discussion

In our female patient, highly misleading features, such as fever of unknown origin, high C reactive protein level and chronic meningitis were related to FD because (a) specific ongoing CNS involvement was demonstrated, with bilateral thalamic infarcts, (b) no other cause was elicited after a thorough investigation panel and (c) such inflammatory features have already been reported in male patients with FD.[3 4]

One of these patients had fever of unknown origin at onset[3] and (as in our female patient) was treated with antituberculous therapy before the diagnosis of FD. Of note, a transient improvement in meningitis was also observed in two cases receiving corticosteroid therapy alone.[3 4]

The pathophysiology of cerebrovascular involvement in FD, including dolichoectasia of the large arteries and progressive occlusion of the small arteries, is poorly understood. Cardioembolic events may also complicate specific hypertrophic cardiomyopathy, valvulopathies and arrhythmia. Accelerated atherosclerosis related to end stage renal failure may occur. The fact that a genetic disorder such as FD may be associated with spontaneous wax and wane fever and inflammation is intriguing. The mechanism of inflammation in FD may reside beyond the schematic ''vascular deposits'' model. Interestingly, among the genetic modifiers addressed in FD, some are implicated in inflammation, thrombosis or both.[5]

FD might to some extent belong to the genetic autoinflammatory disorders spectrum. Diseases such as familial Mediterranean fever (FMF, OMIM 249 100) and tumour necrosis factor receptor superfamily 1A associated periodic syndrome (TRAPS, OMIM 142 680) may cause periodic fever and recurrent CNS inflammation.

In conclusion, FD may cause steroid responsive CNS inflammation in both men and women and should be included in the list of the causes of chronic meningitis.

Acknowledgements

We wish to acknowledge Catherine Caillaud, MD, PhD, and Roselyne Froissart, MD, PhD for their technical assistance.

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doi: 10.1136/jnnp.2006.108464

Competing interests: Dr Lidove has received support from TKT Europe AB (Shire Human Genetics, Basingstoke, UK), Actelion Pharmaceuticals Ltd and travel fees from Genzyme Corporation; Professor Papo has received support from Genzyme Corporation; Dr Chauveheid, Dr Benoist, Dr Alexandra and Dr Klein have no conflicts of interest to declare.

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Reversible hypertensive cerebellar encephalopathy and hydrocephalus

Hypertensive encephalopathy (HTE) usually presents with progressive headache, confusion, visual disturbance and generalised seizures and may progress to coma and death. It is a common cause of the reversible posterior leucoencephalopathy syndrome,[1] now more commonly referred to as the posterior reversible encephalopathy syndrome, as grey matter is often also involved. Cranial imaging typically reveals parieto-occipital subcortical white matter oedema. The preferential involvement of the parietal and occipital lobes is unexplained but may be linked to the relative paucity of sympathetic innervation of the posterior cerebral arterial circulation. Impairment of autoregulation of cerebral blood flow because of an uncontrolled rise in arterial blood pressure, dilatation of cerebral arterioles and endothelial dysfunction are thought to underlie the vasogenic oedema which occurs.[1] We report a rare presentation of uncontrolled hypertension with episodic vertigo and ataxia, isolated cerebellar oedema on cranial MRI and secondary obstructive hydrocephalus.

Case report

A 52-year-old man presented with a 3 week history of recurrent episodes of severe vertigo, nausea, ataxia and mild headache. The initial episodes improved spontaneously over the course of several days but onset of the third such episode led to his admission to hospital. He had experienced mild persistent bifrontal headache and nocturia for 1 month. He had no visual symptoms. There was no history of head or neck trauma.

Five years previously he was noted to have a tonic left pupil and absent lower limb reflexes and was diagnosed with Holmes–Adie syndrome. He had a 15-pack-year history of smoking. There was no other significant past medical history but he did not recall having had his blood pressure measured for many years. His mother had developed hypertension in her forties.

