MATTERS ARISING

Cut off selection in anti-acetylcholine receptor antibody determination

We have read the interesting paper by Somnier,¹ and want to make an observation about cut off selection in anti-acetylcholine receptor antibody (AChR-Ab) determination. The value 0.5 nmol/l is chosen in an arbitrary way, and so assay specificity and sensibility are also arbitrarily determined.² Receiver operating characteristic (ROC) analysis, combined with information theory, is the most exact approach to cut off selection in a continuous variable.^{2,3} Because the author mentions that AChR-Ab titres of myasthenic patients have a log normal distribution (although no Kolmogorov-Smirnov goodness-of-fit test is reported) and, as control serum sample titres probably also follow a log normal distribution, a ROC analysis could be performed assuming the binormal hypothesis (two overlapping normal curves, one from control patients and other from myasthenic patients). In this way a maximum likelihood estimation could be obtained to plot a ROC curve^{4,5} (figure A). The point nearest (0,1) is the one where sensitivity and specificity are optimal, therefore the one for a proper cut off selection. A further and more accurate cut off selection could be achieved by taking into account the prevalence of myasthenia gravis in the sample as, according to Bayes' theorem, post-test probability is dependent on prior-probability (prevalence). Using ROC analy-

A. ROC curve, true positive rate (sensitivity) v false positive rate (1-specificity). The point of the curve nearest (0,1) is the one that provides an optimal sensitivity-specificity, so usually the best cut off selection. B. Information v antibody titre (log(nmol/l)) at a predetermined prevalence (for this example we have chosen an arbitrary prevalence value of 0.34). The point that offers more information, log(nmol/l) = -0.22, is the one that yields a proper cut off selection, at this prevalence.

sis and Bayes' theorem, the point that should be chosen as cut off is the one that offers more information at the prevalence of the sample⁶ (figure B).

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- 1 Somnier FE. Clinical implementation of anti-acetylcholine receptor antibodies. *J Neurol Neurosurg Psychiatry* 1993;56:496-504.
- 2 Swets JA, Pickett RM, Whitehead SF, et al. Assessment of diagnostic technologies. *Science* 1976;205:753-9.
- 3 Metz CE. ROC methodology in radiologic imaging. *Invest Radiol* 1986;21:720-33.
- 4 Metz CE. Basic principles of ROC analysis. *Semin Nucl Med* 1978;8:283-98.
- 5 Metz CE, Kronma HB, Wang PL, Shen JH. *ROCIT: A modified maximum likelihood algorithm for estimating a binormal ROC curve confidence rating data*. Chicago: University of Chicago, 1985.
- 6 Somoza E, Soutullo-Esperon L, Mossman D. Evaluation and optimization of diagnostic tests using receiver operating characteristic analysis and information theory. *Int J Biomed Comput* 1989;24:153-89.

Sommier replies:

The cut off selection (0.5 nmol/l)¹ was based on a 10 year experience consisting of analysis of more than 3000 serum samples from 366 patients with myasthenia gravis (MG) and 540 control serum samples from healthy individuals and patients with neuromuscular diseases other than MG. The choice of cut off point was made on account of these experimental data and with the objective of providing a maximum of specificity without undue loss of sensitivity. The cut off point was certainly not chosen in an arbitrary way.

Anti-acetylcholine receptor (AChR) antibody titres of patients with MG appear to have a normal log distribution.¹ The goodness-of-fit was $\chi^2 > 0.44$ (χ^2 square test) and $2p > 0.38$ (Kolmogorov-Smirnov test). In control serum samples, the distribution of titres (linear estimates and logarithmic transformed values) has a negative skewness. Provided that this is not a disqualifying feature, a receiver operating characteristic (ROC) analysis assuming the binormal hypothesis² could be performed. Figure 1 shows the leftmost section of the normal deviate of the ROC curve, ΔM (delta mean of normalized curves) = -5.6189 and S (slope) = 0.3518. The location of various cut off points from 0.1 to 1.0 nmol/l is marked on the graph, enabling the

Figure 1 Normal deviate of ROC curve. Anti-acetylcholine receptor antibodies radio-immunoassay.

Figure 2 Maximum information. Cut off point v prevalence.

reader to estimate the corresponding Z scores. Figure 2 shows the cut off points for maximum information as a function of the prevalence of MG serum samples. As 0.10-0.20 is the most likely occurrence in relation to a centralised laboratory, the ROC analysis confirms the choice of 0.5 nmol/l as the most appropriate cut off point for a diagnostic application of radio-immunoassay. The table shows the ratio of true and false positive samples as a function of cut off point. The theoretical (ROC analysis) and the observed true positive ratios are in agreement, but false positivity appears to be underrated by the ROC analysis. Consequently, ROC analysis does not add any new feature to the clinical implementation of the anti-AChR antibodies RIA.

- 1 Somnier FE. Clinical implementation of anti-acetylcholine receptor antibodies. *J Neurol Neurosurg Psychiatry* 1993;56:496-504.
- 2 Somoza E, Soutullo-Esperon L, Mossman D. Evaluation and optimization of diagnostic tests using receiver operating characteristic analysis and information theory. *Int J Biomed Comput* 1989;24:153-89.

Anti-AChR antibodies radioimmunoassay

Cut-off (nmol/l)	Theoretical true positive	Observed true positive	Theoretical false positive	Observed false positive
0.3	0.897	0.900	0.021	0.050
0.4	0.876	0.890	0.010	0.025
0.5	0.859	0.885	0.005	0.000
0.6	0.842	0.871	0.003	0.000