

LETTERS

White matter abnormalities on MRI in neuroacanthocytosis

Neuroacanthocytosis denotes a group of uncommon heterogeneous neurodegenerative disorders associated with acanthocytosis in the absence of any lipid abnormality. A variety of modes of inheritance have been proposed (X linked and autosomal recessive are clearly described, but a recent report of dominantly inherited chorea acanthocytosis¹ appears to be caused by Huntington's disease-like type 2 expansions in the *junctophilin-3* gene²) and mutations in two genes have been identified, the *XK* gene (in the X linked McLeod phenotype) and the *CHAC* gene (9q21; autosomal recessive)³. A wide variety of clinical features including chorea, orofacial dyskinesia, dysphagia, dysarthria, peripheral neuropathy, myopathy, seizures, and dementia has been described in these disorders.³

Case reports

Case 1

This patient was briefly described as case 19 in the report of Danek *et al.*⁴ He was a 61 year

old white male who had been well until 3 years previously, when he took early retirement from teaching owing to "disillusionment". He subsequently developed a progressive dementing illness, associated with facial tics, grunting noises, dysarthria, and chorea over the subsequent 3 years. There was no family history of neurodegenerative disease. He first presented to a neurologist having had an isolated generalised tonic-clonic seizure. On examination, he had a frontal dementia (Mini Mental State Examination (MMSE) score of 27/30) with evidence of self neglect and choreiform movements in all four limbs, and a prominent facial tic. He had little insight into his current illness. All tendon reflexes were absent. Investigation demonstrated numerous acanthocytes on blood films. Creatine kinase was raised at 1125 IU/l. Kell antigens were only weakly positive, which conformed to the McLeod phenotype. DNA analysis for Huntington's disease was negative, but a R133X mutation in exon 2 of the *XK* gene was found.⁴ All other investigations were negative (full blood count, copper studies, lipid studies, protein electrophoresis, vasculitis screen (antinuclear antibody, antineutrophil cytoplasmic antibody, double stranded DNA antibodies) syphilis serology, CSF analysis, and urinary amino acids. An

electroencephalogram showed no evidence of seizure discharge, but excess generalised slow wave activity. Nerve conduction studies were within normal limits. An MRI scan of the head (fig 1A) showed widespread areas of increased signal within the white matter of both cerebral hemispheres, especially within the lentiform nucleus bilaterally, but also within the thalamus, cerebral peduncles, and pons, and involving the corpus callosum (white arrow, fig 1B).

Case 2

This 56 year old Italian male developed chorea at the age of 42 years, and subsequently neuropsychological problems. The clinical aspects of this case have been reported previously.⁵ Numerous acanthocytes were seen on blood films, with weak Kell antigen. Analysis of the *XK* gene identified a R133X mutation. An MRI scan of the head showed mild increased signal within white matter on T2, proton density and fibre linked array image formatter (FLAIR) MRI sequences (fig 1C) in the posterior periventricular white matter.

Case 3

A 32 year old Indian male, born of consanguineous parents, who presented with progressive disinhibition, altered personality and chorea over a 2 year period. His clinical details have not been reported previously. His family had noticed intermittent unusual head movements in which he would appear to be looking around the room into empty spaces while conversing. Although these movements were involuntary, he was able to stop them temporarily if asked to do so. His personality had become more volatile with emotional outbursts and frequent loss of temper. On examination, his MMSE was 27/30. There were continuous choreiform movements of head and neck, and of all four limbs. He was able to interrupt these temporarily if asked to do so. His speech was slightly dysarthric but there was no involuntary tongue protrusion or evidence of self mutilatory behaviour affecting the tongue or lips. The remainder of his neurological examination was normal. Numerous acanthocytes were seen on blood films (fig 1D). Kell serology was normal, with exclusion of the McLeod phenotype. All other investigations including Huntington's mutational analysis, CSF, and white cell enzyme analysis were negative. Analysis of the *CHAC* locus is ongoing, but no mutations were identified in the *XK* gene. MRI head scan (fig 1E,F) demonstrated abnormally high signal in the periventricular white matter bilaterally, with involvement of the corpus callosum and cerebellar atrophy, but without contrast enhancement.

Discussion

Both computed tomography and MRI have been reported to show caudate and more generalised cerebral atrophy in neuroacanthocytosis.⁴ Although increased signal on T2 weighted MRI in the caudate and putamen has been noted previously, the increased signal throughout the cerebral hemispheres (including the corpus callosum in cases 1 and 3) reported here has not been reported previously. Extensive investigation for alternative causes of white matter abnormalities (vasculitic screen, and analysis

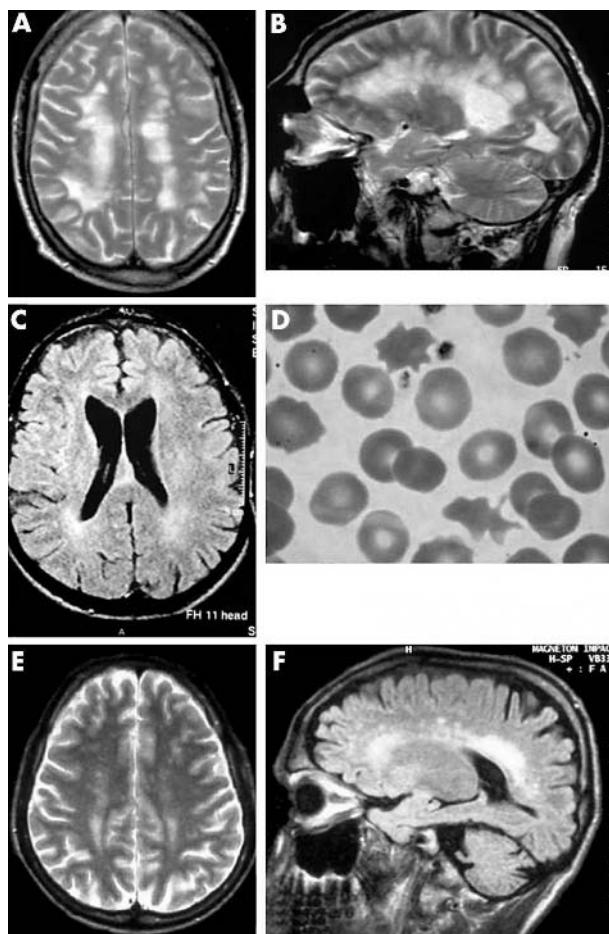


Figure 1 Axial T2 weighted (A) and sagittal (B) MRI from case 1, showing numerous areas of signal increase within the white matter, and involving the corpus callosum (arrow). (C) Axial T2 FLAIR MRI from case 2 showing mild signal increase within the white matter in the posterior periventricular area. (D) Blood film from case 3 showing numerous acanthocytes (arrow). Axial T2 weighted (E) and sagittal (F) MRI from case 3 showing similar, but less marked, white matter abnormalities to case 1, involving the corpus callosum (arrow).

