Matters arising

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.1 The rationale for either treatment in this syndrome was a possible autoimmune etiology. The differential treatment response was remarkable after plasma exchange: the symptoms of continuous muscle activity almost disappeared, whereas after IV Ig treatment muscle cramps gradually increased. The authors state that the reason for this divergence is unclear, and suggest that IV Ig may have a similar adverse effect in Isaacs' syndrome as has recently been reported in patients with Guillain-Barré syndrome.1

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

Recently we investigated the effect of IV Ig 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dose dependent release of calcium from the sarcoplasmic reticulum (van Engelen, BGM, Benders AAGM, Veerkamp JH, et al, Unpublished data).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 IV Ig in Isaacs' syndrome may also be the result of a direct effect of IV Ig on muscle cells, including intracellular calcium and subsequent muscle cramps. Although muscle cramps are generally not reported as adverse effects of IV Ig 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 IV Ig might be due to an altered excitability of motor terminals in this syndrome.


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 IV Ig treatment would be helpful for Isaacs' syndrome, but unexpectedly, the IV Ig treatment actually worsened the symptoms of our patient. These symptoms (myokymia, myotonia, cramps, and muscle cramping) were not different from the previous ones, but were more intense.

The findings suggest that our patient may exhibit a hypersensitivity 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.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 Odaka et al reported that there were extensive terminal arborisations in the endplates, and some of these extended away from the original endplate area.4 They suggested that the nerve terminal 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 IV Ig 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 IV Ig treatment (Wintzen et al and A R Wintzen, personal communication). It would seem, therefore, that the effect of IV Ig 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 from patients with Isaacs' syndrome2 and showed the suppression of potassium channels in the neuronal cell line in serum taken from such patients, including our case.5

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2 Nagashima T, Kamagari M, Hirose K, et al. Antibodies to 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.5

Somatisation in neurological practice

I was interested to read the article by Ron 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. A study 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,6 one would have expected probably some 50% of these patients to show some hysterical symptomatology.

As for the role of hysterotonic reactions, and even of hypnosis, in neurological practice, I would stress that it would be very useful to have a better understanding of the phenomenon of conversion hysteria, perhaps by use of experimental techniques, such as the use of hypnosis in controlled situations. The ability to make a specific diagnosis in neurological practice is something that I referred to in a paper published in this Journal in 1989. A study 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,6 one would have expected probably some 50% of these patients to show some hysterical symptomatology.


patients to have features of Briquet's syndrome.

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1 Ron MA. Somatisation in neurological prac-
tice. J Neurol Neurosurg Psychiatry 1994;57:
1161-4.

2 Perkin GD. An analysis of 7836 successive new
outpatient referrals. J Neurol Neurosurg Psychiatry

3 Perkin GD. Pattern of neurological outpatient
referrals. Implications for undergraduate and

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.

The National Hospital has, as the authors of the
letter state, been at the centre of neuro-
ological learning and development over many
decades. In addition, it has been an impor-
tant centre to which difficult and unusual
cases could be sent. I personally am grateful for
the help that I have received from col-
leagues at The National Hospital over many
years. There will also be general acknowl-
edgement and 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 pos-
sible 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 consider-
able 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 charac-
terised by their frequency and their
diversity. The vast majority of major
disorders such as stroke, head and
epilepsy are managed at general
hospitals throughout Great Britain.
The increasing number of neurolo-
gists now working mainly in such
hospitals is ensuring an, improved
spread of neurological expertise.

(3) There are now well established neu-
rological 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 influ-
ence our debate about the future role of
The National Hospital. The question now arises
as to whether a "stand alone" specialist neu-
rological hospital with its somewhat atypical
and selective clinical practice, a depleting
number of referrals, and no local obvious
population to serve, is viable in the 1990s.

The National Hospital would undoubted-
ly achieve much support from clinical neu-
rologists 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-
sions. National and international referrals
would still be attracted, and the Institute,
which would continue to be highly associ-
ed 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, disloca-
tion, and considerable expense. These can
surely be tolerated. Future generations of
patients and doctors will have cause to cele-
brate the foresightfulness 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.

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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;
Functioning investigational choice; Choice of
drugs in childhood and adult epilepsies; Epilepsy
and the law; Intellectual disabilities and epilepsy;
and 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; Fax: +61 2 956 5154.

Announcement from the British Neuro-
psychiatric Association

The 1995 Summer meeting—to include joint
sessions with the British Associa-
tion for Psychopharmacology—will
be held on 15–19 July. On 16 July BNPA
will hold a scientific meeting with the theme of
"movement disorders" and its AGM. On 17 July BNPA/
BAPF will have a joint session on neuroimag-
ing, 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, Stokie Lane,
Stapleton, Bristol BS16 1QT, UK.

BOOK REVIEWS

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Searching for the Causes of Schizophrenia. By EVE C. JOHNSTONE.

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 privi-
leged 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 indus-
try. In addition to the first of the CT study of schizophrenia there were a series of clinical
trials—the fluphenixol stereosomers study,
the study of the adverse effects of anti-
psychotic drugs, The Northwick Park
study of first episodes of schizophrenia and
the Northwick Park "vindication of psychosis" study to which Eve Johnstone's contribu-
tion was pivotal and each of which to my
mind significantly clarifies major aspects of the mechanism/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 detection of a large
catchment area (Harlow) 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 it is 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, which we felt was 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
infectious agent and consider it a "missed
opportunity". I suspect that Eve Johnstone
shares, 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? What clue came from the
finding in the post-

mortem work that the changes are
asymmetrical. This suggests that they represent a
developmental/late component of brain re-

vention, and leads to the more precise hypothesis that the disorder relates to
genetic variation that is homo sapiens spe-
cific. But this hypothesis and the aspects of the work which are reviewed here
(although Eve contributed as coauthor) get no
mention in this volume.

What I conclude is that there are scien-
tists who views schizophrenia from a Baconian
in their approach and others who are
hypothesis driven. Eve is towards one
extreme and I am towards the other.

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Somatisation in neurological practice.

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