On examination he was alert and orientated; he was not encephalopathic. There was persistent severe hypertension with systolic pressures of 230–255 mm Hg and diastolic pressures of 140–150 mm Hg. There was no postural hypotension. A tonic left pupil was noted. Fundoscopy revealed bilateral papilloedema, arteriovenous (A–V) nipping and exudate formation. Horizontal pursuit eye

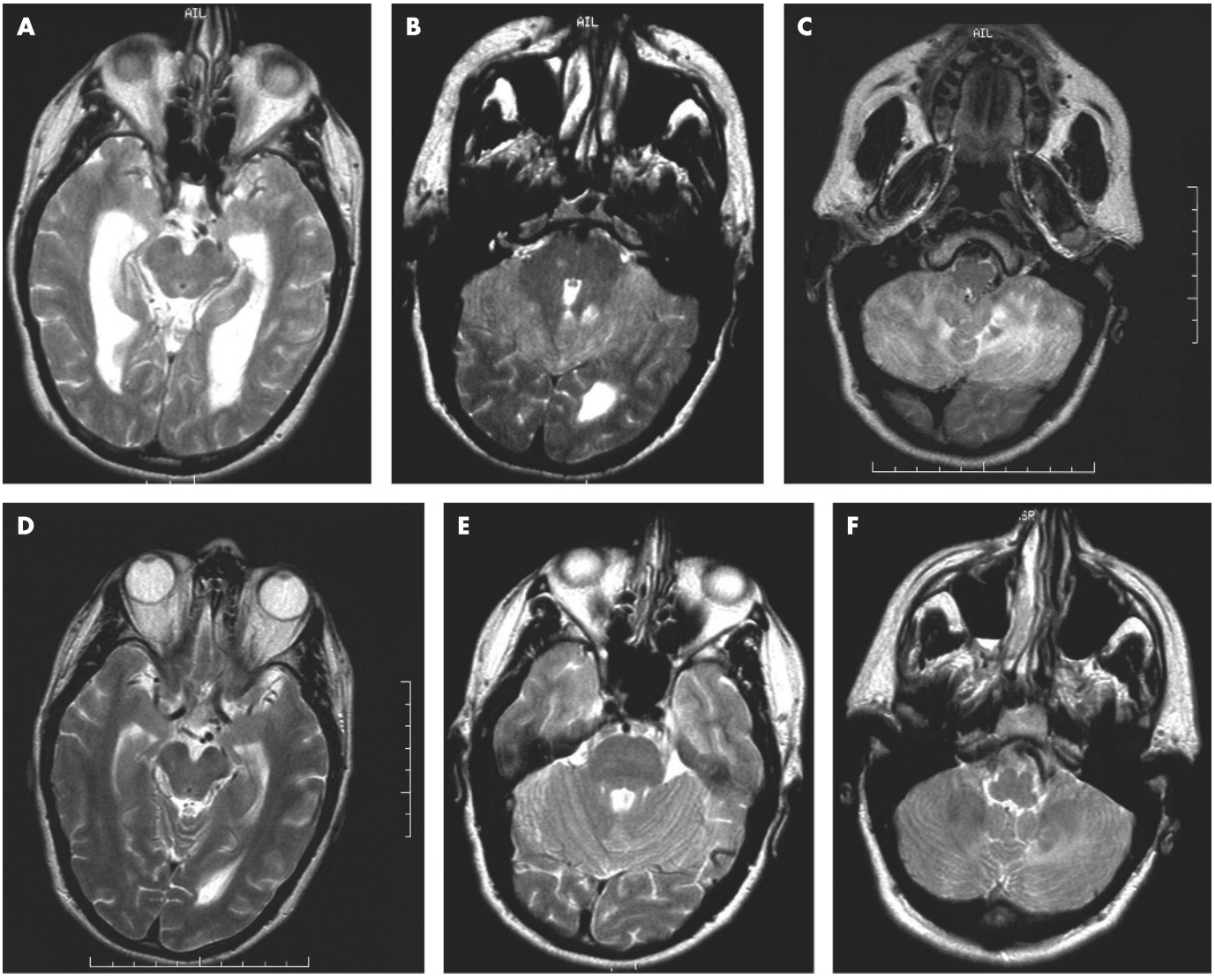

Figure 1 Sample magnetic resonance images of the brain acquired in the axial plane, with mainly T2 dependent contrast (repetition time 3320 ms, effective echo time 108 ms). Images (A–C) were made before treatment; uncontrolled blood pressure. Images (D–F) were made 5 days later. The pretreatment images show dilation of the lateral ventricles, swelling and signal change in the cerebellar white matter and compression of the fourth ventricle. The post-treatment images show resolution of the hydrocephalus and compression of the fourth ventricle and almost complete clearing of the signal abnormalities in the cerebellar white matter.