Leukocyte glutamate dehydrogenase in patients with degenerative neurological disorders

Sir: Aubby et al 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 indicating that low leukocyte GDH activity occurs in clinically heterogenous disorders, including multiple system atrophy, atypical Parkinsonism and progressive supranuclear palsy (PSP).

Aubby et al 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, 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, argue against the possibility of GDH deficiency being a random, artificial 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. 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. 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% and 78% 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.

However, Aubby, et al, 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, 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. Therefore, recent evidence that multiple forms of GDH exist in human tissues probably encoded by separate genes. 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 lead to elucidating the etiopathogenesis of these disorders.

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References


A prospective study of acute idiopathic neuropathy II Antecedent events

Sir: Recently Winer et al reported a study on the antecedent events of Guillain-Barré syndrome (GBS). Serological evidence of a 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.

The GB-like syndrome accompanying borreliosis differs, however, from typical GBS; in fact it is not ascending or symmetric, and the CSF shows a pleocytosis and not the usual albuminocytologic dissociation. 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. 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 eritematous 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.
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