

imens from patients with ankylosing spondylitis.<sup>3</sup> Inflammatory changes of the muscles in patients with ankylosing spondylitis have rarely been described. The muscle changes described here, however, together with two previous reports,<sup>4,5</sup> suggest that inflammatory changes may occur in the skeletal muscles of patients with ankylosing spondylitis.

MASAAKI WARAGAI  
HITOSHI SHINOTOH  
Department of Neurology,  
School of Medicine,  
Chiba University,  
Chiba, Japan

Correspondence to: Dr Waragai, Department of Neurology, Kofu Municipal Hospital 14-6 Saiwai-cho, Kofu-shi, Yamanashi 400, Japan.

- 1 Calabro JJ, Dick WC. *Ankylosing spondylitis*. Lancaster: MTP Press, 1987.
- 2 Whitfield AGW. Neurological complications of ankylosing spondylitis. In: Vinken PJ, Bruyn PW, eds. *Handbook of clinical neurology*. Vol. 38, Amsterdam: Elsevier, North Holland Biochemical Press, 1979:505-20.
- 3 Hopkins GO, McDougall L, Mills KR, et al. Muscle changes in ankylosing spondylitis. *Br J Rheumatol* 1983;22:151-7.
- 4 Rouzaud M, Chevallerier PLL, Jobard P, et al. Polymyosite chronique et spondylarthrite ankylosante. *Semin Hôp Paris* 1960;18:1153-9.
- 5 Simmons EH, Graziano GP, Heffner R. Muscle disease as a cause of kyphotic deformity in ankylosing spondylitis. *Spine* 1991;16(suppl):S351-60.

#### Incorrect diagnosis of myotonic dystrophy and its potential consequences revealed by subsequent direct genetic analysis

Myotonic dystrophy (MyD) is a multisystem disorder with prominent features in skeletal and cardiac muscle. It shows genetic anticipation with a tendency for members of successive generations to be affected more severely by the disease and at a younger age.<sup>1</sup> At its most severe it may cause a characteristic foetal and neonatal syndrome, which can be fatal.<sup>1</sup> For genetic reasons and also to identify patients at risk from cardiac complications,<sup>2</sup> screening of patients at risk for MyD is now recognised as important. Classically, a combination of clinical examination, needle EMG, and slit-lamp examination of the eyes has been used to identify patients who carry the disease<sup>2</sup> but only about 92% of obligate carriers are detected. The sensitivity could be increased by genetic linkage studies, but clearly this requires that the correct parent be identified as a carrier in cases where both are asymptomatic. The recent introduction of a direct DNA test<sup>3</sup> to demonstrate an increase in the number of [CTG] repeats at the 3' end of the myotonin protein kinase gene has now improved diagnostic accuracy and removed the need for linkage analysis. We report here two cases in which an incorrect assignment of carrier status on clinical and EMG criteria was revealed by the direct genetic test.

#### Case 1

A 60-year-old woman and her 70-year-old husband were seen in 1990 for screening for myotonic dystrophy after the diagnosis had been made in their 31-year-old daughter. Clinical examination showed no evidence of myotonia in the husband and his EMG and slit-lamp examination were negative. On examination of his wife there was no grip

myotonia or percussion myotonia but a consultant neurologist considered that percussion myotonia of the tongue was present. Needle EMG showed occasional myotonic discharges and there were minor non-specific changes on slit-lamp examination. Based on these findings the mother was assumed to be the carrier of the gene for MyD. A clinically unaffected daughter sought genetic advice and was assigned a low risk on the basis of negative EMG and slit-lamp examination and by linkage analysis. When the direct genetic test became available in 1992 the samples were retested and the mother found not to carry the expansion associated with MyD. Her husband carried a minimally expanded allele (EO)<sup>4</sup> and thus was a carrier of the disease. Fortunately the unaffected daughter, who had been given a low risk based on the incorrect linkage result, was found to carry no expansion and therefore not to carry the disease.

#### Case 2

A 51-year-old woman was screened for MyD after the diagnosis was made in three of her siblings. No abnormalities were found on neurological examination or needle EMG. She had bilateral posterior subcapsular cataracts and low intraocular pressure. The cataracts were not of the stellate form usually seen in MyD, but as there was also low intraocular pressure (which is associated with MyD) she was assigned carrier status. Linkage analysis for her asymptomatic daughter was complicated by the fact that the biological father was no longer in contact with the family so that no linkage diagnosis could be offered. For this reason the entire family was retested with the direct DNA test and the woman in question was found not to be a carrier of the disease.