of CSF, very long chain fatty acids, mitochondria, white cell enzymes and plasma lysosomal enzymes) was negative and there was no history of hypertension. In view of the ages of cases 1 and 2 when these patients were initially assessed, not much weight had been given to their MRI appearances; it was in the assessment of case 3 (a normotensive young male who was being investigated for a possible leukodystrophy) that the significance of both his abnormal blood film and his MRI prompted us to review the previous two cases.

Until we have a better understanding of the functional basis of these rare neurogenetic disorders, it is difficult to speculate as to the mechanism via how such abnormalities appear. Although the appearances reported in these cases are not specific, they widen the spectrum of MRI abnormalities that have been reported in neuroacanthocytosis. Thus, clinicians need to be particularly aware of the possibility of neuroacanthocytosis in any patient presenting with unexplained chorea,³ as the MRI appearances are so variable.

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Disruption of facial affect processing in word deafness

Word deafness (also known as auditory agnosia for speech, or as auditory verbal agnosia) is a rare neurobehavioral syndrome characterised by an inability to understand spoken language in spite of intact hearing, speaking, reading, writing, and ability to identify non-speech sounds. The lesions associated with this condition tend to be bilateral and symmetrical in nature, and include cortical-subcortical tissue of the anterior part of the superior temporal gyri. However, Heschl's gyrus is not always damaged completely in the left hemisphere. Moreover, there have been documented cases of word deafness caused by unilateral left hemisphere cortical and subcortical lesions.¹ Although these lesions are anatomically different, they represent an effective partial hemispheric disconnection.

Hemispheric disconnection has been associated with unusual disruptions of emotional processing. Bowers and Heilman² reported a patient with a lesion of the deep white matter of the right occipito-temporo-parietal region. This patient could name famous faces and discriminate affectively neutral faces, but could not name facial emotions or select emotional faces reflecting a named emotion. Bowers and Heilman hypothesised a visual-verbal disconnection resulting in an anomia for affective faces. More recently, Bowers, Bauer, and Heilman³ further articulated this idea, suggesting that this patient's performance resulted from a disconnection between a hypothesised non-verbal affect lexicon in the right hemisphere and the verbal lexicon in left hemisphere, which normally communicate via the deep white matter pathways damaged in their patient.

The documented association between hemispheric disconnection and anomia for facial emotion raises the possibility that similar deficits in emotion processing may be observed in word deafness.

Case report

WD1 was a 45 year old man who had suffered a left posterior temporal lobe hemisphere CVA two years previously. MRI had demonstrated an acute lesion of the left temporal lobe and a chronic lesion of the right temporal lobe. His new stroke produced an initial Wernicke's aphasia. A pre-existing high frequency sensory hearing loss was also documented. By 18 months after the stroke, the aphasia had resolved and WD1 underwent formal neuropsychological testing with the following results.

- Auditory comprehension was limited to single (maximum of two syllables) concrete nouns—for example, square or circle from the token test and adjectives such as yellow or red. The words he did understand had to be spoken slowly, loudly, and at a low pitch. He seemed to have general difficulty with rapid tonal transitions that mimic speech sounds, as in the speech sounds perception test and the seashore rhythm test.
- Reading comprehension was grossly within normal limits. He did demonstrate problems with complex syntax and evidenced occasional paraphasic errors. This may have been residual from his acute Wernicke's aphasia. On the whole, his speech was functional.

- He was able to differentiate and accurately recognise a range of environmental sounds, although he had trouble with high pitched sounds. His recognition was fast and accurate.
- He had no apraxia or other motor problems, and he was able to communicate by gestures.

Overall, the results of his neuropsychological evaluation were within normal limits. His specific deficits were consistent with those seen in word deafness.

Emotion processing

We administered a modified version of the Florida Affect Battery (FAB),⁴ including both facial and vocal prosody subtests, in an attempt to determine whether word deafness was associated with a disruption in the processing of affective prosody. The FAB consists of 10 subtests that evaluate emotion processing by different modalities: visual (facial expression), auditory (prosody), and visual/auditory cross-modal. WD1's performance was compared with that of 20 healthy adult controls. The test was modified, in that all instructions and emotion labels were presented in written form rather than orally.

WD1 performed at chance level on the prosody tasks, regardless of their affective content. This may have been related to a pre-morbid occupational sensory hearing loss. The possibility that his word deafness also contributed to his poor performance cannot be ruled out. However, the relative influence of word deafness cannot be determined in the absence of control subjects with impaired hearing.

WD1 was able to complete the visual subtests of the FAB, and his ability to discriminate facial identity and facial affect was within normal limits (table 1). His ability to match a stimulus facial expression with one from a target array was also within normal limits. However, he was moderately impaired relative to controls in his ability to match a printed affective name to facial expressions. He was also severely impaired in his ability to select the correct affective face from an array of faces when presented with a printed emotion label—that is, happy, sad, angry, frightened, neutral—despite intact reading and ability to discriminate affective facial expressions.

