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 acanthocytosis appears to be caused by Huntington’s disease-like type 2 expansions in the \textit{junctophilin-3} gene\textsuperscript{2}) and mutations in two genes have been identified, the \textit{XK} gene (in the X linked McLeod phenotype) and the \textit{CHAC} gene (9q21; autosomal recessive)\textsuperscript{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\textsuperscript{4}.

Case reports

Case 1

This patient was briefly described as case 19 in the report of Danek \textit{et al}\.\textsuperscript{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 \textit{XK} gene was found.\textsuperscript{5} All other investigations were negative (full blood count, copper studies, lipid studies, protein electrophoresis, vasculitis screen (antinuclear antibody, anti-neutrophil 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.\textsuperscript{6} Numerous acanthocytes were seen on blood films, with weak Kell antigen. Analysis of the \textit{XK} gene identified a R133X mutation. An MRI scan of the head showed mild increased signal within white matter predominantly in the pons, proton density and T1 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).

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 \textit{CHAC} locus is ongoing, but no mutations were identified in the \textit{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.\textsuperscript{7} 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 investigations for alternative causes of white matter abnormalities (vasculitic screen, and analysis.
of CSF, very long chain fatty acids, mitochon- 
dria, white cell enzymes and plasma 
lyosomal 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 signifi-
cance 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 neuroge-
nic disorders, it is difficult to speculate as to 
the mechanism via which 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,7 
as the MRI appearances are so variable.

Acknowledgements
We are grateful to the Dr J A Spillane and the late 
Professor S Bundey for their evaluation and referral 
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D J Nicholl, I Sutton 
Department of Neurology, Queen Elizabeth Hospital, 
Birmingham, UK

M T Dotti 
Department of Neurological and Behavioral Sciences, 
Università di Siena, Siena, Italy

S G Supple 
Institute of Haematology, Royal Prince Alfred Hospital, 
Camperdown, Sydney, Australia

A Danek 
Neurologische Klinik, Ludwig-Maximilians Universität, 
Munich, Germany

M Lawdon 
Department of Neurology, Leicester Royal Infirmary, 
Leicester, UK

Correspondence to: Dr D J Nicholl, Department of 
Neurology, Queen Elizabeth Hospital, Birmingham 
B15 2TH, UK; d.j.nicholl@bham.ac.uk
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nucleoside and neuroacanthocytosis with a novel 

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 
cortical-subcortical tissue of the 
association and motor cortex may 
be involved. 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 asso-
ciated with unusual disruptions of emotional 
processing. Bowers and Heilman1 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 Heilman2 further articulated this 
idea, suggesting that this patient's perfor-
ance 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 demon-
strated 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 under-
went 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 evi-
cenced 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 prob-
lems, 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), 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 perfor-
mance 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 
premorbid 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 ruled out.

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 emotional label—that is, when 
matched to control subjects with impaired 
hearing.

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

<table>
<thead>
<tr>
<th>Table 1 Florida Affect Battery results</th>
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<tr>
<td><strong>FAB face subtests</strong></td>
</tr>
<tr>
<td>Identity</td>
</tr>
<tr>
<td>Discrimination Affect</td>
</tr>
<tr>
<td>Discrimination Name the affect</td>
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<tr>
<td>Select the affect</td>
</tr>
<tr>
<td>Match the affect</td>
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</table>

| 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. 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.

K W Greve, M T Heinly
Department of Psychology, University of New Orleans, LA, USA

K W Greve, C L Joffe, K J Bianchini
Jefferson Neurobehavioral Group, University of New Orleans, LA, USA

K J Bianchini
Department of Psychology, University of New Orleans, LA, USA

Correspondence to: Dr K W Greve; kgreve@uno.edu
doi: 10.1136/jnnp.2003.021790

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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.1–8 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 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.6–7 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.

