Leukocyte glutamate dehydrogenase in patients with degenerative neurological disorders

Sir: Aubby *et al*¹ recently published the results of an extensive study which evaluated the levels of glutamate dehydrogenase (GDH) in patients with cerebellar and/or extrapyramidal disorders of various types. They reported that GDH activity was significantly decreased in the groups of patients with ataxic disorders, multiple system atrophy, Parkinson's disease, Steel-Richardson-Olszewski syndrome and juvenile Parkinsonism. As such, the study confirms our previous reports^{2,3} indicating that low leukocyte GDH activity occurs in clinically heterogeneous disorders, including multiple system atrophies, atypical Parkinsonism and progressive supranuclear palsy (PSP).

Aubby *et al*¹ interpreted their findings of reduced GDH activity as representing no more than the lower end of a normal distribution. However, there is no indication in their report how normality in distribution was established. The sign test used is designed to evaluate symmetry, but not necessarily normality. Moreover, inspection of fig 3 of the paper by Aubby *et al*,¹ which shows the data points of all groups studied, suggests that the distribution pattern of the ataxic disorders is skewed by a preponderance of low values with about 60% of the data points falling below the mean value (fig 3 shows 64 points instead of the 66 described). Almost all five patients with GDH deficiency appear to belong to one subgroup among the four major categories of ataxic disorders studied. These results, which are in fact in agreement with previous studies on ataxic patients^{2,4,6} argue against the possibility of GDH deficiency being a random, artifactual finding.

In addition, the authors write that four of their patients with "typical" Parkinson's disease had GDH deficiency. However, in three of these, onset of disease had occurred during the second and third decade of life which is atypical for idiopathic Parkinson's disease.

With regard to the methodology used in this study, there is no indication in the paper as to whether the white blood cells were disrupted prior to homogenisation by several cycles of freeze-thaw as done in other laboratories.^{2,5} Moreover, the Teflon homogenisers, used for tissue preparation in the study, have been specifically designed to preserve subcellular organelles. Since GDH is known to be localised in such organelles, failure to disrupt them might have affected enzyme fractionation and heat inactivation.

This could account for the variability reported and the failure to heat inactivate a substantial number of control leukocytes. The authors have limited their heat inactivation studies to those patients with total GDH activity of less than 50% of normal, which may represent a particular subgroup among those with GDH abnormalities.⁶ Previous studies, showing a selective defect in the heat labile GDH, were carried out in multi-system atrophic disorders with mean GDH activity of 67%² and 78%⁶ of normal. Also, a similar defect was reported in patients with PSP and atypical Parkinson's disease whose mean total GDH activity was 85% of normal.³ However, Aubby, *et al*,¹ did not report heat labile and heat stable GDH values in such patients. Since the heat labile component constitutes only 30% of total normal activity,² a deficiency limited to this component, cannot theoretically result in a reduction in total activity by more than 50%.

The authors claim that old age might have been a factor responsible for the decreased GDH activity found in neurologic patients. However, their data are at variance with this explanation. Thus, in the method section of their paper they describe that they found no correlation between leukocyte GDH levels and age. Notably, within the group of Parkinson's disease patients the subgroup with GDH deficiency was of younger age than those without GDH deficiency.

Lastly, it may be argued that the modest reduction found in GDH activity as well as the clinical heterogeneity associated with this reduction are against a primary role for the enzyme defect in the pathogenesis of these disorders. There is, however, recent evidence that multiple forms of GDH exist in human tissues probably encoded by separate genes.⁷ Hence, the possibility of a genetically determined heterogeneity of the biochemical defect cannot be excluded. Further studies are therefore needed to determine whether the GDH abnormalities, found in human neurodegenerative disorders, constitute non-specific abnormalities or leads for elucidating the etiopathogenesis of these disorders.

ANDREAS PLAITAKIS, MD
Department of Neurology,
Mount Sinai School of Medicine,
New York, NY 10029,
USA

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A prospective study of acute idiopathic neuropathy II Antecedent events

Sir: Recently Winer *et al*¹ reported a study of the antecedent events of Guillain-Barre syndrome (GBS). Serological evidence of recent infective disease was identified in 31% of patients. We report here that GBS can be preceded also by a *Borrelia burgdorferi* infection. A GB-like syndrome has been previously reported in association with borreliosis.²⁻⁵ The GB-like syndrome accompanying borrelia infection differs, however, from typical GBS; in fact it is not ascending or symmetric,⁴ and the CSF shows pleocytosis and not the usual albuminocytologic dissociation.³ Probably the GB-like syndrome accompanying borreliosis is directly caused by the infective agent and is not an immune-mediated disorder such as GBS. We report a retrospective study of serum and CSF of 13 consecutive patients who completely fulfilled the diagnostic criteria for GBS.⁷ All of them had rapidly evolving progressive motor weakness with elevated protein concentration and normal cell count in the CSF. In the past clinical history a tick bite or skin erythematous changes were not reported. Sera and CSFs of GBS cases sampled two or three weeks after the onset of neurological disturbances, were examined with indirect immunofluorescence technique using *Borrelia burgdorferi* as antigen.⁸

