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) for 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 IVIg treatment with muscle cramps gradually increased. The authors stated that the reason for this divergence is unclear, but they believe continuing 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 study for differences in the 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 Unpublished). 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, leading to 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.

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.

BAZIEL O.M, VAN ENGELLEN AD A G M BENDERS, FONS J M GABREELS in JULIUS H VEERKAMP

Departments of Neurology and Biochemistry, University Hospital Nijmegen, PO Box 9101, 6500 HB Nijmegen, The Netherlands


Hayashi et al reply:

We thank van Engelen et al for their comments on our paper. 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, neuromyotonia, 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 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 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.

Another candidate may be the nerve terminal, because morphological abnormalities, such as sprouting of the intramuscular nerve, have been reported in Isaacs’ syndrome. 1-3 Odaka et al have suggested there were extensive terminal arborisations in the endplates, and some of these extended away from the original endplate area. 2 They suggested that these abnormal discharges were 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 1993; 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 samples of 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.

AKITO HAYASHI
AKIKO ISHII
NOBUO OHKOSHI
HIDEHIRO MIZUASA
SHIN’ICHI SHOJI

Department of Neurology, Institute of Clinical Medicine, University of Tsukuba, Tsukuba, 305, Japan

We thank the authors for their comments. In our study, the effect of IVIg treatment was not significant; however, muscle cramping in a patient with Isaacs’ syndrome was improved. We believe that the use of IVIg in Isaacs’ syndrome needs further investigation.

P. ANNUNZIATA
Institute of Neurological Sciences, University of Siena, viale Bracci 2, 53100 Siena, Italy


Somatisation in neurological practice

I was interested to read the article by Ron1 on somatization 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 interesting to know that among the 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
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B G Van Engelen, A A Benders, F J Gabreels and J H Veerkamp

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