LETTERS TO THE EDITOR

Hypogammaglobulinaemia with absent B lymphocytes and agranulocytosis after carbamazepine treatment

We report a case of symptomatic hypogammaglobulinaemia with absent B lymphocytes and agranulocytosis in association with carbamazepine treatment. Both these side effects of carbamazepine are exceedingly rare. The use of granulocyte colony stimulating factor (G-CSF) was required to treat the agranulocytosis, but the hypogammaglobulinaemia and B lymphopenia recovered spontaneously on drug withdrawal.

A 63 year old white man presented in February 1995 with anorexia, weight loss, and cough. Sputum grew *Haemophilus influenzae* and sinus radiographs showed an opaque right maxillary sinus. There was no history of frequent or unusual infections. In July 1994, he had had a cerebral haemorrhage consequent on hypertension and complicated by a grand mal convulsion. He had been taking carbamazepine (400 mg twice daily) with lisinopril and atenolol to control his blood pressure.

Investigations disclosed a panhypogammaglobulinaemia (IgG 3·9 g/l (normal 7·0–15·7), IgA < 0·1 g/l (normal 0·7–3·7) and IgM < 0·2 g/l (normal 0·4–1·9). Subclasses of IgG showed concentrations of IgG1, IgG3, and IgG4 at the lower end of the normal range and a reduced IgG2 at 0·09 g/l (normal 0·5–7·5). Specific antibacterial antibodies showed low concentrations of antibodies to tetanus at 0·08 IU/ml (normal > 0·1), pneumococcal polysaccharide at 6 U/ml (normal > 20), and low normal concentrations of diphtheria antibodies at 0·15 IU/ml (normal > 0·1). Viral serology showed the presence of specific antibodies to measles (1/20), poliovirus type 1 (1/32), EBV capsid IgG (1/20), and rubella. Lymphocyte surface markers showed complete absence of CD19 + B lymphocytes and a reduction in CD3 + CD4 + T helper cells at 0·58 × 10^9/l (normal 0·7–1·1). At this point the granulocyte count was normal at 2·8 × 10^9/l. The lisinopril was discontinued, as it was considered that it was contributing to his cough, and amlodipine substituted but carbamazepine was continued at a reduced dose of 100 mg twice daily.

By mid-March, he was unwell with "flu"-like symptoms, fever, nausea, and a large ulcer on the inside of his lower lip. Automated differential full blood count showed a white blood cell count of 1·4 × 10^9/l, with 0·8 × 10^9/l lymphocytes and 0·5 × 10^9/l granulocytes. Review of the blood film confirmed the virtual absence of mature granulocytes. CD3 + CD4 + T cells were low and B lymphocytes were still absent. Bone marrow aspirate and trephine confirmed arrest of myeloid cells at the promyelocyte/myelocyte stage, with no mature granulocytes seen. Carbamazepine was stopped and sodium valproate (200 mg twice daily) was substituted. He was treated with granulocyte colony stimulating factor (G-CSF; 300 μg/day subcutaneously for three days) with prompt restoration of neutrophil count. Extensive microbiological, fungal, and viral cultures were negative. He was treated with acyclovir, ciprofloxacin, flucloxacillin, and amoxycillin. His fever settled as soon as the neutrophil count rose to normal. By June 1995, mature B lymphocytes were once more detectable in the peripheral blood and the IgG had risen to 4·98 g/l and IgA and IgM were once more detectable (0·11 and 0·23 g/l respectively). IgG2 was still reduced at 0·32 g/l. There were no further infective problems.

No pretreatment immunological results were available, but none the less it seems most likely that the adverse effects were associated with carbamazepine, as they did not improve until this drug was withdrawn. Although ACE inhibitors (captopril) have been associated with neutropenia, the lisinopril was withdrawn one month before the development of agranulocytosis.