Discussion

WD1's pattern of performance on the FAB was identical to that of Bowers' and Heilman's patient,² and consistent with a visual-verbal disconnection. This finding

Table 1 Florida Affect Battery results

FAB face subtests	Correct (%)	z Score
Identity	90	1.3
discrimination		
Affect	85	−.8
discrimination		
Name the affect	80	−2.6*
Select the affect	75	−14.4*
Match the affect	90	−1.8

FAB, Florida Affect Battery.
z Scores are based on the distribution of the control group. *WD1's score is significantly different from controls, at $\alpha < 0.05$.

raises the possibility that a very specific disturbance of visual affect processing is a component of the word deafness syndrome. However, many neurocognitive syndromes lack a unitary functional basis and instead are an artefact of the behavioural geography of the brain.⁵ That is probably so with the affective processing disturbance observed in this case. The documentation of intact naming of affect in another word deafness case would answer this question definitively. At the same time, the functional auditory deficits and characteristic neuroanatomy of word deafness raise intriguing questions about the status of auditory emotion processing in word deafness, in view of this patient's preserved ability to identify non-speech sounds.

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A case of acute urinary retention caused by periaqueductal grey lesion

Diseases of the central nervous system often cause disturbances in micturition. These diseases include lesions in the spinal cord, pons, cerebellum, hypothalamus, basal ganglia, and cerebrum. Of these regions, the dorsomedial pontine tegmentum (pontine micturition centre, PMC), frontal lobe, and sacral spinal cord are considered important in controlling micturition. Recent studies in healthy humans using positron emission tomography (PET) have shown a significant increase in blood flow in the PMC and midbrain periaqueductal grey (PAG) during micturition and urine storage.^{1–3} Thus, in addition to the PMC, the PAG may play an important role in micturition control. However, to our knowledge, there is no clinical report that identifies the role of the PAG in micturition. Here we report a case of acute urinary retention caused by a small lesion in the PAG. A favourable response to

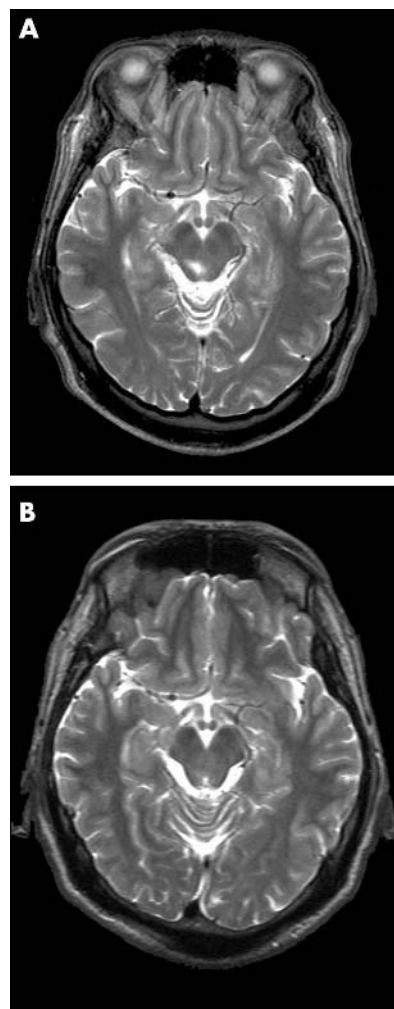


Figure 1 (A) T2-weighted magnetic resonance image (T2-WI) showing hyperintensity in the periaqueductal grey (PAG) where a significant increase in blood flow has been observed on positron emission tomography during micturition and urine storage in healthy humans.¹ (B) T2-WI showing a reduction in the intensity of the PAG lesion after steroid therapy.

steroid therapy resulted in the normalisation of micturition.

Case report

A 31 year old man had sudden voiding difficulty resulting in urinary retention and was referred to a neurologist. Although no particular abnormalities were observed except for an abnormal signal intensity on magnetic resonance imaging (MRI) in the right dorsal portion of the midbrain, he was suspected to have a demyelinating or inflammatory disease and 30 mg of oral prednisolone daily was prescribed. On the day he began prednisolone therapy, he was able to void but this was transient, and he was unable to void again two days later. He was referred to our department for further evaluation.

The patient's personal and family histories were negative for neurological disorders. Physical examination was unremarkable. Neurological examination revealed nothing but the inability to void. His cranial nerve

functions, motor and sensory systems, and autonomic nervous system were intact with preserved anal reflex, penile erection, and ejaculation. Nerve conduction studies on all four extremities and thermography of the upper extremities were normal.

A filling cystometrogram revealed an atonic bladder with diminished bladder sensation. There was no overflow incontinence.

Laboratory tests and analysis of the cerebrospinal fluid were all within normal reference ranges including immunological examinations. However, MRI of the brain showed a small abnormal signal in the right dorsal part of the PAG that was hypointense on T1-weighted image (WI) and hyperintense on T2-WI and fluid-attenuated inversion recovery (FLAIR) (fig 1A). The lesion was not enhanced with contrast material. No other abnormalities were found on the MRI.

Although we were unable to establish a diagnosis despite the thorough work up, we considered the PAG lesion to be responsible for his urinary symptoms and a disease originating from an immunologic abnormality such as vasculitis, was suspected based on the MRI findings and the favourable response to the steroid therapy. Therefore, 1 g methylprednisolone was given intravenously for three days (steroid pulse therapy), followed by 60 mg oral prednisolone for two weeks which was then tapered at a rate of 10 mg/week. After the steroid therapy was initiated, the patient's symptoms and the PAG lesion on subsequent MRI of the brain improved and he was able to void (fig 1B). However, the inability to void recurred, and a second course of pulsed steroid therapy was given. Day by day his symptoms improved again and resolved completely.

Comment

The patient reported here presented with acute urinary retention and diminished bladder sensation. The only abnormality detected by imaging, laboratory, and electrophysiological studies was a small PAG lesion. Therefore, we concluded that the PAG lesion was responsible for his symptoms. Unfortunately, we could not establish a diagnosis. However, on the basis of the favourable response to steroid therapy he was suspected to have a disease caused by some immunological abnormality.

