Clinical implementation of anti-acetylcholine receptor antibodies

Dr Somnier summarises his experience with testing for antibodies to acetylcholine receptors in 193 validated myasthenia gravis patients. 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. It is of interest that all his 26 patients with amyotrophic lateral sclerosis had titres within the reference range, contrasting with other reports.

Some disparity exists in the sensitivity figures for generalised and ocular myasthenia, when compared with previous studies that reported 45-53% and 71%. 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 prior 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 long-standing, 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). It is that persistence (12%) in group B cases that poses considerable diagnostic problems.

Sensitivity figures for generalised myasthenia gravis are similar to the ones reported by Howard et al, but lower than in our study. 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 others or have low circuits which remain 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 using lymphocytes from patients to severe combined immunodeficiency mice. 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 anti-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 located to extraocular muscles and eyelid (ptosis), and therefore, these patients were not considered to have other striated muscles. (2) Unspecific effect of cholinesterase inhibitory drugs (edrophonium, pyridostigmine, etc.) was observed on at least one occasion. (3) Neurophysiological signs of generalisation were not a disqualifying feature, that is, repetitive nerve stimulation in 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. A total of 187 patients were followed for more than one year. Serum samples were available from 155 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 (10%) 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 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. Repeating 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. Toyka's observation that many patients with recent onset of myasthenia gravis will develop generalised disease was confirmed by the long-term assessment of group A (15 of 33 patients, 45%).
Assessing tremor severity with long-term tremor recordings

We have read the paper by Bain et al 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.

Firstly, we would like to investigate the validity of a clinical rating scale and of short-term, upper-limb accelerometry by comparing the results to various measures of functional impairment, clearly demonstrating the superiority of the rating procedure over the neurophysiological approach. On the basis of our own results it seems most likely that one of the main reasons for the weak validity of the accelerometry is the short duration of the recordings, which do not take into account the marked diurnal variations of tremor severity, and the exceptional situation in a clinic laboratory.

In order to overcome these problems which are a general feature of short-term tremor quantification, we have developed a method for measuring tremor for up to 24 hours by recording the EMG of wrist extensors and flexors with a small portable tape recorder. During the recording period the outpatients are free to move around and maintain their usual activities, allowing us to measure exactly the voluntary movements 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 reflects the tremor-occurrence rate) seems to correlate better with a patient’s self-rating of functional impairment than the doctor’s clinical assessment.

We have investigated this issue in a preliminary manner by evaluating treatment effects in 15 parkinsonian patients with different 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-ratings 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 = 0.99; self-rating—long-term EMG: r = 0.860, p < 0.001.

Although our setup is not directly comparable to the one used by Bain et al. we studied parkinsonian patients instead of patients with essential tremor. Furthermore EMG and accelerometry might differ in their correlation with functional impairment; our data allow the following conclusion: 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 functional impairment seems to be higher than in any short-term method, including clinical rating.

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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 assessing 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).

We do, however, have some reservations about their approach. Firstly, the equipment is costly and not widely available. Secondly, the time involved in recording and analysing the technique precludes its routine clinical use except in specialist departments. Thirdly, their measurement of tremor-occurrence rate was compared with a six-point clinical rating scale and a five-point patient 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 essential tremor other factors, namely bradykinesia, rigidity, and postural instability, would have influenced any measures obtained by an assessment of handicap or disability.

One factor that we have studied and consider 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 coefficients of amplitude and temporal suppression respectively). This point was nicely illustrated by Jager and King who describe a man with marked hereditary essential tremor who could nonetheless shoot deer with a rifle at a hundred yards. Any method that solely examines tremor-occurrence rate cannot account for variations in tremor suppressibility or the functional consequences of different types of tremor (for example rest, postural, and intention tremors).

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

NOTICES

The XIlth 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 Neuro-pathologists Annual Meeting and the Canadian Association of Neuropathologists Annual Meeting. For further information please contact Dr. J.J. Gilbert, Victoria Hospital Research Institute, 375 South