

Figure 1 Brain CT showing a low density area involving the frontal right lobe.

attainment (phonological and semantic word fluency, sentence construction test); verbal memory (Rey's 15 word memory test); visual memory (immediate visual memory test); and abstract thinking (simple analogies, Raven's coloured progressive matrices). The overall cognitive performance was measured by the mental deterioration battery⁵ which takes into account results obtained on eight tests: phonological word fluency, sentence construction, short term recall, delayed recall, immediate visual memory, simple copy, copy with landmarks, and Raven's coloured matrices. The global cognitive performance was normal. As expected, of the individual cognitive tasks, only the simple copy and copy with landmarks were abnormal.

The most interesting findings were made assessing his ability to play the piano and write music. The patient was requested to play what he saw on one page of unfamiliar music using both hands. Next, he was instructed to search for and cross out all the

notes previously played, with a pencil in his right hand and without a time limit. The sheet of music was placed with respect to the midline of his body and this placement was held constant across all the different tasks. Almost without exception, the patient accurately played all notes on both sides of the page, using the entire keyboard and all pedals appropriately. Despite this good performance, when asked to cross out the notes he had just played, he cancelled the notes on the right side of the page and neglected 75% of those on the left side. Moreover, when he attempted to write a new musical theme or a simple scale, he again omitted the left side of the page (fig 2). To better understand the patient's awareness of the notes on the left side of the page, the patient was requested to sing the musical pieces before playing them. Again, when singing he did not neglect words or notes on the left side.

Unilateral visuospatial neglect syndrome is characterised by a broad range of presentations that may be apparent only during specific situations or when performing different tasks. More commonly, it is not an "all or none phenomenon", such that separate tests may not identify the neglect syndrome in all patients.⁴ Additionally, single deficits are not always evident with the same aspect and extent during different tasks.⁶

According to other authors,⁷ patients with non-dominant right lobe injury may be unable to focus their attention on single components on the left side of a global figure, yet they may have a well structured global perception. These patients have an implicit awareness of stimuli that are not separately perceived and identified. Our patient's neglect was particularly evident when focal attention was concentrated on single elements of a more complex presentation. As shown by his capacity to play the piano and to sing music, our patient could have a global perception of the music but he was clearly unable to shift his attention on single notes. The modularity of music perception and reproduction has previously

been shown.⁸ Indeed, it has been suggested that musical competence might be shifted to the left hemisphere in persons with higher musical education.⁹ Perhaps, our patient's neglect was similar to that of a patient recently described by Marshall and Halligan: "He can perceive the whole forest, but only half the trees".¹⁰ Interestingly, whereas the patient described by Marshall and Halligan showed both parietal and frontal lesions, CT of our patient showed only a frontal infarction, which may represent the real culprit in this syndrome.

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- 1 Marshall JC, Halligan PW. Imagine only the half of it. *Nature* 1993;364:193-4.
- 2 Marshall JC, Halligan PW. Blindsight and insight in visuo-spatial neglect. *Nature* 1988; 336:766-7.
- 3 Heilman KM, Watson R, Valenstein E. Neglect and related disorders. In: Heilman KM, Watson R, eds. *Clinical neuropsychology*. 3rd ed. New York: Oxford University Press, 1993.
- 4 Cermak SA, Lin K. Assessment of unilateral neglect in individuals with right cerebral vascular accident. *Topics in Geriatric Rehabilitation* 1994;10:42-55.
- 5 Caltagirone C, Gainotti G, Masullo C, Miceli G. Validity of some neuropsychological tests in the assessment of mental deterioration. *Acta Psychiatr Scand* 1979;60:50-6.
- 6 Herman EW. Spatial neglect: new issues and their implications for occupational therapy practice. *Am J Occup Ther* 1992;46:207-16.
- 7 Halligan PW, Marshall JC. Toward a principled explanation of unilateral neglect. *Cognitive Neuropsychology* 1994;11:167-206.
- 8 Basso A, Capitani E. Spared musical abilities in a conductor with global aphasia and ideomotor apraxia. *J Neurol Neurosurg Psychiatry* 1985;48:407-12.
- 9 Bever T, Chiarello R. Cerebral dominance in musicians and non-musicians. *Science* 1974; 185:357-9.
- 10 Marshall JC, Halligan PW. Seeing the forest but only half the trees? *Nature* 1995;373: 521-3.

