LETTER

mtDNA mutations in Chilean patients with optic neuropathy

The aetiology of acute unilateral (AUON) and bilateral optic neuropathies (BSON) is unknown in most patients in Chile, after compressive lesions, collagen vascular diseases, and toxin exposure are ruled out. By contrast, up to 85% of white patients with clinically isolated AUON will develop multiple sclerosis. In Chile, both the incidence of multiple sclerosis and the risk of developing it after an acute unilateral or bilateral optic neuropathy, is significantly lower (4.3%).[1] It has been suggested that K and J mitochondrial DNA (mtDNA) haplotypes, characteristic of the European genetic background, might contribute to susceptibility to multiple sclerosis.[2] Research in the genetic epidemiology of cholesterol cholelithiasis among Chileans showed that 88% of Chilean Hispanics harbour Amerindian mtDNA haplotypes.[3]

Clinically isolated BSON is less well understood than AUON. A study conducted in London reported that four out of 23 patients (17%) with BSON had mtDNA mutations related to Leber hereditary optic neuropathy (LHON), and that a similar proportion developed multiple sclerosis.[4] As in multiple sclerosis, mtDNA lineage may have a role in the expression of LHON. Brown *et al* demonstrated the clustering of patients with LHON, especially those with the 14484 mutation, on European haplogroup J.[5]

Three mtDNA point mutations are considered primary mutations for LHON at mtDNA nucleotide positions (np) 3460,11778, and 14484. All of them alter the first enzyme complex of the mitochondrial electron transport chain. Most Native American mtDNAs fall into four distinct haplotypes (A-D). Given that in our population the mtDNA background is predominantly Amerindian and that we have a low incidence of multiple sclerosis developing after optic neuropathy, we studied the primary LHON mtDNA mutations and the mtDNA haplotype in Chilean patients with unexplained AUON or BSON.

Patients who had a history of toxin exposure, alcohol and tobacco misuse, evidence of a generalised demyelinating disease, CNS infections, collagen vascular disorders, increased vascularity around the optic disc at presentation, or family history of optic neuropathy were excluded. The same criteria were used in Morrisey *et al*.[4] We identified 58 patients. The ethics committee of the Hospital Clínico de la Universidad Católica de Chile approved the study. Total DNA was extracted from peripheral blood samples. Polymerase chain reaction (PCR) amplification and RFLP analysis evaluated the presence of the primary mutations at np 3460, 11 778, and 14 484. The mtDNA genotype analysis was performed similarly.

All Native American mtDNAs cluster into one of four distinct lineages, defined by restriction site variants: group A, defined by an *Hae*III site gain at np 663; group B by a nine base pair (9 bp) COII-tRNA^{Lys} intergenic deletion; group C by a *Hinc*II site loss at np 13 259, and group D by an *Alu*I site loss at np 5176.

There were 27 men and 31 women. Fourteen had AUON and 44 had BSON. The mean age at onset of AUON was 31.2 years (range 12–52) and of BSON 30.2 years (range 7–64). Seven males and one female had the mtDNA mutation at np 11 778. One male had the np 14 484 mutation (table 1). We did not find the np 3460 mutation. All the patients with mtDNA mutations had BSON. Most of the patients with BSON had a native American mtDNA haplotype (79%). The number was smaller for the AUON (56%). The nine patients with BSON carrying mtDNA mutations belonged to the D group of Native American mtDNA.

The longest duration of follow up for AUON was 36 months and for BSON 48 months. None of these patients had developed multiple sclerosis during this period of observation.

Our results are interesting in three main areas: pathogenicity of the primary LHON mtDNA mutations, mtDNA background as modulating factor for disease expression, and causes of BSON.

We found patients with BSON carrying the mtDNA np 11 778 and 14 484 mutations. All of them had a native American mtDNA haplotype. This confirms the pathogenicity of both mutations as they are related to disease in a different mtDNA background, extends it to the Native American mtDNA, and suggests that this mutation has arisen independently in several mtDNA lineages. We did not find any patient with the mtDNA 3460 mutation. There are several possible explanations. Among them, the 3460 may have not occurred in the Native American mtDNA lineages, or its clinical expression might depend in the presence of an unknown secondary mutation. It also could be due to the small sample size.