In both of these cases, asymptomatic patients were diagnosed as being minimally affected by MyD based on limited clinical features, and in the first case an assessment of genetic risk was made for a third party (the patient's younger daughter) on the basis of incorrect linkage assignments. It was fortunate that the incorrect result did not lead to a missed diagnosis and the birth of a congenitally affected child. There was, however, considerable psychological trauma to the first patient both at the time of her misdiagnosis and when the diagnosis was revised. The importance of making a correct clinical diagnosis before applying linkage analysis is again brought home by these cases.

The direct demonstration of the mutation in MyD, either by restriction enzyme analysis or by the polymerase chain reaction, detects at least 99% of cases of MyD.<sup>5</sup> Also, cases where myotonia has coexisted with features not considered typical of MyD have been shown to have the MyD mutation and the test has proved useful in detecting cases of congenital MyD in which the mother has not previously been known to have MyD. We feel that there is now a demonstrable need to review critically all minimally affected persons who have been diagnosed on the basis of clinical (including EMG and slit-lamp examination) or linkage analysis criteria. Linkage analysis in this condition should now be considered outmoded. Finally, we advise that whereas clinical examination, EMG, and slit-lamp examination are still relevant in trying to understand the relation between genetic

abnormality and clinical features, the gold standard for diagnosis and screening must be direct DNA analysis.

PHILLIP R J BARNES  
DAVID HILTON-JONES  
Oxford Muscle and Nerve Centre,  
University Department of Clinical Neurology,  
Radcliffe Infirmary, Oxford OX2 6HE, UK  
GAIL NORBURY  
Oxford Medical Genetics Laboratories,  
Churchill Hospital, Oxford OX3 7LJ, UK  
ANNE ROBERTS  
SUSAN M HUSON  
Oxford Regional Genetics Service,  
Churchill Hospital, Oxford OX3 7LJ, UK

- 1 Harper PS. *Myotonic dystrophy*. 2nd ed. London: WB Saunders, 1989.
- 2 Barnes PRJ. Clinical and genetic aspects of myotonic dystrophy. *Br J Hosp Med* 1993;50:22-30.
- 3 Brook JD, McCurrach ME, Harley HG, et al. Molecular basis of myotonic dystrophy: expansion of a trinucleotide (CTG) repeat at the 3' end of a transcript encoding a protein kinase family member. *Cell* 1992;68:799-808.
- 4 Tsilifidis C, MacKenzie AE, Mettler G, Barcelo J, Korameluk RG. Correlation between CTG trinucleotide repeat length and frequency of severe congenital myotonic dystrophy. *Nature Gene* 1992;1:192-5.
- 5 Suthers GK, Huson SM, Davies KE. Instability versus predictability: the molecular diagnosis of myotonic dystrophy. *J Med Genet* 1992;29:761-5.

## MATTERS ARISING

#### Lactate responses to exercise in chronic fatigue syndrome

We were interested to read the recent account of exercise characteristics in patients with chronic fatigue syndrome by Gibson *et al*,<sup>1</sup> which concluded that there was no abnormality of neuromuscular function in this condition. Patients reached the limits of exercise tolerance at lower heart rates than controls during incremental exercise to exhaustion but their peak work rates and duration of exercise did not differ significantly from the control group, although the total work done (the product of these variables) would appear to have been less; the authors had previously reported that patients with this condition showed a reduction in maximal work rate achieved in such tests.<sup>2</sup> Despite this, plasma lactate levels at the end of exercise were as high in the patients as the controls.

In an earlier study using incremental exercise on a treadmill, Riley *et al*<sup>3</sup> had found higher heart rates and increased lactate levels compared with normal controls at submaximal work rates but similarly noted no differences at peak exercise.

We have found that a proportion of patients with chronic fatigue syndrome exhibit abnormally raised lactate levels following steady state exercise at work rates below the anaerobic threshold, corresponding to roughly half the peak work rates achieved in the incremental test paradigm.<sup>4</sup> It is thus possible that lactate levels in some patients increase more rapidly than normal at lower work rates.