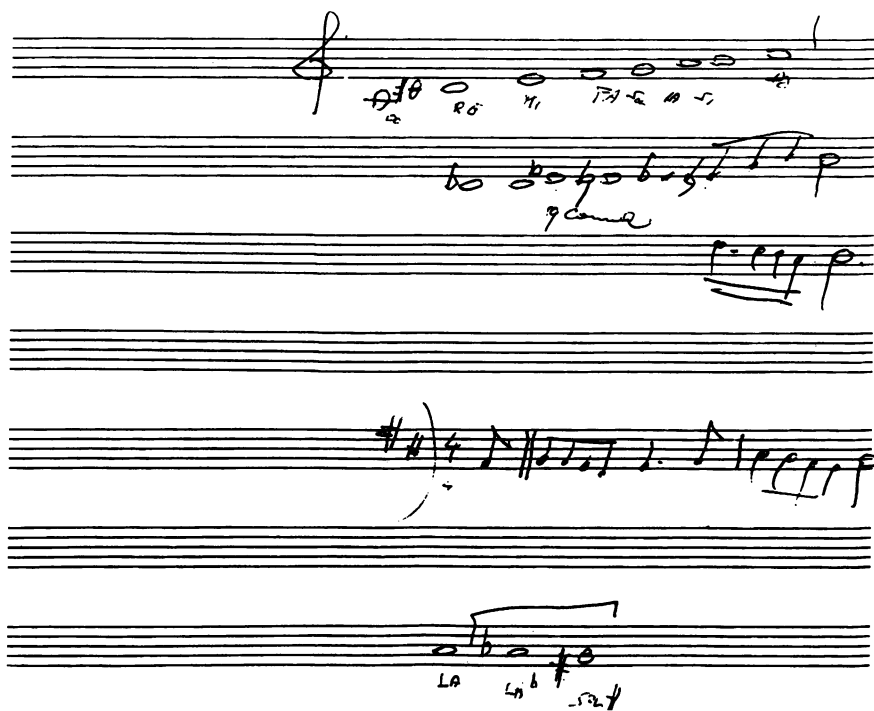


Figure 2 The patient's attempts to write a musical scale (top) and to draft a composition. Both series were begun from the centre of the page. The left hand side was systematically ignored.

Two unusual clinical presentations of the mitochondrial DNA A3243G point mutation in adult neurological practice

The most often identified mitochondrial tRNA gene point mutation is at position 3243 (A to G) in the mitochondrial transfer RNA gene for leucine (UUR). It was originally described in association with the mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) phenotype, but is increasingly recognised to occur in association with other phenotypes. Disease associated with this point mutation presents in childhood or early adult life in the vast majority of cases and there are often other affected family members in the matrilineal line.¹⁻³ In this report we describe two patients presenting with unusual phenotypes over the age of 50 years without any family history. We highlight the importance of considering mitochondrial disease associated with this mutation in this age group and show that it may have important investigative and prognostic implications.

Patient 1 was a right handed 51 year old man who presented with a three day history of progressive difficulty using his left side, and left sided inattention. A year previously he had presented with a nocturnal seizure and

a few days later developed fluent dysphasia over the course of a day. Brain CT at that time was reported as showing a left temporo-parietal infarction. His speech had recovered completely but residual mild cognitive difficulties had been noted by his family. Normal investigations at that time included transthoracic echocardiography, carotid Doppler imaging, autoimmune screen, and thrombophilia screen. There was no family history of stroke or other neurological disease.

Neurological examination showed left sided neglect. He had a non-dominant parietal lobe syndrome. He showed pronounced dressing apraxia, left sided astereognosis, dysgraphaesthesia, left/right disorientation and was disoriented in the ward environment. He persistently held his left arm in an extended elevated posture. Muscle power was normal throughout. General and cardiovascular examination were normal.

Brain MRI was abnormal (figure). The T2 axial scan showed extensive abnormal signal involving the cortex and white matter of the right parietal and temporal lobes. The affected gyri were swollen with sulcal effacement and mild ventricular compression. The right occipital lobe was also involved to a lesser degree. Intra-arterial angiography showed an area of neovascularisation in the right parietal lobe supplied predominantly by small new vessels arising from the distal right pericallosal artery. The MRI appearances had initially raised the possibility of a space occupying lesion; however the presence of neovascularisation on angiography suggested that the abnormality seen was primarily infarction although not conforming to a single vascular territory. This combination of MRI and angiographic appearances was suggestive of a MELAS type lesion and a muscle biopsy was therefore undertaken. This was diagnostic of a mitochondrial myopathy showing ragged red fibres and fibres demonstrating both increased and absent cytochrome c oxidase (COX) staining. Analysis of mtDNA extracted from muscle showed 87% A3243G point mutation. Resting serum lactate was normal. The patient was managed conservatively and made a good functional recovery.