It was proposed that in the European white population, the mtDNA haplotype J plays a role in the expression of both 14 484 and 11 778 mutations, as they show a strong preferential association with that haplotype.[5] Interestingly, all the patients in our study in whom a BSON was related to a primary mtDNA mutation belonged to the haplotype D. In our aboriginal population the D haplotype is predominant (47%), and this figure likely represents the general population with Hispanic last names, but this needs to be formally ascertained. We found an absolute predominance of the D haplotype among our patients with mtDNA mutations, which could be due to a founder effect. It is possible that this haplotype promotes mtDNA related optic neuropathy. Further work is needed to better define the proportion of the different mtDNA lineages in the Chilean population.

Nine out of 44 (21%) patients with BSON had LHON based on carrying mtDNA mutations characteristic of the disease. This number is similar to what was reported in the English study,[4] and therefore stresses the need to test for these mutations in BSON. We do not have a longer follow up to rule out multiple sclerosis with certainty, as the cause for the disease in some of our patients. It is unlikely though, as we know that this is an uncommon evolution in our patients with optic neuropathy.[1] We did not find the primary mtDNA mutation related to LHON in any of 14 patients with unexplained AUON. Although LHON is classically bilateral, these patients were investigated due to the particular natural history of AUON in Chileans and because we knew that they most likely had an Amerindian mtDNA lineage. Studies of additional patients should clarify the role of mtDNA mutations in AUON.

Table 1 mtDNA mutations and haplotypes in Chilean patients with optic neuropathy

Patient	Sex	Age	Visual acuity	mtDNA mutation	MtDNA haplotype
1	M	29	fc/fc	11778	D
2	M	38	fc/0.05	11778	D
3	M	35	0.05/0.05	11778	D
4	M	28	fc/fc	11778	D
5	F	33	0.05/0.05	11778	D
6	M	35	0.1/0.1	14484	D
7	M	24	0.05/fc	11778	D
8	M	17	0.05/0.05	11778	D
9	M	42	fc/fc	11778	D

fc=finger count.
Only the positive patients for mtDNA mutations are shown.

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CORRESPONDENCE

Dementia as a complication of schizophrenia

De Vries *et al*[1] suggested that dementia in schizophrenia seems to be a real entity with neuropsychological signature similar to that of frontotemporal dementia. This was based on clinical data in eight patients with chronic schizophrenia aged 28 to 64 years presenting with cognitive impairment and evidence of a dementia syndrome not sufficiently explained

by their schizophrenic symptoms, However, except for frontal or temporal hypoperfusion on SPECT, they found no characteristic structural imaging abnormalities and, in accordance with Harrison,[2] concluded that dementia in elderly schizophrenic patients shows no evidence of any known neurodegenerative disorder and, therefore, requires novel neuropathological explanation. Several recent postmortem studies on such patients showed no excess of Alzheimer's disease or other organic dementing syndromes. This is in line with a personal retrospective study of 99 consecutive necropsy cases of schizophrenic patients aged over 55 (mean age 69.5 (SD 8.25) years) with mean duration of illness of 35.15 (SD 10.1) years, 56% with clinical signs of moderate to severe dementia, where we found a total incidence of definite and probable Alzheimer's disease (using CERAD criteria and Braak staging) of 7.1%, or of 8.7% for those over the age of 65 years. In addition, there was one case each with multi-infarct encephalpathy and Parkinson's disease pathology, and 11 brains showed a lacunary state in the basal ganglia.[3] Brain weight in demented elderly schizophrenic patients was significantly lower (mean 1119.5 (SD 106.1) g) than in non-demented ones (mean 1216.3 (SD 36.2) g; p<0.001). These data are in line with previous studies showing that cognitive decline in chronic schizophrenic patients seems best related to loss in brain weight, decrease in brain length, and increased ventricular size.[4 5] However, demented patients in our cohort were significantly older (mean age 73.36 (SD 6.85) *v* 64.02 (SD 6.54) years; p<0.001), and had a significantly longer duration of illness (mean 41.1 *v* 28.9 years; p<0.001), suggesting a progressive cognitive decline with both age and duration of the disorder. This, at least in part, could be explained by recent studies demonstrating reduction of synaptophysin (a synaptic plasma membrane protein) immunoreactivity in the prefrontal cortex[6] and significant negative correlations between age and concentrations of synaptic plasma membrane proteins and syntax in mRNA in the temporal cortex of schizophrenic patients[7] reflecting abnormalities in synaptic connectivity; this may cause functional impairment of the limbic circuitry that is thought to be central in the integration of behaviour and cognition.[3] These findings are consistent with the hypothesis that changes in synaptic function in both prefrontal or limbic circuits in patients with chronic schizophrenia may contribute to the pathophysiology including cognitive dysfunctions in this disorder.[3 7 8] However, future prospective clinicopathological and molecular genetic studies using validated methods are necessary to elucidate the bases of cognitive impairment and dementia in chronic schizophrenic patients.