H Yaguchi, H Soma, Y Miyazaki, J Tashiro, I Yabe, S Kikuchi, H Sasaki
Department of Neurology, Hakkaido University Graduate School of Medicine, Sapporo, Japan

H Kakizaki
Department of Urology, Hakkaido University Graduate School of Medicine, Sapporo, Japan

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proximal or truncal muscles remains obscure. The recent report of Kim et al. demonstrated that stereotactic surgical ablation of the thalamic nucleus ventrointermedius (Vim) markedly improved Holmes’ tremor in a patient with midbrain tumour, corroborating our earlier findings. In their patient, Vim thalamotomy alleviated tremor in both the distal and proximal segments of the upper extremity. However, controversy continues to surround the advisability of using this surgical approach for proximal tremors because the placement of larger lesions carries increased risks and the somatotopy of the frontopontine segment of the Vim nucleus makes safe placement of such lesions difficult. 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 right 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. Ataxia, he could not remain upright without assistance. There was coarse and severe truncal and gait ataxia in February 2000. He was admitted to our hospital in December 2001. 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. Surface electromyograms showed rhythmic grouping discharges of 3.6 Hz in the right forearm muscles. His preoperative score on the Tremor Rating Scale (TRS) 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. The optimal target was determined to be 7 mm posterior and 14.5 mm lateral to the mid-point 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 postoperative 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 paresthesia 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 pallidotomy and obtained informed consent prior to the procedure. In April 2003, left GPI pallidotomy was performed according to the method we described previously. 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.
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 (rRNA<sup>Leu</sup>(CUN)) gene mutation of mitochondrial DNA (mtDNA), the most common heteroplasmic mtDNA mutation. It is responsible for ~80% of cases of MELAS (mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes), and is also associated with other phenotypes including maternal inherited diabetes and deafness (MIDD) and chronic progressive external ophthalmoplegia (CPEO).<sup>1</sup>

Only 50% of patients carrying the A3243G mutation have stroke-like episodes<sup>1</sup> 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.<sup>1</sup> 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,<sup>1</sup> suggesting that additional environmental and genetic factors may influence the phenotypic expression of this mutation.

One possibility is that the background mtDNA sequence variation influences phenotype. There is a well-received association between the mtDNA genetic background (or haplogroup) and the risk of developing vascular failure in another mtDNA disorder, Leber’s hereditary optic neuropathy,<sup>2</sup> and a similar mechanism may influence the incidence of stroke-like episodes in patients harbouring the A3243G mutation. Intracranial clustering of clinical phenotypes in A2434G 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 also reported an increased risk of stroke associated with the presence of a homoplasmic, polymorphic (A12308G) variant in 48 patients with the A3243G mutation.<sup>2</sup> The A12308G polymorphism, which is associated with the second mitochondrial tRNA gene encoding leucine (tRNA<sup>Leu</sup>(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 (A14167G and G12372A). As haplogroup U has also been reported to be a risk factor for sporadic occlusive stroke in patients with migraine,<sup>2</sup> 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, and 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); 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’ GATTGTGAACTCAGACACAGGG CTT 3’; nt 12164–12189) and a reverse primer (5’ GGTTAAGCAGGCTGTGAAGCTG 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 a 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.<sup>3</sup> Meta-analysis of all available data however, including the present study (n = 107) and the published study of Pulkes et al. (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 (z = 2.35, 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 mutation was reflected in a larger study group. In agreement with previous reports, 52% of our patients experienced stroke-like episodes<sup>3</sup> and 30% harboured the A12308G polymorphism, confirming that our cohort of

References

A12308G polymorphism and stroke-like episodes in our group to be younger than those with a tendency for patients with stroke-like episodes. We have previously shown a correlation between clinical phenotype and mutation load in muscle. 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 phenotype 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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M Deschauer, P F Chinnery, A M Schaefer, D M Turnbull, R W Taylor
School of Neurology, Neurobiology and Psychiatry, The Medical School, University of Newcastle upon Tyne, UK

M Deschauer, S Zierz
Department of Neurology, Martin-Luther-University Halle-Wittenberg, Halle/Saale, Germany

S Shanske, S DiMauro
Department of Neurology, Columbia University College of Physicians and Surgeons, New York, USA

K Majamaa
Department of Neurology, University of Oulu, Finland

E Wilichowsky
Department of Paediatrics and Neuropaediatrics, Georg-August University Göttingen, Germany

D R Thorburn
Murdoch Childrens Research Institute, Royal Children’s Hospital, Melbourne, Australia

Correspondence to: Dr R W Taylor, School of Neurology, Neurobiology and Psychiatry, The Medical School, Framlington Place, University of Newcastle upon Tyne, Newcastle upon Tyne NE2 4HH, UK, r.w.taylor@ncl.ac.uk; doi: 10.1136/jnnp.2003.026278

Table 1

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

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 neurocognitive 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 last 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 to these patients so often need.

