Sodium valproate and neutropenia

Sir,

We read with interest the recent report by Barr et al.,\(^1\) in which they noted that 12 of 45 patients receiving valproic acid developed absolute neutropenia, but that in all cases this phenomenon was transient and self-limiting.

Recently we saw a more severe manifestation of this problem. A 9 year old girl suffered from mental retardation and severe fits after hypoglycaemia in the neonatal period. She had previously been treated with a number of different anticonvulsant drugs. Because of continuing fits and her mother’s concern about behaviour problems her anticonvulsant therapy was changed to sodium valproate. With monitoring of valproate blood levels her dose of sodium valproate was gradually increased to 600 mg four times a day. Twenty-five days after starting valproate her neutrophil count, which had previously been normal fell to 0.66 x 10\(^9\)/l. This appeared to be a transient phenomenon and 3 days later the neutrophil count had risen again to 4.8 x 10\(^9\)/l, without alteration of the valproate dose. At this point she was discharged from hospital. Her other treatment at this time was diazoxide, 50 mg in the morning and 100 mg at night, and trimethaphene 60 mg at night.

She was seen again 2 months later and was noted to have a severe neutropenia of 0.2 x 10\(^9\)/l. This persisted for 3 weeks despite reducing her dose of sodium valproate and the drug was therefore stopped. Within 3 days her neutrophil count had returned to normal and has remained normal for 5 months. No alteration was made to her other drug therapy. There was never any evidence of viral infection as a possible cause of the neutropenia.

Neutropenia was first described during sodium valproate treatment by Jaeken et al.,\(^2\) who reported a single case in a 3 month old boy. More recently Coulter et al.,\(^3\) have reported a fall in the neutrophil count in 27 of 100 patients treated with valproic acid, but their minimum count of 2.0 x 10\(^9\)/l is of little clinical significance. Although the thrombocytopenia found with valproate therapy may be due to immune platelet destruction immunofluorescence studies have failed to show antibodies against granulocytes.\(^4\)

We would suggest that neutrophil counts as well as the customary platelet count should be performed on all patients treated with sodium valproate.

References


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Nature of complement deficiency in sickle cell disease

Sir,

The work of Larcher and colleagues\(^1\) was of great interest, as it confirmed and expanded our observations,\(^2\) cited by Dr Larcher et al., on the nature of complement deficiency in sickle cell disease. We feel, however, that in discussing their findings, Dr Larcher et al. could have taken account of our further studies of this problem,\(^3\) which they seem to have overlooked. These studies, as well as our more recent work,\(^4\) indicate that about half of 'steady state' (intercritical) subjects with homozygous sickle cell disease have hypercatabolism of the alternative complement pathway, as judged by the in vivo factor B metabolic turnover rate,\(^5\) and C3d levels in plasma.\(^6\) Mean factor D serum level is depressed in these patients,\(^2\) but this finding was statistically significant only when we...
studied a large number of patients. Koethe et al. whose work on factor D was apparently cited by Dr Larcher et al. made no measurements of factor D in sickle cell disease.

The complement system deficiency and its relationship to high infection rates in sickle cell disease deserve further attention. Our studies currently indicate that the ratio of haemolytic to immunochemical factor B level may be a convenient and relatively simple index of the complement abnormality in sickle cell disease. We have shown that the abnormality is not produced by reduced synthesis of complement proteins, as speculated by Dr Larcher et al. but rather by excessive complement activation which depletes functionally active factor B and possible other factors from serum. These factors may therefore not be as available for defence against infection. We have also shown that hypercatabolism of C3 is linked to the intravascular component of the haemolytic process in sickle cell disease.

The therapeutic implications of these and other studies of immunity related phenomena in sickle cell disease are not clear. Because of their rapid catabolism (normally 2% of the plasma pool per hour in the case of factor B) it may not be rational to attempt to correct the abnormality by replacing deficient proteins as fresh plasma. However, if factor B hypercatabolism is in fact produced by the haemolytic process in sickle cell disease, it may be possible to reverse this abnormality (temporarily) by exchange transfusion with normal compatible erythrocytes. Such transfusions have been shown to reverse the functional abnormality of the spleen in early childhood in sickle cell disease, and may therefore benefit those patients with fulminant or resistant infections.

References

Dr Larcher and co-workers comment:

We thank Dr Wilson for his interest in our work on complement deficiency states in children with sickle cell disease and apologise for our oversight in not citing the further work which he and his co-workers have published in elucidating the nature of these defects. However, in this preliminary study, whose major purpose was the identification of complement deficient states in a UK population of children with sickle cell disease, it seemed inappropriate to speculate comprehensively on the precise mechanism of these defects, especially since we did not have the data which Dr Wilson cited on the children we studied. Although we speculated that defective synthesis of complement components might contribute to the observed deficiency states we feel that we did not give this possibility more weight than the alternative explanation of excessive complement activation which Dr Wilson and his co-workers demonstrated in about half of their adult patients.

The patients in our series were younger than those in whom metabolic studies were performed (none of the latter being less than 18 years of age.) Ethical problems in performing isotope studies in children are considerable and such studies might be difficult to justify along the guidelines laid down by the British Paediatric Association for research in children, until more is known about the relationship between complement deficiency and infection in these subjects. The establishment of normal ranges in such turnover studies in age matched controls would also be difficult to justify but crucial in the interpretation of data obtained from children with sickle cell disease. Measurement of C3d levels in plasma would be a more acceptable means of detecting complement activation in children, but levels of C3d were normal in the limited number of plasma samples we examined.

Our finding of at least two distinct complement defects suggests that further studies of the alternative pathway of complement in children with sickle cell disease are indicated. The possible role of factor D would seem to require further study since, although Koethe et al. did not measure factor D they concluded that 'sera from patients with sickle cell disease have reduced C3 proactivator convertase activity' (factor D activity). The nature of the complement defect in yeast opsonisation deficiency awaits elucidation although deposition of C3b on yeasts is slow in sera from such patients. Such defects appear to be in part genetically determined so that defective synthesis of regulator proteins in children with this deficiency cannot yet be excluded.

We agree with Dr Wilson that complement appears to be important in maintaining host defences against infection, especially as the occurrence of severe defects in patients with severe liver disease appears to be related to their high incidence of infection. Plasma infusion does have some apparent therapeutic benefit in these patients though it clearly cannot be advocated as a prophylaxis. In this context, the recent report of the beneficial effects of plasma infusion on patients in sickle cell crisis is of interest, although such infusions were given for non-immunological reasons.