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The calcified intracorporeal vacuole: an aid to the pathological diagnosis of solitary cerebral cysticercus granulomas

I read with interest the paper by Chacko *et al* reporting the significance of calcified intarcorporeal vacuole:an aid to the pathological diagnosis of solitary cysticercus granulomas.[1] I appreciate the efforts of the authors for once again proving that the aetiology for single small enhancing CT lesions is neurocysticercosis. The investigators are right in stating that in 26 patients there was no evidence of tuberculosis or fungal pathology. The presence of histiocytes and eosinophils favour a parasitic aetiology. It would be of interest to know the radiological correlation of oval calcified bodies that were detected in six patients. Did they have type A or type B lesions? The authors, in their earlier study, had concluded that neither the duration of seizures nor the type of lesion on CT was predictive of the presence of the parasite in the granuloma.[2] I am keen to know the seizure control of these patients with oval calcified bodies, as the authors have stated that a small proportion of study patients had intractable epilepsy. Single small enhancing CT lesions are reported to be the cause of the seizure in 26% of Indian patients who present with partial seizures.Cysticercus granulomas and tuberculomas are the two common differential diagnoses that are considered in a patient with seizures and solitary enhancing lesion on CT.[3] The authors have demonstrated very well the aetiology, diagnosis, and management of single small enhancing CT lesions in their previous studies.[3-4] This study adds one more feather to their cap in confirming the aetiology of such leisons. It is heartening to see that general practioners, physicians, and even neurologists in this part of the country treat these patients with antituberculous drugs. Educating general practioners and general physicians about the nature and aetiology of these lesions will definitely improve the management of patients.

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Chacko replies:

All six patients with oval calcified bodies had type A lesions, of which two were ring lesions and four were discs.

Follow up of 6 months to 3 years is available for four of these patients and they are all seizure free, with three of them still on antiepileptic medication.

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Change in oxcarbazepine (Trileptal®) formulation is associated with more side effects and higher blood concentrations

In an *editorial*, Marson and Chadwick review some of the evidence for the effectivity and tolerability of new drug treatments for epilepsy.[1] They discuss the role of randomised clinical trials for providing data that satisfy the requirements of the licensing bodies but that do not reflect day to day clinical practice. With oxcarbazepine (Trileptal®) we recently experienced another complicating factor, a change in formulation, which may influence interpretation of results of clinical trials.

Oxcarbazepine had recently been licensed in the United Kingdom and the United States but was already registered in The Netherlands in 1991. In our epilepsy centre we have had extensive clinical experience with oxcarbazepine since 1986.[2] In 2001 we noticed new symptoms such as diplopia, dizziness, dysarthria, and ataxia in patients on a stable drug regimen, including oxcarbazepine. These symptoms had a fluctuating course during the day. In the autumn of 2000 the manufacturer Novartis substituted the formulation of oxcarbazepine in The Netherlands for the formulation which had been licensed in the United Kingdom and the United States. Taking into consideration this change in formulation we hypothesise that these new symptoms could be side effects of oxcarbazepine, probably caused by higher blood concentrations of the active compound in relation to this new formulation.

