Clinical implementation of anti-acetylcholine receptor antibodies

Dr Somnier summarises his experience with testing for antibodies to acetylcholine receptors in isolated muscular values. The confirmation of a reference range obtained with a large number of disease controls. His data completely agree with our study on 193 validated disease controls.5 His specificity values of almost 1 also agree with our earlier reports.23 It is of interest that all his 26 patients with amyotrophic lateral sclerosis had titres within the reference range, contrasting with other reports.5

Some disparity exists in the sensitivity figures for generalised and ocular myasthenia, when compared with previous studies that reported 45-53% and 71.6%

Somnier's figure of 80% clearly stands out. It is not obvious how these cases were validated as not having generalised myasthenia gravis at any time during their disease, which would put them into the other disease group. It is not uncommon for myasthenia gravis to start with ocular symptoms and signs of generalised myasthenia gravis to develop within the next months. On the other hand, some patients may have very mild generalised signs which may be too subtle to be detected by an inexperienced examiner. For diagnostic use in ocular cases (Osserman I) it seems reasonable to come up with two sensitivity figures: in a case of recent onset, the a priori chance to find elevated titres may be approximately 70% or even higher as stated by Somnier. If patients are observed over six or 12 months, some will have developed generalised myasthenia which shifts them into another group. In the remaining patients with longstanding, purely ocular myasthenia gravis, the test sensitivity will gradually decrease. By using these criteria we have indeed found a positivity rate of initially close to 70%, dropping to 45% (above 0-5 nM/L) or 53% (above 0-4 nM/L) (fig). It is that persistence of 12% in group II of ocular cases that poses considerable diagnostic problems.

Sensitivity figures for generalised myasthenia gravis are similar to the ones reported by Howard et al18 but lower than in our study.2 The reason may be that all patients were examined by one of our clinical research group and any questionable patients were excluded from this analysis. The definition of what remains to be "seronegative" is not trivial because permanent seronegativity often calls for tedious further studies to search for unusual myasthenias and myasthenic syndromes. In the few percent of negative cases some may have other types of autoantibodies, as discussed by Somnier and others24 or have low circulations within the reference range. Seronegative patients with acquired autoimmune myasthenia gravis may indeed have autoreactive B cells capable of producing antibodies, as demonstrated by the elegant experiments on transferring lymphocytes from patients to severe combined immunodeficiency mice.4 Furthermore, serum immunoglobulin of seronegative patients with ocular or generalised myasthenia gravis may increase degradation of junctional acetylcholine receptors.

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1 Somnier FE. Clinical implementation of anti-acetylcholine receptor antibodies. J Neurol Neurosurg Psychiatry 1993;54:496-504.

Dr Somnier replies:
I am pleased to learn that my data completely agree with the experiences of Toyka and colleagues with the exception of the diagnostic sensitivity of the non-acetylcholine receptor (AChR) antibodies assay in ocular myasthenia gravis.

Ocular cases were validated as not having generalised myasthenia gravis exclusively on clinical or pharmacological criteria or both.
(1) Complaints and signs of fatigability with or without weakness were localized to extracocular muscles and eyelid (ptosis), and there were no generalized other striated muscles. (2) Unequivocal effect of cholinesterase inhibitors (dextraphonium, pyridostigmine, etc.) was observed on at least one occasion. (3) Neurological signs of generalisation were not a disqualifying feature, that is, repetitive nerve stimulation (RNS) may or may not show a decrement of action potential or twitch in adductor pollicis, brachial biceps, or deltoid muscle. (4) All patients were assessed several times by an experienced examiner (the author).

In eastern Denmark, 202 incident cases of myasthenia gravis were identified during the 20-year period from 1 January 1970 to 31 December 1989.23 A total of 187 patients were followed for more than one year. Serum samples were available from 153 of these patients (group A). The number of long-standing, purely ocular myasthenia gravis was five (16%) among the 32 cases without a serum sample compared with 18 (12%) in group A. The sensitivity of the latter group may therefore be taken as unbiased estimates of the whole patient population.

In cases of recent onset of myasthenia gravis, the chance to find elevated anti-AChR antibodies titres was 84-9% in ocular myasthenia gravis and 92-6% in generalised myasthenia gravis. After a duration of the disease longer than one year, the sensitivity of the anti-AChR antibodies assay was 77-8% in ocular myasthenia gravis compared with 92-7% in generalised cases. Redefining ocular myasthenia gravis with a decrement at RNS as generalised myasthenia gravis (transferring four ocular cases to the other group), yielded a sensitivity of 78-6% in persistently ocular cases, in agreement with the observation that no prognostic conclusion can be drawn from non-longitudinal measurement of decrement.2 Toyka's observation that many patients with recent onset myasthenia gravis will develop generalised disease was confirmed by the long-term assessment of group A (15 of 33 patients, 45%).
shift from ocular to generalised myasthenia gravis was a more common feature of anti-
AChR antibodies-positive myasthenia gravis (14 of 28 patients, 50%) than that of
seronegative myasthenia gravis (one of five patients, 20%). Subsequent to a follow-up
period of more than one year, the group of anti-AChR antibodies-negative patients
consisted of four (3%) ocular cases and 10 (7%) generalised cases.

