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Glycolytic enzymes in the CSF as tumour markers

Sir: In agreement with Twijnstra and colleagues¹ I find measurements of glycolytic enzymes in cerebrospinal fluid (CSF) such as lactate dehydrogenase (LDH) or phosphoglucoseisomerase (PHI) easy to perform, readily available and economical. A drawback in the detection of meningeal metastases is their limited specificity. The following suggestions may help to reach a greater specificity.

Although the authors have considered the possible influence of age and sex on enzyme activity in the CSF, they have apparently not taken into account the state of the blood brain barrier (BBB) and the enzyme levels in the blood. In evaluating plasma protein concentrations in CSF such as IgG, it is common practice nowadays to correct the CSF value for the serum derived fraction. A similar approach was recently undertaken for the estimation of another tumour marker, carcinoembryonic antigen in CSF.²

CSF/serum ratios range from 1/230 for albumin to 1/500 for IgG. The permeability of the BBB for these plasma proteins is governed by their molecular radii.² By analogy, for LDH, an enzyme with 140 000 D molecular weight, one would expect a quotient of about 1/360. With a serum value of 240 U/l (the upper limit of normal with standardised methods) one then arrives at $240/360 = 0.7$ U/l for the LDH activity in the CSF. However, the normal value given by Twijnstra *et al*¹ lies at 10 U/l. Therefore, in great contrast to plasma proteins, only approximately 7% of the LDH activity in CSF originates from the blood under normal conditions. Accordingly corrections for serum LDH may appear unnecessary. While this is probably true for controls with normal LDH and intact BBB, it is different for cancer patients. Meningeal affection often causes considerable impairment of the BBB and in the

presence of systemic metastases LDH serum activity may be elevated several fold. Erroneously high CSF values may result especially when both conditions coincide. For PHI a correction formula analogous to Tourtellotte's calculation of the IgG synthesis rate has been proposed.³

It would be interesting to know if the three control persons with pathological CSF values above 26 U/l in Twijnstra's patients¹ displayed elevated serum LDH and/or BBB disturbances. Likewise the observed augmentation of CSF LDH in older subjects may be connected to the greater permeability of the BBB for people aged over 60 years. In addition, simultaneous measurement of CSF and serum enzyme activities often reveal a beneficial effect of the CNS-directed therapy, when at the same time the systemic cancer cannot be controlled.³

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Shoulder abduction fatiguability

Sir: I read with considerable interest the recent article by Nicklin *et al* entitled *Shoulder abduction fatiguability*.¹ Having previously read and admired the work of two of the authors, I was encouraged to observe that their work continues in the application of hand-held dynamometry to assess the neurological patient. I have, nevertheless, several concerns with what the authors have recently presented in this journal.

My chief concern is their apparent failure

to take into account the influence of gravity during testing. By either testing shoulder abduction against gravity and not correcting for its influence or mixing the results of tests performed against gravity (in sitting) with those of tests performed with gravity eliminated (when supine) a potential source of error was introduced. Winter *et al* calculated that a failure to correct for gravity effects resulted in an absolute percentage difference of 2.4 (range –6.5 to 26.0) for knee extension.² The potential error associated with a failure to take gravity into account can be illustrated as follows: Suppose a subject's arm places 15 Newtons of force on a dynamometer, at its point of application. That is, with the arm abducted to 90° and the elbow flexed to 90° but resting on the dynamometer, a force of 15 Newtons is registered because of gravity. Next, suppose that the seated subject generates 140 Newtons of abduction force when tested as suggested by the authors. A 6.0% decline in this force over a series of 10 contractions would be 8.4 Newtons. This value, 8.4 Newtons, is only 5.4% of 155 Newtons, the actual force produced (140 Newtons + 15 Newtons to hold the arm against gravity). Thus, the fatigue index is decreased by $(6.0 - 5.4)/6.0 = 10\%$ by including the weight of the arm. Now let us assume that the same subject is affected with a disorder that renders her weak. Gravity still results in 15 Newtons of force from the arm. The subject now generates 30 Newtons of force while seated. A 6.0% decline in this force equals 1.8 Newtons, which is 4.0% of 45 Newtons (30 Newtons + 15 Newtons to hold the arm against gravity). Thus, the fatigue index is decreased by $(6.0 - 4.0)/6.0 = 33.3\%$ by including the weight of the arm. Granting that this is a highly hypothetical situation; the error resulting from a failure to correct for gravity, particularly in a weak arm, could be quite serious.

My second concern is with the muscle group selected by the authors for their study. Although good reasons probably exist for the authors' choice of the shoulder abductors, these muscles are probably more difficult than some others to test accurately. In a study in which I tested supine subjects, I found that forces obtained during repeated tests of shoulder abduction, unlike forces obtained during most other actions, differed significantly from one another.³ I have observed that subjects tend to flex the trunk toward the contralateral side during shoulder abduction testing. This tendency, which is particularly apparent when subjects are tested in sitting, magnifies actual force production. Even the subject in the authors' fig 1 seems to be flexed to the right during testing.