Oxcarbazepine is a 10-keto analogue of carbamazepine (CBZ) with similar anticonvulsant efficacy, but with a different pharmacokinetic profile and possibly a better tolerability.[3 4] It is rapidly reduced to a 10-monohydroxy derivative (MHD) with an elimination half life of 1.3–3.8 hours. Oxcarbazepine acts as a prodrug of MHD, the clinically relevant metabolite of oxcarbazepine; MHD is cleared with a half life of 8.8–24.5 hours.

We evaluated steady state oxcarbaepzine and MHD serum concentrations obtained before and after change of the oxcarbaepzine formulation from four patients with presumed side effects. The mean (range) MHD concentrations increased from 27.0 (25.4−32.7) μg/ml to 38.4 (37.5−39.6) μg/ml. Routinely, we do not measure oxcarbaepzine concentrations, because they are usually very low or not detectable. As we still had all serum samples from these four

patients in the freezer, analysis could be done retrospectively. The mean (range) oxcarbazepine concentrations increased from 0.7 (0.5–1.1) µg/ml to 3.2 (2.0–5.6) µg/ml. In four other patients on the new formulation and with the presumed side effects, we found that the mean (range) MHD fluctuation calculated as 100. (Cmax –Cmin)/Cmin was 55.1 (36.3—72.9)%, which is higher than the described mean fluctuation of 32.5% with the first formulation.[5]

Our results suggest that the new formulation of Trileptal® has a faster rate of absorption and a higher bioavailability than the old one. It is possible that the higher oxcarbazepine and MHD concentrations are due to a food effect.

It was reported that the systemic availability of the old formulation increased 17% when oxcarbazepine was administered with food, but that this effect of food was absent with the new formulation. However, it is more likely that the changes in the composition of the dosage form have influenced the rate and extent of absorption of oxcarbazepine.

The prescribers of oxcarbazepine should be aware when patients change to the new formulation that the daily dosage will probably have to be decreased in patients with high MHD concentrations. A shorter dosage interval should be considered. Monitoring in blood concentration is advised before and after the change and should not only include MHD but also the parent drug oxcarbazepine itself.

These findings support the plea of the authors for trials that better reflect the needs of the clinician and the patient. A fast clinical and pharmacological evaluation of the new formulation is necessary to avoid the reputation of oxcarbazepine as a valuable anticonvulsive drug being impaired by its unnecessary side effects.

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Friedreich's ataxia presenting as an isolated spastic paraparesis

We read with interest the recent report by Castlenovo *et al* of the first reported case of Friedreich's ataxia presenting with a pure spastic paraparesis.[1] Since the identification of the frataxin gene in 1996 the phenotypic range of Friedreich's ataxia has been greatly expanded. After this report we therefore analysed the GAA repeat length in the first intron of the frataxin gene by polymerase chain reaction, using techniques previously described,[2] in affected members from eight families with a spastic paraparesis and evidence of autosomal recessive inheritance. In each case the presenting feature was of a slowly progressive spastic paraparesis. At least one affected member of each family had undergone a full series of investigations based on those proposed by the Hereditary Spastic Paraplegia Working Group to exclude other causes of a spastic paraparesis.[3] The age of onset ranged from 5 to 50 years. Additional neurological features such as peripheral neuropathy, mild ataxia, and intellectual impairment developed later in the course of the disease in affected members from four of the families. The GAA repeat lengths in all patients tested fell within the normal range. We therefore conclude that the presentation of Friedreich's ataxia as an autosomal recessive spastic paraparesis is likely to be rare.

