Are muscle cramps in Isaacs' syndrome triggered by human immunoglobulin?

Ishii *et al* reported the clinical evaluation of plasma exchange and treatment with high dose intravenous immunoglobulin (IVIg) in a patient with Isaacs' syndrome.¹ The rationale for either treatment in this syndrome was a possible autoimmune aetiology.² The differential treatment response was remarkable: after plasma exchange the symptoms of continuous muscle activity almost disappeared, whereas after IVIg treatment muscle cramps gradually increased. The authors state that the reason for this divergence is unclear, and suggest that IVIg may have a similar adverse effect in Isaacs' syndrome as has recently been reported in patients with Guillain-Barre syndrome.³

We would like to draw attention to another explanation for the differential treatment response of plasma exchange and IVIg, and propose the possibility of a direct effect of IVIg on muscle cells, causing muscle cramps in the patient with Isaacs' syndrome. Supplying IgG molecules by IVIg administration may induce effects that disappear with IgG elimination by plasma exchange.

Recently we investigated the effect of IVIg on normal human muscle cells in culture, and found a dose dependent release of calcium from the sarcoplasmic reticulum (van Engelen, BGM, Benders AAGM, Veerkamp JH, *et al*. Unpublished data). Because of these *in vitro* results, we suggest that *in vivo* the differential effect of plasma exchange and IVIg in Isaacs' syndrome may also be the result of a direct effect of IVIg on muscle, by an FIVlg mediated increase of intracellular calcium and subsequent muscle cramps. Although muscle cramps are generally not reported as adverse effects of IVIg treatment, myalgia, which is difficult to distinguish from muscle cramps, is one of the most frequent side effects of such treatment.⁴ In addition, in Isaacs' syndrome the increase of muscle cramps after treatment with IVIg might be due to an altered excitability of motor terminals in this syndrome.²

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- 1 Ishii A, Hayashi A, Ohkoshi N, *et al*. Clinical evaluation of plasma exchange and high dose intravenous immunoglobulin in a patient with Isaacs' syndrome. *J Neurol Neurosurg Psychiatry* 1994;57:840-2.
- 2 Sinha A, Newsom-Davis J, Mills K, Byrne N, Lang B, Vincent A. Autoimmune aetiology of acquired neuromyotonia (Isaacs' syndrome): report of five cases and literature review. *Lancet* 1991;338:75-7.
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Hayashi *et al* reply:

We thank van Engelen *et al* for their comments on our paper.¹ In that paper, we reported that we had anticipated that IVIg treatment would be helpful for Isaacs' syndrome, but unexpectedly, the IVIg

treatment actually worsened the symptoms of our patient. These symptoms (myokymia, pseudomyotonia, and muscle cramping) were not different from the previous ones, but were more intense.

The findings suggest that our patient may exhibit a hyperexcitability response even to human immunoglobulin. In other words, some trigger zones sensitive to immunoglobulin apparently exist in our patient. The mechanism is yet unclear, and thus it is important to find out where the trigger zone for immunoglobulin is. The letter of van Engelen *et al* gives an important clue.

One candidate for the trigger zone is the muscle tissue itself. Nagashima *et al* reported on the presence of a complex in the muscle fibre membrane and motor endplate from immunofluorescence studies on muscle biopsy samples from a patient with Isaacs' syndrome.²

Another candidate may be the nerve terminal, because morphological abnormalities, such as sprouting of the intramuscular nerve, have been reported in Isaacs' syndrome.^{3,5} Oda *et al* noted that there were extensive terminal arborisations in the endplates, and some of these extended away from the original endplate area.⁵ They suggested that the trigger zone for abnormal discharge was in the distal segment of the intramuscular nerve axon, including the nerve terminal.

Our report is the first study of the use of IVIg in Isaacs' syndrome, and thus we cannot really assess the effectiveness of this treatment. There is, however, one patient with Isaacs' syndrome who improved with IVIg treatment (Wintzen *et al*⁶ and A R Wintzen, personal communication). It would seem, therefore, that the effect of IVIg may be dependent on the specifics of each case. There is likewise the possibility that the effect may be altered by the type or dose of human immunoglobulin.

