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dependent release of calcium from the sarcoplasmic reticulum (van Engelen, BGM, Benders AAGM, Veerkamp JH, *et al.* Unpublished data).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 IVIg 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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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 immunofluoresence 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' syndrome[7] 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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Complement alterations in the CSF of patients with amyotrophic lateral sclerosis

Recently, Tsuboi and Yamada[1] 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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Somatisation in neurological practice

I was interested to read the article by Ron[1] 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