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

Ishi et al reported the clinical evaluation of plasma exchange and treatment with high dose intravenous immunoglobulin (IVIg) in a patient with Isaacs' syndrome. The rationale for either treatment in this syndrome was a possible autoimmune etiology. The differential treatment response was remarkable for the relief of symptoms of continuous muscle activity almost disappeared, whereas after IVIg treatment muscle cramps gradually increased. The authors state that 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.

We would like to draw attention to another explanation for the different 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, BG, Benders AAGM, Veerkamp R, 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 Unpublished data).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 cells, causing 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. 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.

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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 myalgia) or cramping) were not different from the previous ones, but were more intense.

The findings suggest that our patient may exhibit a bystander-effect response to human immunoglobulin. In other words, some trigger zones sensitive to immunoexcitability 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 in 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.

Another candidate may be the nerve terminal, because morphological abnormalities, such as sprouting of the intramuscular nerve, have been reported in Isaacs' syndrome2. We postulated that there are extensive terminal arborisations in the endplates, and some of these extended away from the original endplate area. They suggested that the nerve terminal abnormal discharges 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 and A R Wintzen, personal communication). It would seem, therefore, that the effect of IVIg may be dependent on the specific 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 al3 studied antibodies acting on the cell membrane of PC12 in serum samples from patients with Isaacs' syndrome and showed the suppression of potassium channels in the neuronal cell line in serum taken from such patients, including our case.

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2 Nagashima T, Kamegai M, Hirose H, et al. Reduced serum albumin and, more significantly, with the CSF protein concentrations. We proposed that the increase in C3 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 lead to complement deposit in nervous tissues. This interpretation focuses on the biochemical and functional changes in cell membranes from patients with amyotrophic lateral sclerosis.4 The role of the immunological alterations in amyotrophic lateral sclerosis pathogenesis needs further investigation.

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Somatisation in neurological practice

I was interested to read the article by Roni 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. An analysis of 7836 successive new referrals to my clinics established that some 25-50% did not have a specific diagnosis, even in some cases after extensive investigation. Roni 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, one would have expected probably some 50% of these patients to be a candidate for a specific diagnosis.