The cause of this apparent 'left shift' of the anaerobic threshold is unclear. Neither we nor Gibson *et al*<sup>2</sup> found evidence of

"deconditioning" in terms of cardiac responses to exercise in our patients, and phosphorus spectroscopy of muscle in the syndrome has shown no consistent disturbance of muscle energy metabolism.<sup>5</sup> The phenomenon may be of significance in the pathogenesis of "fatigue" in some patients, and it may be premature to conclude that neuromuscular function in all patients is normal, or that the "fatigue" is exclusively "central" in origin. Indeed, it may be presumptuous to consider chronic fatigue syndrome as a unitary entity.

RUSSELL J M LANE  
DAVID WOODROW  
LEONARD C ARCHARD  
Charing Cross and Westminster Medical School,  
London, UK

- Gibson H, Carroll N, Clague JE, Edwards RHT. Exercise performance and fatigue-ability in patients with chronic fatigue syndrome. *J Neurol Neurosurg Psychiatry* 1993; 56:993-8.
- Carroll N, Gibson H, Coakley J, Edwards RHT. Cycle ergometry in patients with chronic fatigue syndromes. *Eur J Clin Invest* 1990 (suppl);20:A29 [abstract].
- Riley M, O'Brien CJ, Bell N, Nicholls DP, McCloskey DR. Aerobic work capacity in patients with chronic fatigue syndrome. *BMJ* 1990;301:953-6.
- Lane RJM. Neurological features of myalgic encephalomyelitis. In: Hyde BM, ed. *The clinical and scientific basis of myalgic encephalomyelitis/chronic fatigue syndrome*. Ottawa: Nightingale Research Foundation, 1992;395-9.
- Barnes PRJ, Taylor DJ, Kemp GJ, Radda GK. Skeletal muscle bioenergetics in the chronic fatigue syndrome. *J Neurol Neurosurg Psychiatry* 1993;56:679-83.

#### PET assessment of brain metabolic recovery in aphasia

The paper by Cappa *et al*<sup>1</sup> deals with the important issue of the mechanisms of recovery from aphasia. The authors longitudinally assessed two patients both neuropsychologically and by <sup>18</sup>F-2-fluoro-2-deoxy-D-glucose (<sup>18</sup>F-FDG) PET measurements of the local cerebral metabolic rate of glucose (LCMRGI). Each patient was studied twice with a three month interval. The LCMRGI values (19 brain regions on each side) were assessed for significant abnormalities at each study by comparison with values from a group of seven healthy subjects, while changes in LCMRGI from first to second PET study were assessed in each patient individually by an analysis of variance with one between-factor (acute and chronic stage) and one within-factor (left and right hemisphere). The authors conclude that (1) significant reductions in the LCMRGI of many brain regions were present in both patients at initial evaluation, and in one patient at second evaluation only; and (2) there was a significant increase in LCMRGI from first to second evaluation in each of the two patients.

We wonder whether the statistical procedures used were appropriate. Firstly, regarding the comparison with the control group, Cappa *et al* used two standard deviations below control mean as the cut-off for  $p < 0.05$ ; however, since the control group consisted of only seven subjects, the two-tailed  $t$  value for six degrees of freedom, or 2.447, should have been used instead. As this value is substantially larger than 2.0, it is likely that several of the LCMRGI values listed in tables 1 and 2 as statistically significantly reduced were, in fact, not. In addition,

the authors do not acknowledge the fact that there is a multiple testing problem as they are simultaneously assessing the atypicality of all regions.

Secondly, the analysis of variance procedure used to assess changes in LCMRGI from one study to the next in each subject is of serious concern. Apparently, it was run on the set of  $38 \times 2$  data (19 regions for each side of brain, two determinations), and yielded inordinately low probability levels (down to  $< 0.0001$ ) for single subject studies. Their way of using the analysis of variance in this and another study<sup>2</sup> would appear inadequate and possibly misleading. The authors do not point out the fact that region must also be a within-subject factor. In the case of measurements of LCMRGI, there exists a global scaling factor (the mean brain CMRGI), itself influenced by both physiological and methodological factors, that affects all regional values of a given subject. Thus, in the comparison of the two sets of LCMRGI data obtained in a single subject at two sequential studies, any change in this global factor will be repeated over all brain regions such that the more regions analysed, the larger the degrees of freedom and, in turn, the more statistically significant the findings. One way of turning around this problem would have been to covary for this global factor by, for example, an analysis of covariance.