Axial T2 weighted image of brain of patient 1 illustrating areas of increased signal in the right temporo-parietal and occipital regions.

Patient 2 was a 69 year old man who had a two year history of progressive generalised muscle wasting, weight loss, and decreasing exercise tolerance. He gave a six month history of slurring dysarthria. He had previously been fit and well and had been an active sportsman. He had a brother who had developed epilepsy as a boy and had insulin treated diabetes mellitus. There was no other family history of neurological disease.

Neurological examination showed pronounced generalised muscle wasting. Eye movements were normal but he had a slight right ptosis. There was a mild bulbar slurring dysarthria and mild weakness of neck flexion. He had global proximal and distal limb weakness MRC grade 4. He was areflexic. There were occasional fasciculations.

Creatine phosphokinase was persistently mildly increased at three times the upper limit of normal. Electrophysiological studies showed normal sensory studies and conduction velocities. There was no evidence of conduction block. Needle EMG was consistent with widespread denervation and reinnervation showing positive sharp waves, spontaneous fasciculations, and giant motor unit potentials in all four limbs. The progressive muscular atrophy variant of motor neuron disease was considered but in view of the absence of any upper motor neuron signs a muscle biopsy was performed. This showed characteristic features of a mitochondrial myopathy. There were many ragged red fibres and there were fibres showing increased and absent staining with the COX stain. ATPase staining showed fibre grouping consistent with denervation and reinnervation. Analysis of mtDNA extracted from blood and muscle showed the A3243G point mutation (5% in blood and 56% in muscle). This mutation was not detected in his brother's blood. The patient's resting lactate was twice the upper limit of normal. He was treated with ubiquinone and subjectively feels better although objectively examination nine months later showed no change in his limb weakness but evidence of an early external ophthalmoplegia. His resting serum lactate remains increased.

Although the mitochondrial encephalomyopathies are a group of disorders which have the common theme of disordered respiratory chain function they are recognised to be clinically and biochemically heterogeneous.⁴ This has made classification difficult. The discovery of primary mutations of mtDNA initially suggested that there may be genotype-phenotype correlations.⁵ However, it is increasingly apparent that the same genotype can be associated with a range of phenotypes which are separate. This seems to be especially the case for disease associated with the A3243G point mutation. This mutation was originally described in association with the MELAS phenotype which has been defined by Hirano and colleagues⁶ using the following "invariant" criteria: (1) multiple stroke-like episodes before the age of 40 years, (2) encephalopathy characterised by seizures, or dementia, or both, and (3) lactic acidosis or ragged red fibres, or both. They suggest that the diagnosis may be considered secure if there are at least two of the following: normal early development, recurrent headache, or recurrent vomiting. However, only about half the patients harbouring the A3243G point mutation exhibit the MELAS phenotype in most series.^{1,2} The other phenotypes described include chronic progressive ophthalmoplegia, other encephalopathic ill-

nesses without stroke, diabetes mellitus alone, and with deafness and, rarely, myopathy alone.^{1,3} In the vast majority of reported cases disease onset is in childhood or young adult life. Hammans *et al* reported three out of 20 probands harbouring the A3243G mutation presenting over the age of 50. Two of these had progressive external ophthalmoplegia, an easily recognisable mitochondrial disease phenotype.¹ Ciafaloni *et al* reported that one of 21 typical MELAS (A3243G) cases presented at the age of 50 years.² Moraes *et al* reported that none of their 16 cases with atypical A3243G phenotypes presented over the age of 42.³

Although patient 1 reported here has radiological features consistent with the MELAS syndrome⁷ the clinical presentation is quite different from that of typical MELAS cases and he does not meet the "invariant" criteria proposed by Hirano *et al*.⁶ It is well recognised that the A3243G mutation should be looked for in cases of young atypical stroke but the patients illustrated here indicate that it should be considered as a cause of stroke in older patients, particularly if the clinical evolution and radiological features are atypical. The findings of mild fibre type grouping and electrophysiological changes consistent with denervation and reinnervation in patient 2 suggest that the A3243G mutation may be causing anterior horn cell dysfunction in this patient.