Blok *et al* reported that in human PET studies the right dorsomedial pontine tegmentum and the PAG were significantly activated during micturition.¹ In addition, the results of various studies also suggest that the PAG, especially the right dorsal part, plays a critical role in the control of micturition, possibly as the relay centre from the spinal cord to the PMC.^{2,3} The PAG lesion in the present case was located at the site identified in PET studies to be significantly activated during micturition. Although more similar cases are needed to establish a true relation, our findings in the present case provide direct clinical evidence of the role of the PAG in integrating the micturition reflex in humans.

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Combination of thalamic Vim stimulation and GPi pallidotomy synergistically abolishes Holmes' tremor

The recent report of Kim *et al.*,¹ who demonstrated that stereotactic surgical ablation of the thalamic nucleus ventrointermedius (Vim) markedly improved Holmes' tremor in a patient with midbrain tumour, corroborated our earlier findings.² In their patient, Vim thalamotomy alleviated tremor in both the distal and proximal segments of the upper extremity.¹ However, controversy continues to surround the advisability of using this procedure for proximal tremors because the placement of larger lesions carries increased risks and the somatotopy of the proximal or truncal muscles remains obscure in the human Vim.^{3–5} Here we present a patient with a pontine haemorrhage in whom the combination of thalamic Vim deep brain stimulation (DBS) and globus pallidus internus (GPi) pallidotomy abolished Holmes' tremor.

This 53 year old right-handed man with a history of essential hypertension suddenly developed right hemiparesis and cerebellar ataxia in February 2000. He was admitted to a hospital where radiological examinations showed a left upper brainstem haemorrhage (fig 1A). His neurological state gradually improved. However, in October 2001 a coarse, slowly progressive tremor arose in his right upper extremity. It was severely disabling and he could not use his right arm. He was admitted to our hospital in December 2001.

On admission, he was alert and oriented. His speech was mildly dysarthric and slurred. There was palatal tremor. Mild hemiparesis with increased stretch reflexes and Babinski sign were noted on the right side. There were mild deficits of position, vibratory sense, and superficial sensation of light touch and pain in his right upper and lower extremities. Dysmetria was more pronounced on the right. Because of severe truncal and gait ataxia, he could not remain upright without support; he was unable to walk even with assistance. There was coarse and severe tremor in the right upper extremity. It persisted at rest and its amplitude increased during maintenance of a fixed posture and intentional voluntary movements. It rendered the right arm useless and prevented him from feeding and caring for himself. He was exhausted because of the severe tremor that persisted throughout his waking hours.

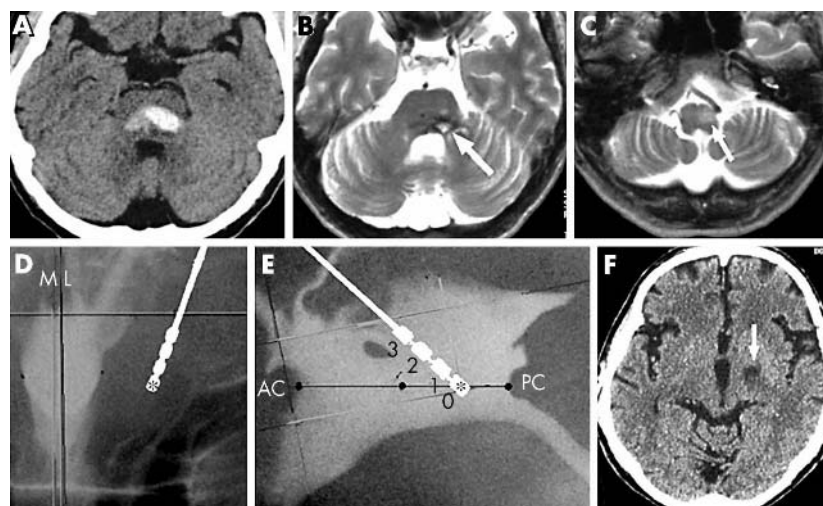


Figure 1 (A) Computed tomography (CT) scan showing a haematoma in the pontine tegmentum. (B, C) Axial views of T2-weighted magnetic resonance images at chronic stage (22 months after onset) demonstrating a haemosiderin ring around the lesion in the pontine tegmentum (B, arrow) and a high signal intensity area in the left inferior olivary nucleus indicating hypertrophic olivary degeneration (C). (D, E) Location of the electrode superimposed on the frontal (D) and lateral (E) view of a selective third ventriculography. The target point is indicated by the asterisk. (F) CT scan demonstrating the coagulative lesion made by the left GPi pallidotomy (arrow). The CT scan was carried out 10 days after pallidotomy. AC, anterior commissure; PC, posterior commissure; ML, midline.

Surface electromyograms showed rhythmic grouping discharges of 3.6 Hz in the right forearm muscles. His preoperative score on the Tremor Rating Scale (TRS)⁶ for his right upper extremity (Part A, score 5) was 11. Magnetic resonance imaging (MRI) study (December 2001) showed a haemosiderin ring around the lesion in the left pontine tegmentum (fig 1B). On T2-weighted images, a high signal lesion was seen in the left inferior olive, as consistent with the hypertrophic olivary degeneration (fig 1C). As sequential pharmacotherapy using clonazepam (3×0.5 mg/day) and benserazide/levodopa (3×25/100 mg per day) was only slightly effective, he was referred for surgery. Prior informed consent was obtained from the patient and his family.

In January 2002, a quadripolar DBS electrode (Model 3387; Medtronic Inc., Minneapolis, MN, USA) was implanted in the left thalamic Vim nucleus with the aid of MRI, third ventriculography, and microelectrode guidance, as previously described.² The optimal target was determined to be 7 mm posterior and 14.5 mm lateral to the midpoint of the anterior to posterior commissure (AC–PC) line, and on the AC–PC line. The most ventral contact was placed precisely on the target point (fig 1D, E). As stimulation tests, performed for 5 days, confirmed the beneficial effects of DBS, a programmable pulse generator (Soletra, Model 7426; Medtronic Inc.) was implanted. His post-operative course was uneventful.