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BOOK REVIEWS

How to read a paper. The basics of evidence based medicine. By TRISHA GREENHALGH. (Pp 222, £16.95). Published by BMJ Books, London, 2001. ISBN 0 7279 1578 9

The title of this slim paperback is somewhat misleading, as it covers considerably more than reading scientific papers (including how to deal with a visit from a drug rep!). There are two chapters which orientate the reader on why and how to keep abreast of the medical literature, including its electronic forms, nine on various aspects of reading papers, and one on implementing evidence based data. All necessary skills for the medical academic, of course, or for someone approaching a little aired but thorny issue. However, the author works in primary care, and much of her guidance seems directed towards drug trials, and particularly to the needs of her colleagues who may be wondering "how shall I treat the patient actually sitting in my surgery today?". Good as the advice she gives may be, it is difficult to picture the general practitioner, medical registrar, or even less the tyro casualty officer, asking the patient to wait while he or she boots the computer and searches the medical literature, starting with a couple of systematic reviews and delving into an article published in *Revista Médica Española*, for example, only to do the same during the next consultation and, possibly, repeating the process next week, as an important new contribution may have appeared. (It is not until the penultimate chapter that we read of the existence of computerised decision support systems!)

I apologise if my first paragraph seems somewhat tetchy because, like many hospital doctors, and particularly many long suffering radiologists, my experience has led me to appreciate only too clearly the messages Dr Greenhalgh is putting across. Maybe I was overly alienated by the almost insufferably smug image she conjures up. The Preface begins "When I wrote this book in 1996, evidence based medicine was a bit of an unknown quantity. A handful of academics (including me) were enthusiastic . . ." and on page 55 the author tells us she was a junior doctor not in any old centre, but in "a world renowned teaching hospital". The term "evidence based medicine" may have been novel in 1996, but many of my former colleagues would, I am sure, reject the idea that the concept was new. Many more might feel miffed by her suggesting that "if you are a practising (and non-academic) physician, your main contact with published papers may well be what gets fed to you by a drug rep".

A book like this inevitably contains criticism of previous publications, although Dr Greenhalgh refrains from naming too many names. However, the right to be highly critical of other people's sloppy work brings with it the corresponding duty to make one's own above criticism. Medical students are among the intended targets of this book, and the literary style ("we need to hang out, listen to what people say"; "check out the literature"; researchers should "describe in detail where they are coming from") may irritate readers more advanced in years, as may the habit of customarily according peers and professors their title(s), while using demotic forms (Dave, Nick, Andy, Sandy) for others, presumably to indicate a degree of familiarity.

One may also quibble with certain of her ideas. She does *not*, for example, mention that one of the reasons a piece of research which is not original might be undertaken is that one simply does not believe the results in published papers, despite their apparently impeccable methodology; there are enough examples of fraudulent work in the literature for one not to be overly coy about mentioning this as a possibility. About a third of the references to the chapter entitled "Papers that tell you what things cost", to which the author helpfully appends "(economic analyses)" are from American sources, but Dr Greenhalgh fails to make the crucial observation that most transatlantic analyses deal with *charges*, not *costs*, a major shortcoming which a comparison of costs of, for instance, MRI in non-profit and for-profit centres makes abundantly clear. To me, she also seems repeatedly to cop out (as she might say) when faced with rather basic philosophical questions, such as how we define health and disease and what, other than simple efficacy, can reasonably determine choices of management strategy. As a result of the first of these, she paints herself into a corner on what seems to be one of her main topics of interest, referring to the WHO definition of diabetes mellitus as the "gold standard", so that if you conform to it "you can call yourself diabetic", then parenthetically noting that it had changed since her first edition.

Having got that off my chest, I must add that this book contains innumerable useful insights and thought provoking reflections

(some of both original) on the biomedical literature and on research. It clearly fulfills a need, and was reprinted no fewer than six times between its original publication in 1997 and this second edition. I would guess its most appropriate audience would be medical students and young people embarking on biomedical research themselves; one would hope that they would soon pass on to the more detailed texts in the bibliography. I would be most unhappy to think that anybody could get through specialist registrar training without repeatedly having heard many of the principles expounded here from the mouths of their teachers. If they do not, they should present their seniors with a copy when they leave!

IVAN MOSELEY

Drug effects on psychomotor performance. By RANDALL C BASELT (Pp 475, US$109.00). Published by Biomedical Publications, Foster City, 2001. ISBN 0-9626523-4-2.