When studying the changes in brain metabolism in a longitudinal fashion, more appropriate ways of testing whether a significant change in LCMRGI has occurred from one investigation to the next would be to assess each brain area either across a sufficiently large group of patients or, in single subjects, by checking the numerical changes observed against confidence limits established for the same region in a set of control subjects studied twice at similar time intervals (that is, confidence limits for reproducibility). The results presented by Cappa *et al* regarding recovery of LCMRGI must therefore be taken as descriptive only, pending confirmation from a better designed investigation.

J C BARON  
INSERM U320,  
Blvd H Becquerel, BP 5027,  
14021 Caen Cedex, France  
I FORD  
Robertson Centre for Biostatistics,  
Boyd Orr Building,  
University of Glasgow,  
Glasgow G12 8QQ, UK

- Cappa SF, Perani D, Bressi S, Paulesu E, Franceschi M, Fazio F. Crossed aphasia: a PET follow up study of two cases. *J Neurol Neurosurg Psychiatry* 1993;56:665-71.
- Perani D, Vallar G, Paulesu E, *et al*. Left and right hemisphere contribution to recovery from neglect after right hemisphere damage. A <sup>18</sup>F-FDG PET study of two cases. *Neuropsychologia* 1993;31:115-25.

#### Cappa *et al* reply:

Drs Baron and Ford express their concern about the appropriateness of the statistical methods used to support the two major findings of our paper, namely that (1) a significant reduction of local cerebral metabolic rate for glucose was present in several regions, not only of the right, but also of the left hemisphere in two patients with crossed aphasia in the acute stage; and (2) a significant increase of metabolism occurred between the first and the second examination, three months after onset, in the same two patients.

Baron and Ford consider a cut off value equal to the mean minus two standard devi-

ations of LCMRGI of normal controls as inadequate, and suggest the use of the two-tailed  $t$  value for six degrees of freedom (2.447 SD). We think that the choice of a two-tailed value is questionable, as pathological values can *a priori* be expected to lie at the lower tail of the distribution (in the latter case, the cut off can be calculated as 1.943 SD—that is, approximately the same value used in our paper). Nevertheless, we have re-analysed our data using this ultra-conservative approach. Even adopting this criterion, the main finding of bihemispheric metabolic reduction was unchanged, and the regional results were only marginally different (case 1—examination I: no change; examination II: right 04 and 05 and left T3, T8, and T9 above the cut off; case 2—examination I: right and left T3, T4, T8, and T9 above the cut off). On the other hand, it is noteworthy that the latter values also fall below the fifth centile of the distribution of normal values from a larger sample of normal controls, which has been collected in our laboratory after the completion of this study.

Baron and Ford suggest that region should have been included as a within-subject factor in the analysis of variance. This design would, of course, be the most informative in the study of the regional correlates of functional recovery. Given the characteristics of our sample, however (two cases, with a very low probability to increase sample size within a reasonable time span), we had to forsake the important issue of regional effects and limit ourselves to the assessment of changes in hemispheric metabolism between the baseline evaluation and the follow up study in a  $2 \times 2$  factorial design. We think that any effort to remove "global" effects on the hemispheric values in this context would be questionable, given that the mean global cerebral metabolic rate is necessarily affected by intrahemispheric and transhemispheric diaschisis, namely, by the phenomenon under scrutiny.

Having said that, we appreciate that the description of two single cases is, by definition, "descriptive". Given the limited current understanding of crossed aphasia and of other instances of atypical cerebral dominance, to ascribe further explanatory power to our observations would be far fetched. The methodological suggestions by Baron and Ford, however, are rather impractical. To collect a "sufficiently large number of patients", given the incidence of crossed aphasia, would require a dedicated multi-centre study. For radioprotection reasons, in some countries it would be difficult to perform two repeated studies with <sup>18</sup>F-FDG in normal subjects within three months.

We have proposed that patients with crossed aphasia may be particularly liable to distant effects, due to their bilateral language representation. Larger studies of the clinical correlations of distant effects and of their relationships with lesion characteristics, as well as with patient related variables (such as age, gender, handedness) are warranted to prove or disprove this specific hypothesis.

S CAPPA  
S BRESSI  
D PERANI  
F FAZIO  
Department of Nuclear Medicine,  
University of Milan,  
Scientific Institute H San Raffaele,  
Via Olgettina 60,  
20132 Milan, Italy

Correspondence to: Professor Fazio