After extensive trials, stimulation was carried out using contacts 0 and 1 (fig 1D, E). The optimal stimulation parameters were determined to be 160 Hz frequency, 90 µsec pulse width, and 2.9 V and 3.4 V amplitude at the first and final session. Stimulation with amplitude exceeding 3.4 V induced unpleasant electrical paraesthesia on the right side of his face and right upper extremity. Under optimal stimulation, the tremor was markedly alleviated in the distal

part of his right arm: the TRS score for his upper extremity tremor (Part A, score 5) was reduced to 6. Upon discontinuation of stimulation, the distal tremor reappeared immediately and returned to the preoperative state. The proximal tremor of his right arm was unresolved.

After discharge, he visited our outpatient department once a month. In January 2003, he complained of gradual worsening of the remaining proximal tremor; the distal tremor remained completely suppressed by thalamic Vim stimulation. We discussed GPi pallidotomy⁷ and obtained informed consent prior to the procedure.

In April 2003, left GPi pallidotomy was performed according to the method we described previously.⁷ The optimal target for the posteroventral part of the GPi was determined to be 2 mm anterior and 20 mm lateral to the midpoint of the AC–PC line, and 1 mm dorsal to the floor of the third ventricle. After creating a test lesion (42 °C, 60 sec), a permanent anatomical lesion was made by heating the electrode tip to 72 °C for up to 70 sec. The electrode was moved in 2 mm increments in the medial, lateral, and dorsal directions, and the lesioning process was repeated to increase the overall size of the lesion (fig 1F). GPi pallidotomy completely abolished his proximal tremor. However, it produced only a small effect on his distal tremor and discontinuation of Vim stimulation resulted in its reappearance at almost the preoperative level. Without stimulation, the TRS score for his upper extremity tremor (Part A, score 5) was 5. The combination of Vim stimulation and GPi pallidotomy had synergistic effects in abolishing Holmes' tremor in our patient. The therapeutic benefits remain unchanged at the time of writing and the TRS score for his upper extremity tremor (Part A, score 5) is 0. His palatal tremor did not respond to Vim stimulation and pallidotomy and remains unresolved.

Stereotactic Vim surgery, either thalamotomy or thalamic stimulation, is a mainstay in the surgical treatment of parkinsonian or essential tremors.⁸ Its efficacy in tremor suppression is superior to that of pallidotomy in parkinsonian patients. However, as evidenced by our case, it does not always produce satisfactory results in patients with Holmes' tremors, particularly with respect to their proximal tremors. The basal ganglia outflow pathway from the GPi exerts a direct influence on not only the thalamus but also the brainstem motor centres such as the pedunculopontine nucleus related to the mesencephalic tegmental field that controls the axial and proximal appendicular musculature via the descending reticulospinal tract. Therefore, unlike thalamic surgery, which interrupts the thalamocortical output that controls distal appendicular musculature via descending corticospinal and corticobulbar tracts, GPi pallidotomy influences the control of otherwise inaccessible axial and proximal muscles. This may be the reason why GPi pallidotomy produced a marked alleviation of the proximal tremor in our patient. Due to the limited efficacy of thalamic Vim surgery on proximal tremors, the use of other or additional surgeries with greater effects—for example, pallidal surgery⁹ or subthalamic area stimulation,⁹ should be considered for the treatment of Holmes' tremor.

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No association of the mitochondrial DNA A12308G polymorphism with increased risk of stroke in patients with the A3243G mutation

There is a striking phenotypic variability among patients with the A3243G tRNA^{Leu(UUR)} gene mutation of mitochondrial DNA (mtDNA), the most common heteroplasmic mtDNA mutation. It is responsible for ~80% of cases of MELAS (mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes), and is also associated with several other phenotypes including maternally inherited diabetes and deafness (MIDD) and chronic progressive external ophthalmoplegia (CPEO).¹

Only 50% of patients carrying the A3243G mutation have stroke-like episodes^{1,2} and the reason for this clinical variability remains poorly understood. Although the percentage level of the A3243G mutation in clinically relevant tissues appears to be important, this relationship is far from clear.¹ High percentage levels of the A3243G mutation in muscle are associated with stroke-like episodes, but approximately one in five patients harbouring >80% A3243G in muscle remain stroke free,¹ suggesting that additional environmental and genetic factors may influence the phenotypic expression of this mutation.

One possibility is that background mtDNA sequence variation influences phenotype. There is a well-recognised association between the mtDNA genetic background (or haplogroup) and the risk of developing visual failure in another mtDNA disorder, Leber's hereditary optic neuropathy,³ and a similar mechanism may influence the incidence of stroke-like episodes in patients harbouring the A3243G mutation. Intrafamilial clustering of clinical phenotypes in A3243G patients would indirectly support a role for the mtDNA background, though our own clinical experience suggests that there is significant clinical variability between families.

Pulkes *et al* have previously reported an increased risk of stroke associated with the presence of a homoplasmic, polymorphic (A12308G) variant in 48 patients with the A3243G mutation.² The A12308G polymorphism, which is located in the second mitochondrial tRNA gene encoding leucine (tRNA^{Leu(CUN)}), occurs with a frequency of 21% in a population of European origin and defines the mtDNA super-haplogroup U/K together with two other polymorphisms (A11467G and G12372A). As haplogroup U has also been reported to be a risk factor for sporadic occipital stroke in patients with migraine,⁴ these observations could have profound implications for our understanding of mitochondrial genotype and its relationship to the clinical phenotype. Here we report on the investigation of the A12308G polymorphism in a larger group of well-characterised, unrelated A3243G index cases.

Methods

We carried out a large, multicentre study to investigate the A12308G polymorphism in a group of 107 unrelated family index cases harbouring the A3243G mutation. The patients (>95% Caucasian) were from England, Germany, USA, Australia, and Finland. All presented to a neurology clinic, where stroke-like episodes were diagnosed clinically by experienced neurologists based

upon a characteristic clinical history and brain imaging with computed tomography (CT) or magnetic resonance imaging (MRI)⁵; in all cases, a molecular diagnosis of the A3243G mutation was made at a centre with expertise in the investigation of patients with mtDNA disorders.