The haematological complications of carbamazepine treatment have been reviewed by Sobotka *et al*, who have identified 21 cases of agranulocytosis.[1] There seems to be no relation to daily or cumulative dose and the onset of symptoms ranged from 6–1100 days after commencement of the drug. The UK Committee for Safety of Medicines (CSM) voluntary reporting system has recorded 13 cases of agranulocytosis (none fatal), and 78 cases of neutropenia over the period 1963–1995 with carbamazepine. Carbamazepine lies fourth in the list of drugs reported to cause neutropenia, behind clozapine, sulphasalazine, and mianserin. Sobotka *et al* suggest that all patients embarking on carbamazepine treatment should have a full blood count with differential and that those with low-normal or reduced white counts should be viewed as at higher risk of developing red or white cell abnormalities.[1] The rapid reversal of the agranulocytosis by drug withdrawal and G-CSF treatment confirms that this may be an appropriate strategy for management of drug-induced agranulocytosis, as previously reported.[2]

The association of carbamazepine with lymphopenia and hypogammaglobulinaemia is less well established: Sobotka *et al* refer only to "leukopenia", which they dismiss as mostly unimportant, except when agranulocytosis develops.[1] The CSM identified only four cases of lymphopenia. Abnormalities of immunoglobulins are similarly rarely reported, with two cases of "gammaglobulin abnormality" and five cases of hypogammaglobulinaemia. Changes in lymphocyte subpopulations in patients on phenytoin and carbamazepine have been studied by Marcoli *et al*,[3] who have found only a reduction in the percentage of CD3 + CD4 + T lymphocytes; although they do not comment three patients on carbamazepine had significant reductions in surface Ig + lymphocytes (B cells). Gilhus *et al*[4] found slight reductions of IgA and IgM in epileptic patients treated with carbamazepine, but no significant changes in lymphocyte numbers or in vitro responses to mitogens. Basaran *et al*[5] have looked at the effects of monotherapy with phenytoin or carbamazepine on humoral and cellular immunity and have reviewed the previous inconclusive evidence on the effect of carbamazepine on immunoglobulin concentrations. They found that B lymphocyte numbers were unaffected by carbamazepine, but IgM concentrations were significantly reduced: this effect was most pronounced in the first year. CD3 + CD8 + T cells were reduced, by contrast with the findings in our case. It is important to note that this study also identified significant immunological abnormalities in untreated epileptic patients compared with healthy controls, in particular higher B lymphocyte counts, IgM concentrations, and complement C3 concentrations. However, the number of untreated patients was small. Garcia Rodriguez *et al*[6] have described one case very similar to ours, with rash fever, absent B lymphocytes, and profound hypogammaglobulinaemia: the changes reverted to normal when the drug was withdrawn. No rash was present in our patient.

Clinically relevant immunological side effects seem to be a rare feature of carbamazepine treatment. Such immunological abnormalities are much better known in conjunction with phenytoin.[7] It is curious that there is a regular association of anticonvulsant treatment with hypogammaglobulinaemia: this may be due to the sharing of key surface molecules between the lymphoid and nervous systems.

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1 Sobotka JL, Alexander B, Cook BL. A review of carbamazepine's hematologic reactions and monitoring recommendations. *DICP Ann Pharmacother* 1990;**24**:1214–9.
2 Weide R, Köppler H, Heymanns J, Pflüger K-H, Havemann K. Successful treatment of clozapine induced agranulocytosis with granulocyte-colony stimulating factor (G-CSF). *Br J Haematol* 1992;**80**:557–8.
3 Marcoli M, Gatti G, Ippoliti G, *et al*. Effects of chronic anticonvulsant monotherapy on lymphocyte subpopulations in adult epileptic patients. *Human Toxicol* 1985;**4**:147–57.
4 Gilhus NE, Matre R. Carbamazepine effects on mononuclear blood cells in epileptic patients. *Acta Neurol Scand* 1986;**74**:181–5.
5 Basaran N, Hincal F, Kansu E, Ciger A. Humoral and cellular immune parameters in untreated and phenytoin or carbamazepine-treated epileptic patients. *Int J Immunopharmacol* 1994;**16**:1071–7.
6 Garcia Rodriguez MC, de la Concha EG, Fontan G, *et al*. Transient hypogammaglobulinaemia in the adult. Functional assessment of T and B lymphocytes. *J Clin Lab Immunol* 1983;**11**:55–8.
7 Aarli JA. Immunoglobulins in epilepsy (review). *Springer Sem Immunopathol* 1985; **8**:5–28.

Postmeningococcal lumbosacral radiculopathy

A 26 year old man of Zairian origin was admitted to his local hospital having been found incoherent at home. Twelve hours earlier he had been complaining of feeling feverish. On admission he was semicomatose with a fever of 40°C, and there was meningism without papilloedema or focal neurological signs. He was tachycardic, hypotensive, and oliguric. Immediate resuscitation with intravenous colloids and dopamine was instituted. He had a thrombocytopenia of 53 × 10^9/l with abnormal