Matters arising

Sera of 20 patients without neurological disorders were screened for borrelia infection and used as normal control cases. In two of GBS cases (15%) antibodies of IgG class were detected in the serum (at titres of 1:128 and 1:256 respectively), but not in the CSF. In the same sera sampled two months later antibodies to borrelia were no more detectable. The clinical course of the disease in the two positive cases did not differ from other negative GBS patients and they recovered in 6–8 months. Only one of the normal control cases showed antibodies to borrelia at the titre of 1:16, which is not considered as significant of infection.^{9,10}

At least half of the patients with GBS suffer a few weeks before the onset of the disease an infective illness which can trigger an immune-mediated reaction involving the peripheral nervous system.¹¹ Viral infections of the respiratory or gastrointestinal tract, surgical procedures, vaccinations, non-viral agents like *Mycoplasma pneumoniae* or *Campylobacter jejuni* or gram-negative bacteria infections have been described as antecedent diseases.¹² The presence of antibodies in the serum but not in the CSF of typical cases of GBS, together with their disappearance in the following months, suggests that in a few cases a borrelia infection can be the antecedent illness precipitating the immune-mediate disorder of acute inflammatory demyelinating polyneuropathy. Borreliosis should be added in the numerous preceding infections of GBS.

GL MANCARDI
M DEL SETTE
A PRIMAVERA
M FARINELLI

D FUMAROLA*
Institute of Clinical Neurology,
University of Genoa,
Italy
*Institute of Microbiology,
University of Bari,
Italy

Address for correspondence: G L Mancardi MD, Institute of Clinical Neurology, Via De Toni 5, 16145 Genoa.

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Winer and Hughes reply:

We were interested to read the report of Mancardi and his colleagues on the serological identification of borrelia infection on the basis of a transiently raised IgG titre among two out of 13 patients with the Guillain-Barré syndrome. In our own study of one hundred patients with acute idiopathic neuropathy we were able to identify a specific antecedent infection in 31% serologically. A further 24% could recall symptoms of unexplained gastrointestinal or respiratory infection in the month preceding the neuropathy. None of these 24 patients had arthralgia or skin rash. Three had more than 5 white cells/ μ l in the CSF.

A case controlled study of borrelia serology using both IgM and IgG assays of serum and CSF would be of interest. Controls with such a study should include patients with inflammatory conditions which might cause a non-specific rise in total serum IgG.

Book reviews

Neuromuscular Disease, 2nd ed. By M Swash, MS Schwartz. (Pp 456; £99.00.) London: Springer, 1988.

The first edition of this book was widely acclaimed and it achieved a secure place as a "bench book" for those involved in the management of children and adults with disorders of the neuromuscular apparatus. The second and revised edition (with 202 illustrations) is a larger and more comprehensive account of these disorders, particularly the peripheral neuropathies and metabolic muscle disease. It is a welcome addition to the literature on peripheral neuropathology, the photomicrographs of muscle biopsy material particularly being measurably superior to those in the first

edition (although the authors have retained a few illustrations of longitudinal cryostat sections which are pictorially unpleasing, technically unsatisfactory and correspondingly difficult to interpret). However, the question of balance arises when considering the chapters dealing with peripheral neuropathies. There is a profusion of (good) photo- and electronmicrographs of myopathology but only a few illustrations of the commoner peripheral nerve disorders, genetically determined and acquired. Presumably this is a reflection of the special interest of the senior author but it does make for a rather large "bare area" in the middle of an otherwise well-arranged and presented volume. Illustrations of cyclical demyelination/remyelination and axonal degeneration in teased fibre preparations and of some of the more dramatic peripheral neuropathic changes would have been welcome, for examples

"tornaculous" neuropathy and "glue sniffer's" neuropathy. Contrariwise, one wonders why the authors felt it necessary to include references to SMON, lathyrism and syringomyelia in a consideration of predominantly or exclusively lower motor neuron dysfunction. Some of the references in the chapters on peripheral neuropathy appear to be rather antediluvian.

The chapter dealing with disorders of neuromuscular transmission is an admirable summary of an area in which breathtaking progress has been made since the publication of the first edition. Any criticism here inevitably seems carping but the lighting of the patient in Fig 12.2a is poor and a CT scan of the chest might have been more impressive than the lateral chest radiograph illustrated in Fig 12.2b.

It is a pleasure to welcome this new edition of an old friend to the neuromuscular literary