To investigate the A12308G and G12372A polymorphisms, a 249 bp fragment spanning this mtDNA region was polymerase chain reaction (PCR)-amplified using a forward primer (5' GATTGTGAATCTGACAACAGAGG CTT 3'; nt 12164–12189) and a reverse primer (5' GGTTAACGAGGGTGGTAAGGATG 3'; nt 12412–12390). Amplified products were purified and sequenced using BigDye terminator cycle sequencing chemistries on an ABI 377 automated DNA sequencer (Applied Biosystems, Warrington, UK).

Results

The A12308G polymorphism was present in 32 of the 107 patients, while 56 had a history of stroke-like episodes. Nine of the 56 patients with a history of a stroke and 23 of 51 patients without stroke were shown to harbour the A12308G polymorphism. Every patient with the A12308G polymorphism also harboured the G12372A variant, indicating that they belong to the same mtDNA super-haplogroup U/K.

As shown in fig 1, our study alone revealed an apparent negative association between stroke-like episodes and the A12308G polymorphism, an observation in direct contrast to the positive association found by Pulkes *et al.*² Meta-analysis of all available data however, including the present study (n = 107) and the published study of Pulkes *et al.*² (n = 48), revealed that 16 of the 77 patients with a history of a stroke and 25 of 78 patients without stroke harboured the A12308G polymorphism. This did not show a statistically significant association between the A12308G polymorphism and stroke-like episodes ($\chi^2 = 2.53$, p = 0.112).

Discussion

The aim of our study was to examine whether a previously described association between the A12308G polymorphism and an increased risk of stroke in patients with the A3243G mutation² was reflected in a larger study group. In agreement with previous reports, 52% of our patients experienced stroke-like episodes^{1,2} and 30% harboured the A12308G polymorphism, confirming that our cohort of

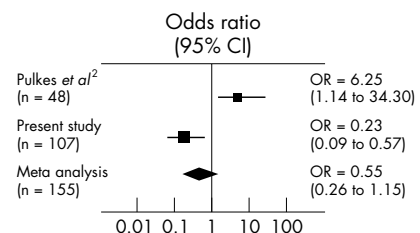


Figure 1 Meta-analysis showing odds ratios (OR) and 95% confidence intervals (CI) for the original study by Pulkes *et al.*² the data generated by this study, and the combined dataset including both studies. The squares represent the OR, with the size proportional to the study size. The horizontal lines show the CI for the OR. The diamond shows the OR for the combined dataset with CI that overlap 1, indicating a non-significant result.

107 A3243G index cases formed a representative sample. Despite studying a larger cohort of patients, we were not able to confirm the positive association between the A12308G polymorphism and an increased risk of stroke in patients with the A3243G mutation as reported previously.² Meta-analysis of all the available data failed to prove any clear association between the A12308G polymorphism and stroke-like episodes.

The clinical diversity associated with the A3243G mutation clearly involves multiple factors. We have previously shown a correlation between clinical phenotype and mutation load in muscle.¹ Age may well be a contributing factor, although there was a tendency for patients with stroke-like episodes in our group to be younger than those without. This argues against age as a risk factor for stroke-like episodes, as seen in common stroke.

Importantly our findings serve to highlight the difficulty of performing association studies on small numbers of patients. This is particularly difficult for mitochondrial genetic association studies because of the high variability of the mitochondrial genome. Understanding the phenotypic differences between patients with specific, pathogenic mtDNA mutations will ultimately involve studies of large cohorts of patients, unless we are able to gain clues from experimental studies that may highlight factors involved in the altered expression or segregation of mtDNA mutations.

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Early symptoms of brain tumours

Malignant cerebral glioma is the most common adult primary brain tumour but surprisingly few studies report how patients with early symptoms present in primary or secondary care. A retrospective audit in south east Scotland found considerable variation in the referral of patients with primary brain tumours: only one quarter of 439 patients were initially referred directly to specialist centres.¹ This must relate in part to the way in which symptoms develop and the difficulty of distinguishing them from more common but less sinister problems. For example, a large case record review of initial symptoms experienced by 653 glioma patients presenting to the National Hospital for Neurology and Neurosurgery, Queen Square, London, between 1955 and 1975 found a relatively low prevalence of neurological problems such as epilepsy (38%), headache (35%), mental change (17%), and hemiparesis (10%); by the time of diagnosis the prevalences were 54%, 71%, 52%, and 43%, respectively.² Few studies focus on the accounts of patients and relatives. One qualitative interview study of 28 Swedish patients suggested that relatives noticed general changes including cognitive and personality change and took the initiative in seeking help more often than the patients themselves.³

The recently published last diaries of the politician and historian the late Alan Clark provoked us to reconsider the significance of early symptoms from the perspective of patients and their close relatives.⁴ Clark provides us with a moving account of the gradual onset of symptoms from a glioma—fatigue, problems with thinking and concentration, and intermittent headache over nine months. He also describes vividly the anxiety of knowing something was wrong but without any explanation, before his tumour was diagnosed.

During a study of quality of life already described,⁵ we had opportunity to visit glioma patients at home after diagnosis, to listen to their accounts, and to question relatives separately. Here we report data on 92 patients (table 1), suggesting a differing development of symptoms and problems from that described in their medical records, and a distinctly similar picture, in some, to that described by Alan Clark. Interviews tended to elicit histories of more subtle problems such as fatigue and cognitive and personality change almost as often as the neurological problems typically associated with brain tumours. Of the 48 patients with headache only two had developed no other symptoms by the time of diagnosis.

Our sample is limited to patients who were well enough for radiotherapy and to receive home visits after diagnosis. It therefore excludes those most disabled and confused at diagnosis and treated with steroids alone. The data only cover problems that had developed before diagnosis. We did not have access to primary care records to explore how symptoms were presented to general practitioners, but 41% (38 of 92) were referred to a neurologist. Of the 64 patients whom we questioned on the topic, 19% (12) were critical of the initial management by their general practitioner and 28% of 88 relatives thought there had been significant delay by the health care system as a whole. This issue remained salient for many, even after the patient had died. Of 56 whom we saw as part of a study after bereavement, one third (17) spontaneously mentioned concerns they continued to have about delay in diagnosis and the effect this might have had on quality of life or survival. The problems they identified ranged across primary, secondary, and tertiary care and included their perception that referrals had not been made quickly enough or that waiting for appointments and imaging had been excessive.