Isaacs' syndrome has been considered as an autoimmune disorder. Arimura *et al* studied antibodies acting on the cell membrane of PC12 in serum from patients with Isaacs' syndrome⁷ and showed the suppression of potassium channels in the neuronal cell line in serum taken from such patients, including our case.⁸

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- 1 Ishii A, Hayashi A, Ohkoshi N, *et al*. Clinical evaluation of plasma exchange and high dose intravenous immunoglobulin. *J Neurol Neurosurg Psychiatry* 1994;57:840-2.
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Complement alterations in the CSF of patients with amyotrophic lateral sclerosis

Recently, Tsuboi and Yamada¹ reported increased CSF concentration of C4d and increased C4d index values in patients with amyotrophic lateral sclerosis and suggested that this finding may be due to complement activation that could play a part in motor neuron degeneration. Since 1985,² we have found high levels of C3c but not changes in C3c index values and other complement fractions in CSF from patients with amyotrophic lateral sclerosis correlating with CSF/serum albumin and, more significantly, with the CSF protein concentrations. We proposed that the increase in C3c fraction could be due in part to leakage through the altered blood-brain barrier but also to decreased binding to specific complement receptors on CNS lymphocytes that leads to complement deposit in nervous tissues. This interpretation focuses on the biochemical and functional changes in cell membranes from patients with amyotrophic lateral sclerosis.^{3,4} The role of the immunological alterations in amyotrophic lateral sclerosis pathogenesis needs further investigation.

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- 1 Tsuboi Y, Yamada T. Increased concentration of C4d complement protein in CSF in amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry* 1994;57:859-61.
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Somatisation in neurological practice

I was interested to read the article by Ron¹ on somatisation in neurological practice. The inability to make a specific diagnosis in neurological outpatient practice is something that I referred to in a paper published in this *Journal* in 1989.² An analysis of 7836 successive new referrals to my clinics established that some 26.5% did not have a specific diagnosis, even in some cases after extensive investigation. Ron might be interested to know that among the same number of patients 297 or 3.8% had some evidence of conversion hysteria. Based on an earlier study, also published,³ one would have expected probably some 50% of these

patients to have features of Briquet's syndrome.

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- 1 Ron MA. Somatisation in neurological practice. *J Neurol Neurosurg Psychiatry* 1994;57:1161-4.
- 2 Perkin GD. An analysis of 7836 successive new outpatient referrals. *J Neurol Neurosurg Psychiatry* 1989;52:447-8.
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British neurology: a national focus

We are grateful to Schapira and Marsden for opening the national debate about the future of The National Hospital and the Institute of Neurology.¹

The National Hospital has, as the authors of the letter state, been at the centre of neurological learning and development over many decades. In addition, it has been an important centre to which difficult and unusual cases could be sent. I personally am grateful for the help that I have received from colleagues at The National Hospital over many years. There will also be general acknowledgement for the excellent work done by the various units that go to make up the Institute of Neurology. This work must continue.

Clinical service and research go together. Both should be practised to the highest possible standards. In the case of The National, an obvious potential conflict exists. Three elements may be considered.

- (1) Most patients prefer to be treated as near as possible to their own home. This would usually be in the nearest general hospital. There is considerable agreement that referral further afield should be the exception rather than the rule, and there should be sound clinical reasons for such referrals.
- (2) Neurological disorders are characterised by their frequency and their diversity. The vast majority of major disorders such as stroke, head injury, and epilepsy are managed at general hospitals throughout Great Britain. The increasing number of neurologists now working mainly in such hospitals is ensuring an improved spread of neurological expertise.
- (3) There are now well established neurological units throughout the United Kingdom and most of these are in general hospitals. They provide a high quality clinical service as well as undertaking teaching and research.

These are three of the elements that influence the debate about the future role of The National Hospital. The question now arises as to whether a "stand alone" specialist neurological hospital with its somewhat atypical and selective clinical practice, a decreasing number of referrals, and no local obvious population to serve, is viable in the 1990s.

The National Hospital would undoubtedly achieve much support from clinical neurologists throughout the length and breadth of the country if it were to physically merge with a major general hospital. A major advantage of this arrangement would be that a high quality, comprehensive neurological service for a defined population could be developed. Such a model service would be most valuable for educational and other rea-

sons. National and international referrals would still be attracted, and the Institute, which would continue to be closely associated with the hospital, would be assured of a long term future.