The patients reported here further highlight the phenotypic variation associated with the A3243G point mutation and indicate the importance of considering mitochondrial disease associated with this mutation in this age group. Both of these patients were sporadic with no other family members exhibiting more typical A3243G associated phenotypes. In patient 1 a brain biopsy had been considered before the correct diagnosis was achieved, whereas in patient 2 the prognosis for his mitochondrial myopathy is likely to be better than that of the progressive muscular atrophy variant of motor neuron disease. The selection of which patients to investigate over the age of 50 years, who do not have classic mitochondrial phenotypes, remains difficult due to the wide range of potential presenting symptoms. However, in younger patients with both complex combinations of CNS symptoms with or without muscle weakness or with purely peripheral neuromuscular symptoms a mitochondrial disorder should enter into the differential diagnosis. The highest yielding investigation remains muscle biopsy for histochemistry, mitochondrial DNA analysis, and biochemical respiratory chain analysis.⁸

The precise explanation for the pronounced phenotypic diversity associated with the A3243G mutation remains unknown. Additional intragenic mutations which modulate the consequence of the mutation have recently been suggested¹ but there are other possibilities. It does not seem to be solely a reflection of the mutation load and its tissue distribution.¹ Further study of such late onset patients who seem to be able to tolerate the presence of the mutation for many years before manifesting disease may help to elucidate the origins of this diversity.

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- 1 Hammans SR, Sweeney MG, Hanna MG, Brockington M, Morgan-Hughes JA, Harding AE. The mitochondrial DNA transfer RNA^{Leu(UUR)} A->G⁽³²⁴³⁾ mutation: a clinical and genetic study. *Brain* 1995;118:721-34.
- 2 Ciafaloni E, Ricci E, Shanske S, et al. MELAS: clinical features, biochemistry, and molecular genetics. *Ann Neurol* 1992;31:391-398.
- 3 Moraes CT, Ciacci F, Silvestri G, et al. Atypical clinical presentations associated with the MELAS mutation at position 3243 of human mitochondrial DNA. *Neuromusc Disord* 1993;3:43-50.
- 4 Morgan-Hughes JA. Mitochondrial diseases. In: Engel AG, Franzini-Armstrong C, eds. *Myology*. New York: McGraw Hill 1995: 1610-60.
- 5 Goto Y, Nonaka I, Horai S. A mutation in the tRNA^{Leu(UUR)} gene associated with the MELAS subgroup of mitochondrial encephalomyopathies. *Nature* 1990;348: 651-3.
- 6 Hirano M, Ricci E, Koenigsberger MR, et al. MELAS: an original case and clinical criteria for diagnosis. *Neuromusc Disord* 1992;2: 125-35.
- 7 Rosen I, Phillips S, Enzmann D. Magnetic resonance imaging in MELAS syndrome. *Neuroradiology* 1990;32:168-71.
- 8 Jackson MJ, Schaefer JA, Johnson MA, et al. Presentation and clinical investigation of mitochondrial respiratory chain disease: A study of 51 patients. *Brain* 1995;118:339-57.

MATTERS ARISING

Brain and spinal cord MRI in motor neuron disease

We read with interest the article by Thorpe *et al*¹ raising the question of the importance of MRI alterations as prognostic factors in motor neuron disease. In a retrospective study at our institute, we also found signal abnormalities in MRI along the pyramidal tracts in 11 of 16 patients affected by amyotrophic lateral sclerosis.² In all of them, symmetric hyperintensity in T2 weighted images were recognisable at the level of the corona radiata, in the internal capsule and the cerebral peduncles; in two of these cases signal changes were also present in the pons. When the patients with and without MRI abnormalities were compared, we failed to find prognostic factors. Age, spinal or bulbar onset, disease severity as assessed by the Norris scale,³ time interval between onset of disease and MRI investigation, duration of disease (time interval between onset and death or study closure) did not differ between the two groups of patients. Conversely, MRI signal abnormalities were associated with more pronounced upper motor neuron signs. Thus in our experience, alterations in MRI do not have a prognostic value but they simply reflect the severity of pyramidal tract degeneration. As Thorpe *et al* suggested,¹ abnormalities of MRI may be helpful in early diagnosis of motor neuron disease. However, this has to be confirmed in further studies, as neuropathological examinations have shown great variability in

the expression of the involvement of the pyramidal tracts even in the typical cases.⁴

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- 1 Thorpe JW, Moseley IF, Hawkes CH, MacManus DG, McDonald WI, Miller DH. Brain and spinal cord MRI in motor neuron disease. *J Neurol Neurosurg Psychiatry* 1996; 6:314-7.
- 2 Carella F, Grisoli M, Savoirdo M, Testa D. Magnetic resonance signal abnormalities along the pyramidal tracts in amyotrophic lateral sclerosis. *Ital J Neurol Sci* 1995;16: 511-5.
- 3 Norris FH Jr, Calanchini PR, Fallat RJ, Panchari S, Jewett B. The administration of guanidine in amyotrophic lateral sclerosis. *Neurology* 1974;24:721-8.
- 4 Bronwell B, Oppenheimer DR, Hughes JT. The central nervous system in motor neuron disease. *J Neurol Neurosurg Psychiatry* 1970; 33:338-57.