The lack of data on the development of symptoms means that current national criteria for urgent referral rely on data from patients presenting to specialised centres rather than on the predictive power of symptoms in the population attending primary and secondary care. The data elicited here confirm the earlier suggestion by McKernan and Thomas that the significance of headache may lie in its association with altered patterns of behaviour and disability.² Although retrospective accounts cannot be used to define predictive factors for earlier diagnosis, they do suggest some implications for future research and practice. First, more detailed study of patients' and relatives'

Table 1 Symptoms at diagnosis of malignant cerebral glioma recorded in hospital records versus those elicited at home interviews

Symptom or problem	Recorded in the hospital records (n = 92)	Elicited from patients and relatives at home interviews (n = 92)
Weakness	55 (60)	51 (55)
Headache	49 (53)	48 (52)
Epilepsy	35 (38)	44 (48)
Sensory loss	32 (35)	37 (40)
Cognitive loss	30 (33)	42 (46)
Dysphasia	29 (32)	23 (25)
Personality change	14 (15)	28 (30)
Fatigue	13 (14)	44 (48)

Values are n (%).

experience might help further define the subacute presentation of cognitive and personality change and their relation to other complaints. Second, the predictive power of neurological symptoms presenting to general practitioners could be explored using existing large primary care research datasets. Third, relatives of patients referred urgently should be asked to attend with them to clarify aspects of the history that the patient may be unaware of. Beginning to discuss openly the difficulty of earlier diagnosis may help families come to terms with this lasting aspect of their concern. This might also help repair unnecessary rifts in relations with general practitioners, who are best placed to provide local support and palliative care these patients so often need.

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Five year follow up of a patient with spinal and bulbar muscular atrophy treated with leuporelin

Spinal and bulbar muscular atrophy (SBMA; MIM 313200) is an X linked late onset motor neurone disease characterised by slowly progressive proximal and bulbar muscle weakness, muscle atrophy, postural hand tremor, gynecomastia, and endocrine disturbances that include signs of partial androgen resistance. SBMA is caused by the expansion of a trinucleotide CAG repeat in the first exon

of the androgen receptor (AR) gene encoding a polyglutamine stretch.¹

Recently, Katsuno *et al*² reported that leuporelin, a luteinising hormone releasing hormone (LHRH) agonist that reduces the level of testosterone release from the testis, rescued motor dysfunction and nuclear accumulation of mutant ARs in a male transgenic mouse model of SBMA. This result indicates that ligand dependent nuclear translocation of mutant ARs containing expanded polyglutamine is the main source of the pathogenesis of SBMA, and that leuporelin suppresses this translocation. We read this report with great interest, because we followed up a patient with SBMA, who has been administered leuporelin for 5 years to treat his coexisting prostate cancer.

Case report

A 75 year old male noticed bilateral finger tremor at age 57. At age 63, he noticed weakness in his arms. He was admitted to our hospital in December 1991, when he was 64 years old. On initial examination, he had bilateral gynecomastia. Neurological examinations revealed facial weakness and lingual atrophy with fasciculations. Mild muscular atrophy was observed in the proximal parts of the upper extremities. Muscle strength was approximately in the range of 3/5 to 4/5 in the proximal parts, and 5/5 in the distal parts of the upper extremities. Fasciculations were observed in upper and lower extremities. Deep tendon reflexes were either lost or markedly diminished. Babinski signs were absent. Laboratory examinations revealed that the serum creatine kinase (CK) level increased to 803 IU/l (normal range 43–239 IU/l). LH (5.9 IU/L; normal range 1.8–5.2 IU/L) and follicle stimulating hormone (20.5 IU/L; normal range 2.9–8.2 IU/L) levels were elevated. After his informed consent was obtained, high molecular weight genomic DNA was extracted from peripheral leucocytes of the patient according to standard protocols. Genetic analysis of the AR gene was performed and the expansion of a CAG repeat (45 repeats) in exon 1 of the AR gene was identified, leading to a diagnosis of SBMA.

At age 67, he developed weakness in the legs, and noticed difficulty in climbing up stairs or standing up from a chair. Serum CK levels gradually increased to 1717 IU/L at age 70. In January 1998, when he was 71 years old, he was diagnosed as having prostate cancer, and was intramuscularly injected with 3.75 mg of leuporelin every 28 days, because leuporelin inhibits production of testosterone and dihydrotestosterone (DHT), which enhances the growth of prostate cancer cells. One month after the start of treatment, he noticed that his gait disturbance was rapidly exacerbated; however, the gait disturbance returned to the level before the start of treatment by April 1998. After the episode of transient exacerbation, his muscle weakness and atrophy exhibited no apparent deterioration to date. On the contrary, an improved muscle strength was recorded in the neck flexor, biceps brachii, and quadriceps femoris muscles. Furthermore, serum CK levels gradually decreased from 1717 IU/L to 834 IU/L after the leuporelin treatment (see fig 1). Levels of LH (<0.6 IU/L) or testosterone (<0.1 IU/L; normal range 1.2–8.0 IU/L) were decreased by the leuporelin injections.

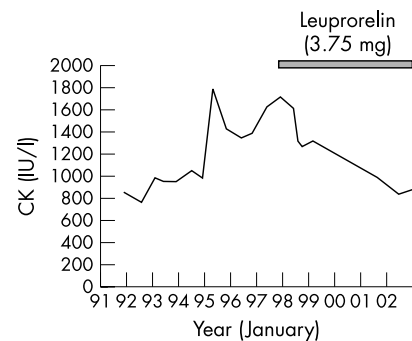


Figure 1 Serum creatine kinase (CK) levels of the patient gradually decreased from 1717 IU/L to 834 IU/L after the leuporelin treatment.