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E Davies
Department of Palliative Care and Policy, Guy's, King's and St Thomas' School of Medicine, Weston Education Centre, Custumbe Road, Denmark Hill, London SE5 9PJ, UK

C Clarke
National Hospital for Neurology and Neurosurgery, University College Hospitals, Queen Square, London WClN 3BG, UK

Correspondence to: Dr Elizabeth Davies; elizabethdavies@doctors.org.uk
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Five year follow up of a patient with spinal and bulbar muscular atrophy treated with leuprorelin

Spinal and bulbar muscular atrophy (SBMA; MIM 313280) is an X linked late onset motor neurone disease characterised by slowly progressive proximal and bulbar muscle weakness, muscle atrophy, postural hand tremor, gynaecomastia, and endocrine disturbances such as 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 al1 reported that leuprorelin, a lutenising hormone releasing hormone (LHRH) agonist, 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 leuprorelin suppresses this translocation. We read this report with great interest, because we followed up a patient with SBMA, who has been administered leuprorelin 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 November 1991, when he was 64 years old. On initial examination, he had bilateral gynaecomastia. 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 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 and reached 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 leuprorelin every 28 days, for 5 years. However, his coexisting prostate cancer. One month after the start of treatment, he noticed that his 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 leuprorelin treatment (see fig 1), decreased to LH (<0.6 IU/l) or testosterone (<0.1 IU/L; normal range 1.2–8.0 IU/L) were decreased by the leuprorelin injections.

Discussion
The experience of a 5 year follow up of this patient treated with leuprorelin is highly indicative of the following. Firstly, leuprorelin treatment induced a transient deterioration of the motor function in humans, as demonstrated in a transgenic mouse model of SBMA. Secondly, after the initial transient deterioration, long term stabilisation of the motor function was obtained. Finally, leuprorelin 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 al1 that leuprorelin 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.1 These phenotypes were markedly rescued 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.1 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 leuprorelin have been used for the treatment of prostate cancer. These drugs eventually inhibit LH production, which in turn inhibits production of testosterone and dihydrotestosterone (DHT), on which growth of prostate cancer cells depend. The alleviation or improvement of muscular weakness and deterioration in the serum CK level in our patient may be due to the anti-androgen effects of leuprorelin. Interestingly, he noticed rapid exacerbation of gait disturbance one month after the administration of leuprorelin. 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

Figure 1 Serum creatine kinase (CK) levels of the patient gradually decreased from 1717 IU/l to 834 IU/l after the leuprorelin treatment.
desensitised and stops releasing LH. 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 leuprorelin causes a transient desensitisation of the pituitary gland, possibly because LH production is high and transient. A similar phenomenon occurs in patients with SBMA due to the transient androgen surge.

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

T Shimohata, T Kimura, M Nishizawa
Department of Neurology, Brain Research Institute, Niigata University, Niigata, Japan
O Onodera
Department of Molecular Neuroscience, Resource Branch for Brain Disease Research, Center for Bioresource-based Researches, Brain Research Institute, Niigata University, Niigata, Japan
S Taji
Department of Neurology, University of Tokyo, Tokyo, Japan
Correspondence to: T Shimohata, Department of Neurology, Brain Research Institute, Niigata University, 1-757 Asahimachi, Niigata 951-8585, Japan; t-shimo@bri.niigata-u.ac.jp
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Cessation of migraine following central retinal vein occlusion

Cases of retinal vein occlusion with migraine have been described since 1882. 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 primary headache 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 papillary 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.

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 papillary 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”. 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. 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. 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 intracranial blood vessels. During a migraine aura cerebral blood flow decreases. The subsequent hypoperfusion 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. The retinal vasculature is very similar to the cerebral vasculature both in structure and response to vasoactive substances. 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. This case therefore demonstrates the potential for intracerebral events to influence the retinal vasculature.

S P Meredith, D K Newman
Department of Ophthalmology, Addenbrooke’s Hospital, Cambridge, UK
Correspondence to: S P Meredith, spmeredith@doctors.org.uk
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Cessation of migraine following central retinal vein occlusion

S P Meredith and D K Newman

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