This book is essentially a compendium of the literature on the effects of various medications on cognitive function. It begins with a brief introduction, which could have done with some expanding. There are many difficulties involved in cognitive testing, and there are many different settings where testing can be carried out. Unfortunately, the limitations to the work discussed in the rest of the book are covered in a single page. Several important theoretical issues with regard to test design, including test selection, controlling for practice effects, using appropriate controls etc, are barely glossed over, but deserve consideration for anybody interpreting the contributions on any single drug.

The bulk of the text (nearly 500 pages) covers the literature on a vast range of drugs that may effect CNS function, from alprazolam to zopiclone, each drug being reviewed in a strict format, covering two to four or five pages. The pharmacology is described, before the laboratory studies. Driving studies and epidemiological data are given where available. There is then a brief paragraph on conclusions. The text is well referenced.

This is obviously a book for reference only, and does not lend itself to anything but the briefest of dipping. It represents a considerable labour of love on behalf of the author, and in the same way that his introduction could have been lengthened, it would have been helpful to have had some overall comments at the end of the book as to what he has learned by digesting this vast amount of literature. It seemed clear to me that nearly all of the studies carried out are short term only, often single dose or short repetitive dosing to volunteers. The more subtle interactions between the drugs and the underlying disorder for which they are given and their relation to cognitive function, an extremely important area, seems hardly to have been explored at all.

The book will be of value to those interested in cognitive function if only because of the many references contained therein, and the ease with which any individual drug can be looked up. It will be of help for clinicians to consult, particularly in a medicolegal context, and is a useful reference book which should be available in the catalogue of any medical library.

MICHAEL TRIMBLE

Magnetic resonance spectroscopy in multiple sclerosis. Edited by M FILIPPI, D L ARNOLD, and G COMI (Pp 160, US$68.00). Published by Springer-Verlag, Milano, 2001. ISBN 88 470 0123 4.

The impetus for this book has arisen from an annual magnetic resonance course which brings together some of the outstanding contributors in the field of magnetic resonance techniques as applied to multiple sclerosis. Magnetic resonance spectroscopy (MRS) is one of a handful of relatively new MR techniques which have proved particularly useful in trying to clarify the pathophysiology of multiple sclerosis. The greatest achievement of MRS in this field has been to provide highly persuasive evidence that axonal loss is likely to be the key determinant in the development of fixed neurological disability in patients with multiple sclerosis. This "axonal hypothesis", championed by Ian McDonald, was supported by the very first (though often forgotten) pathological descriptions of multiple sclerosis dating back to the time of Charcot. The spectroscopic studies however paved the way for two more recent pathological studies by Fergusson and then Trapp which demonstrated axonal transection in cerebral multiple sclerosis lesions. This whole area is well covered in the book.

One small criticism is the way in which the book is set out. The editors might have been expected to start with a chapter explaining the fundamentals of nuclear magnetic resonance and spectroscopy. It does seem slightly perplexing then, that one has to wait until the third chapter before being acquainted with such basic information.

Although not evident from the title, the editors also make an admirable attempt to cover several other NMR techniques including a nice chapter on the application of functional magnetic resonance imaging to the topic of cortical reorganisation and recovery in multiple sclerosis. The areas of magnetisation transfer and diffusion weighted imaging are also covered in a separate chapter.

I think this book covers a lot of useful ground and will be of interest to those who are keen to keep up with the more recent advances in NMR research in multiple sclerosis.

CHARLIE DAVIE

British Neuropsychiatry Association 2002 Annual Meeting

21/22 February 2002

The British Neuropsychiatry Association 2002 Annual Meeting will be held at the Institute of Child Health, central London on 21/22 February 2002.

The meeting will cover four topics:

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For details of membership to the BNPA, open to medical practitioners in psychiatry, neurology, and related clinical neurosciences, please contact: The Secretary, Professor A S David, Department of Psychological Medicine, Institute of Psychiatry, De Crespigny Park, Denmark Hill, London SE5 8AF.