High quality research and a first class clinical service are the obvious objectives. They must both be achievable. There is now a unique opportunity to redefine the role of The National Hospital. The exercise will result in temporary inconvenience, dislocation, and considerable expense. These can surely be tolerated. Future generations of patients and doctors will have cause to celebrate the foresightedness of their forebears.

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- 1 Shapira AHV, Marsden CD. British neurology: a national focus [letter]. *J Neurol Neurosurg Psychiatry* 1994;57:1136.

NOTICES

The 21st International Epilepsy Congress will be held on 3-8 September in Sydney, Australia. Major topics are: Genetics and molecular biology of epilepsy; Surgical treatment of epilepsy in childhood; Functional neuroimaging; Choice of drugs in childhood and adult epilepsies; Epilepsy and the law; Intellectual disabilities and epilepsy; and The role of psychiatry in epilepsy. For further information, contact: The Congress Secretariat, PO Box 1231, North Sydney, NSW 2059, Australia. Tel: + 61 2 956 8333; Facs: + 61 2 956 5154.

Announcement from the British Neuropsychiatry Association

The 1995 Summer meeting—to include joint sessions with the British Association for Psychopharmacology—will be held on 15-17 July in Cambridge

On 16 July BNPA will hold a scientific meeting with the theme of "movement disorders" and its AGM. On 17 July BNPA/BAP will have a joint session on neuroimaging, psychiatry, and psychopharmacology. Short scientific papers and single case videos by members of both associations will also be presented. For further details please contact Ms Sue Garratt, 17 Clocktower Mews, London N1 7BB, UK.

For details of membership of the BNPA, which is open to medical practitioners in psychiatry, neurology, and related clinical neurosciences, please contact Sue Garratt at the address above, or Dr Jonathan Bird, Burden Neurological Hospital, Stoke Lane, Stapleton, Bristol BS16 1QT, UK.

BOOK REVIEWS

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Searching for the Causes of Schizophrenia. By EVE C JOHNSTONE. Published by Oxford University Press, Oxford. (Pp 134). ISBN 0-19-262296-X.

This book consists largely of an account of the work that Eve Johnstone carried out with a number of colleagues whilst she was a member of the Clinical Research Centre Division of Psychiatry, of which I was privileged to be the Head, between 1975 and 1989. By 1988 the work of the Division on schizophrenia was more widely cited than that of any other department or institute in the world and this was in no small measure due to Eve Johnstone's tenacity and industry. In addition to the first CT study of schizophrenia there were a series of clinical trials—the flupenthixol stereoisomers study, the study of the adverse effects of anticholinergic drugs, The Northwick Park study of first episodes of schizophrenia and the Northwick Park "functional psychosis" study to which Eve Johnstone's contribution was pivotal and each of which to my mind significantly clarifies major aspects of the mechanism or scope of efficacy of antipsychotic drugs.

This book gives a full and lucid account of these studies; also of the major surveys of the defects of institutionalised patients with schizophrenia and the detailed follow-up of patients admitted from a single catchment area (Harrow) over a 10 year period. This is a substantial body of work and it is good that this succinct and factual account is on record.

But is it justifiably described as *Searching for the Causes of Schizophrenia*? I noted two curious omissions. The first relates to the work we did between 1977 and 1983 on the viral hypothesis. This surely represented a "search for the causes of schizophrenia", but it is not mentioned in the book. By 1984 I had come to the conclusion that schizophrenia cannot be caused by an exogenous virus, a view which I suspect Eve Johnstone shares. But, if so, it would have been interesting (and relevant to the title) to hear her reasons for dismissing the viral hypothesis, which at one time we both entertained. Again the documentation of structural changes in the brain by CT, MRI, and in postmortem studies tells us something about the disease process. But what does it mean? I consider that a crucial clue came from the finding in the post-mortem work that the changes are asymmetrical. This suggests that they represent a deviation in a late component of brain evolution, and leads to the more precise hypothesis that the disorder relates to genetic variation that is homo sapiens specific. But this hypothesis and the aspects of the work which were relevant to it (even though Eve contributed as coauthor) get no mention in this volume.

What I conclude is that there are scientists who are predominantly empirical or Baconian in their approach and others who are hypothesis driven. Eve is towards one extreme and I am towards the other.