NOTICE

Announcement from the British Neuropsychiatry Association: 1997 summer meeting

The 1997 summer meeting of the BNPA will be held jointly with the American Neuropsychiatry Association on 20-22 July at Robinson College, Cambridge, UK. It will include half day sessions on frontosubcortical circuits and emotion/reward/violence, and the presentation of short scientific papers, posters, and single case videos by members. The winner of the 1997 BNPA Prize will be announced. Two prizes of £200 each will be given to the best paper/poster presentations by junior members. The AGM of the BNPA will be held on 21 July.

For further details of this meeting please contact Suzanne Miller, 44 Roan Street, London SE10 9JT. Telephone 0181 858 2699; fax 0181 853 4416; e-mail wight@compuserve.com.

For details of membership of the BNPA, which is open to psychiatrists, psychologists, neurologists, and those in related fields, please contact Dr Jonathan Bird, Secretary BNPA, Burden Neurological Hospital, Stoke Lane, Stapleton, Bristol BS16 1QT.

BOOK REVIEWS

All titles reviewed here are available from the BMJ Bookshop, PO Box 295, London WC1H 9TE. Prices include postage in the United Kingdom and for members of the British Forces Overseas, but overseas customers should add £2 per item for postage and packing. Payment can be made

by cheque in sterling drawn on a United Kingdom bank, or by credit card (Mastercard, Visa or American Express) stating card number, expiry date, and your full name.

Pituitary Adenomas. Edited by A M LANDOLT, M L VANCE and P L REILLY. (Pp 656; £125.00.) Published by Churchill Livingstone, Edinburgh. 1996. ISBN 0443051348.

I very much enjoyed reviewing this book which has been edited by three neurosurgeons, from Europe, the United States and Australia. It is a very complete text which covers everything that you wanted to know about pituitary adenomas and would previously have had to search widely for contemporary answers. The editors have succeeded in commissioning a wide range of expert opinion covering all related specialist areas. The chapters have been logically arranged and there are many high quality illustrations including colour plates of histological slides. This is essential to achieve adequate clarity for interpretation by the non-expert reader. Inevitably there is some repetition, but in some ways this is no bad thing as the chapters can be read in isolation.

As a surgeon I was particularly interested in the chapters covering radiology, micro surgical anatomy, the history of pituitary surgery and current surgical techniques. The contemporary surgeon largely operates via the transnasal transphenoidal approach with minimal morbidity and high rates of cure. These remarkable achievements rely very much on sophisticated pre and per operative imaging techniques and the use of the operating microscope. Following an excellent and detailed account of the trans-sphenoidal approach there are further chapters on surgical results and prognosis for the various pituitary adenomas.

Following on from surgical considerations are excellent and very readable chapters covering the medical treatment of the different endocrinopathies associated with pituitary tumours. I particularly enjoyed the chapters on the different radiotherapeutic approaches to pituitary tumours. I have never been certain about which patients can safely be spared the potential long term morbidity of this treatment. Although optic neuropathy, brain necrosis and vascular injury are the most feared complications, hypopituitarism requiring hormonal replacement therapy eventually develops in a large proportion of patients after fractionated radiotherapy. It seems increasingly clear that despite full hormone replacement therapy many patients with iatrogenic hypopituitarism have a reduced quality of life.

The clinical features, diagnosis, and management of pituitary apoplexy are covered in a single chapter. This gives sound advice to the non-specialist neurosurgeon who may be called upon to deal with these cases when they present as emergencies. I would concur with the view that the beneficial effects on neurological, visual, and endocrine functions are sound reasons for early surgical intervention by the transphenoidal approach. The improved prognosis of pituitary apoplexy that has been achieved by contemporary management is amply illustrated by the fact that all 12 patients in the first published series of apoplexy were diagnosed at necropsy.

Overall I think that this is an excellent