Discussion

The experience of a 5 year follow up of this patient treated with leuporelin is highly indicative of the following. Firstly, leuporelin treatment induced a transient deterioration of the motor function in humans, as demonstrated in a transgenic mouse model of SBMA.² Secondly, after the initial transient deterioration, long term stabilisation of the motor function was obtained. Finally, leuporelin treatment was effective even when the treatment was started in the advanced stage of the disease, although the patient's muscle weakness and atrophy have not completely disappeared. These findings provide grounds for the proposal made by Katsuno *et al*² that leuporelin is a promising candidate for the treatment of SBMA.

At least nine neurodegenerative diseases are known to be caused by expanded CAG repeats. SBMA is unique among these diseases because the disease protein, AR, has a specific ligand, testosterone. It has been demonstrated that the nuclear translocation of ARs is solely dependent on testosterone. Recently, a transgenic mouse model carrying full length AR containing 97 glutamine repeats has been generated, and this model showed progressive muscular atrophy and weakness.³ These phenotypes were markedly pronounced in male transgenic mice, which were significantly rescued by castration. Female transgenic mice exhibited only a few manifestations that markedly deteriorated with testosterone administration. Furthermore, in a *Drosophila* model of SBMA, it has been demonstrated that androgen agonists induce nuclear translocation of the mutant ARs and toxicity.⁴ Taken together, this raises the possibility that blockade of nuclear translocation of the mutant ARs by hormonal intervention can provide therapeutic benefits in SBMA.

LHRH agonists including leuporelin have been used for the treatment of prostate cancer. These drugs eventually inhibit LH production, which in turn inhibits production of testosterone and DHT, on which growth of prostate cancer cells depend. The alleviation or improvement of muscular weakness and decrease in the serum CK level in our patient may be due to the anti-androgen effects of leuporelin. Interestingly, he noticed rapid exacerbation of gait disturbance one month after the administration of leuporelin. It has been demonstrated that when LHRH agonists are administered continuously, the pituitary gland is initially stimulated, but after 5–12 days, the pituitary gland becomes

desensitised and stops releasing LH.⁵ When that occurs, the testes stop releasing testosterone. During the period of the initial stimulation, more LH is released, consequently there is a surge in the secretion of testosterone and DHT from the testes (so called “androgen surge”). It is reasonable that administration of leuporelin causes a transient exacerbation of muscle weakness in patients with SBMA due to the transient androgen surge.

In conclusion, we report the beneficial effect of leuporelin on SBMA. Our current experience warrants further investigations to determine whether leuporelin may be of benefit for the treatment of SBMA in humans.

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Cessation of migraine following central retinal vein occlusion

Cases of retinal vein occlusion with migraine have been described since 1882.¹ An interesting case of central retinal vein occlusion (CRVO) which coincided with complete

cessation of longstanding, severe migraines is reported.

Case report

A 44 year old lady developed classic migraine at the age of 11 years. Her symptoms comprised a visual aura of flashing lights followed by severe headache (not localised to one side), photophobia, and nausea, which generally lasted for two days. There were no identifiable triggers. Her management consisted of sumatriptan, which she took on experiencing the visual aura. This considerably reduced the severity of her headache and usually limited the duration of her symptoms to one day. The migraines occurred frequently and randomly with the longest migraine-free period being one month.

One morning, she awoke with visual loss in her right eye. She assumed this to be the visual aura of a migraine (although it was atypical since there was no photopsia or subsequent headache), and took her normal dose of sumatriptan. The visual loss occurred before taking the medication. The visual defect fragmented into black patches followed by gradual visual improvement over the next few days. She then consulted her general practitioner who referred her to the eye department.

At presentation to the eye department one week after the initial visual loss, her visual acuity was 6/9 right and 6/4 left. There was a right relative afferent pupillary defect. Funduscopy revealed retinal haemorrhages in all four quadrants with a swollen optic disc. A diagnosis of non-ischaemic CRVO was made. She was advised to take aspirin 75 mg daily.

On follow up, her visual acuity continued to improve with resolution of the retinal haemorrhages and the disc oedema. The following investigations were normal: full blood count, erythrocyte sedimentation rate, electrolytes, fasting glucose, fasting cholesterol, and plasma protein electrophoresis. General medical examination was normal. She is a non-smoker with no family history of cardiovascular disease. At the 18 month follow up her visual acuity was 6/5 right and 6/4 left. There was no relative afferent pupillary defect. The fundal appearance returned to normal.

Follow up to date is two years and she has not experienced a single migraine since developing the CRVO. There have been no other factors to account for the cessation of her migraines during this period.

Discussion

There have been numerous reports of retinal vaso-occlusion and migraine in the context of “complicated migraine”.¹ We have presented an interesting patient who instead experienced complete cessation of migraine in association with the development of a CRVO. In the natural history of migraine there is a gradual reduction in severity and frequency of attacks with age.² The abrupt

cessation of migraine following development of a CRVO suggests a causal relationship. She had no risk factors for a retinal vascular event.

It has been proposed that prophylactic use of platelet antagonists, such as aspirin, may reduce the occurrence of migraine. Serotonin is released locally in cerebral tissue shortly before the onset of a migraine attack. Since platelets contain all of the plasma serotonin platelet function has been implicated as a factor in migraine.³ The role of serotonin in migraine is complex. To the best of our knowledge there is no report of platelet antagonists causing complete cessation of migraine. It seems unlikely that aspirin was solely responsible for the cessation of migraine in our patient, however this remains a possibility.

The pathophysiology of migraine is complex but involves neuronal events linked to alterations in the calibre of intracerebral blood vessels. During a migraine aura cerebral blood flow decreases. The subsequent hyperaemia leads to headache by activation of fibres originating in the trigeminal ganglion. These trigeminovascular afferents reside primarily within the ophthalmic division of the trigeminal nerve.⁴ The retinal vasculature is very similar to the cerebral vasculature both in structure and response to vasoactive substances.⁵ This probably accounts for cases of “complicated migraine” leading to retinal vein occlusion.

We postulate that an initial neuronal event occurred in our patient that resulted in a functional alteration in her trigeminovascular system leading to the complete cessation of migraine. This neuronal event also produced a temporary decrease in central retinal artery perfusion and the subsequent development of a CRVO.⁵ This case therefore demonstrates the potential for intracerebral events to influence the retinal vasculature.

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