Consequently, I am unable to confirm
Toyka’s observation of only 45% anti-
AChR antibodies-positive cases in long-
standing ocular myasthenia gravis. Toyka
also suggests that cases with questionable
myasthenia gravis may have been included in
the analysis of generalised myasthenia gravis1 resulting in lower estimates of the
sensitivity relating to such cases. This is a
very unlikely explanation in view of the
scrutiny of all cases including clinical
assessment by an experienced examiner, all
of which is thoroughly expounded in my
article1 and also in my epidemiological study.2

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AChR antibodies for the diagnosis of myasthenia
2 Sommer FE, Keiding N, Poulsen OB. Epidemiology
of myasthenia gravis in Denmark. A longitudinal and
comprehensive population survey. Arch Neurol 1991;48:
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Assessing tremor severity with long-
term tremor recordings

We have read the paper by Bain et al1 with
great interest. This excellent work will be of
considerable benefit for future studies.
Nevertheless we would like to draw attention
to a fact that has been underestimated in
this contribution.

In order to overcome these problems, we have developed a method for measuring tremor for up to 24 hours
by activating the EMG of the main extensors
and flexors with a small portable tape
recorder.2 During the recording period the
outpatients are free to move around and
maintain their usual activities, allowing us
to measure exactly that voluntary muscle activity which produces the daily living
impairment. Having gained some experience
with this technique, we appreciate such long-term recordings as a reliable tool
for clinical studies. Moreover, our measure of
tremor severity (which actually is the
tremor-occurrence rate) seems to correlate better with a patient’s self-rating of func-
tional impairment than the doctor’s clinical
assessment.

We have investigated this issue in a pre-
liminary manner by evaluating treatment
effects in 15 parkinsonian patients with dif-
ferent premedications. The tremor severity
was assessed before and after the change in
medication, firstly by rating on a six-point
scale, and secondly by a 10-hour tremor
recording. In addition, the patients were
asked to rate the effect on a scale consisting
of five grades of improvement (1), slight
improvement (2), no change (0), slight
deterioration (−1), and marked deterioration
(−2). When the changes in tremor occurrence rate and clinical rating, and the
patient’s self-rating are correlated, the
coefficients (Spearman’s r) and p values are:
doctor’s rating—self-rating: r = 0.25, p = 0.37; doctor’s rating—long-term EMG:
 r = 0.017, p = 0.95; self-rating—long-term EMG: r = 0.860, p < 0.001.

Although our setup is not directly com-
parable to the one used by Bain et al (we studied parkinsonian patients instead of
patients with essential tremor) and furthermore EMG and accelerometry might differ in
their correlation with functional impair-
ment) our data allow the following conclu-
sion: neurophysiological techniques do
have a place in tremor quantification if they
are applied for sufficiently long periods
of observation. When used in this way, they
not only avoid the abovementioned problems,
but most importantly, the correlation with funcional impairment seems to be
higher than in any short-term method, including clinical rating.

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the impact of tremor upon upper limb function. J Neurol
Neurosurg Psychiatry 1993;56:686-73.
2 Bacher M, Scholz S, Scholz E, Bacher M, Dichgans J.
Long-term measurement of tremor. In: Korczyn AD, Kraus PH, Pruntek H, eds. Instrumental

Bain and Findley reply:

We note the findings of Boose et al with considerable interest. Their technique of
recording parkinsonian tremor for prolonged periods of time (up to 10 hours)
and their use of "tremor-occurrence rate" as an
index of tremor severity provide a useful
insight into the problems involved in assess-
ing tremor severity. We agree entirely about the advantages of assessing patients during
their normal activities rather than in an
artificial laboratory environment, where
patients may (at least initially) be unduly tense and anxious. Their point about
diurnal variation of tremor is also well
made, and in the case of parkinsonian
tremor we have observed that further short-
term fluctuations occur from burst to burst in
EMG recordings and can be seen from
minute to minute and hour to hour in patients’ limbs (phenomena that led us to
speculate that parkinsonian tremor may be a fractal process).3

We do, however, have some reservations about their approach. Firstly, the equip-
ment is costly and not widely available.
Secondly, the time involved in recording and analysing tremor recordings precludes
its routine clinical use except in
specialist departments. Thirdly, their mea-
surement of tremor-occurrence rate was
compared with a six-point clinical rating scale and a six-point self-rating scale, which are both clearly measures
of impairment. These scales are not functional measures of disability or handicap in a
conventional sense. Boose et al do not appear to have assessed disability formally. This is
understandable because by choosing to study patients with parkinsonism rather than
total tremor other factors, namely bradykinesia, rigidity, and postural instabil-
ity, would have influenced any measures obtained by an assessment of handicap or
disability.

One factor that we have studied and con-
sidered to be critical in determining the
impact of tremor upon upper limb function
is "tremor suppressibility", namely, the
extent to which tremor amplitude can be
suppressed while performing manual tasks
and the period of time that this suppression
can be maintained by the patient (the coef-
figients of amplitude and temporal suppres-
sion respectively).3 This point was
nicely illustrated by Jager and King who describe a man with marked hereditary
tremor who could nonetheless shoot
deer with a rifle at a hundred yards.4 Any
method that solely examines tremor-occurrence rate cannot account for variations in
tremor suppressibility nor the functional
consequences of different types of tremor
(for example rest, postural, and intention
tremors).

Finally, Boose et al appear to have shown that
patients are reliable witnesses, a fact
that will be of great comfort to the humble
and hard-pressed clinician.

NOTICES

The XLIth International Congress of Neuropathology will be held in Toronto,
Ontario, Canada from 18-23 September 1994. This meeting will be conjoined with
the American Association of Neu-
rophathologists Annual Meeting and the
Canadian Association of Neuropathologists Annual Meeting. For further information please contact Dr J J Gilbert, Victoria
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