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 recovered spontaneously on drug withdrawal.

A 63 year old white man presented in February 1995 with anaorexia, 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.

Investigation 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 diptheria 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 x 10^9/l (normal 0.7-1.1). At this point the granulocyte count was normal at 2.8 x 10^9/l. The lisinopril was discontinued, as it was considered that it was contributing to his cough, and amiodipine 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, rigors, 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 x 10^9/l, with 0.8 x 10^9/l lymphocytes and 0.5 x 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. Blood culture and joint aspiration 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) 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, flucloxacin, and rifampicin, but 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 became detectable (0.11 and 0.23 1g/l respectively). IgG2 was still reduced at 0.32 g/l. There were no further infective problems.

No previous 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 A. philaeum red or white blood cells 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 commencing 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, sulphalazine, 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 having a 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 documented. Gilbert et al refer only to "leukopenia", which they dismiss as mostly unimportant, except when agranulocytosis develops. 3 The CSM identified only four cases of lymphopenia. Abnormalities of immunoglobulin subpopulations are rarely reported, with two cases of "gammmaglobulin abnormality" and five cases of hypogammaglobulinaemia. Changes in lymphocyte subpopulations in patients on phenytoin and carbamazepine have been studied by Marcoli et al, 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 CD8 + CD4 lymphocytes were unaffected by carbamazepine, but IgM concentrations were significantly reduced: this effect was most pronounced in the first year.

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 in severe pain 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 x 10^9/l with abnormal
Magnetic resonance imaging in the present case showed gadolinium enhancement of the cauda equina roots, which has not been reported before. The roots remained discrete, unlike the appearance in arachnoiditis. Gotshall suggested an intra- medullary vasculitis with secondary parenchymal damage as the pathological basis for a presumed conus medullaris lesion, by analogy with the brain pathology findings in an 11 month old infant who died 36 hours into the illness. The time course of the onset and the recovery of the neurological syndrome in both Gotshall's case and the present one seems to be more suggestive of a focal postinfectious inflammatory polyradiculopathy.

An infective or postinfective cauda equina syndrome is an unusual clinical phenomenon. A cauda equina may occur as a result of cytomegalovirus infection in HIV positive patients and usually leads to death within a few weeks. In our patient, the negative serology for HIV antibodies, the absence of cytomegalovirus in the CSF on polymerase chain reaction analysis, and the patient's spontaneous recovery make this unlikely to be the diagnosis. Appearances on MRI, showing gadolinium enhancement of the cauda equina roots, seem to indicate that a postinfectious cauda equina may occur after meningococcal meningitis.

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External anal sphincter electromyography in the differential diagnosis of Parkinsonism

Multiple system atrophy may account for up to 10% of patients with parkinsonism. By contrast with idiopathic Parkinson's disease, patients with multiple system atrophy tend to have pronounced sphincter disturbance, which commonly appears early in the course of the illness. A great part of this is due to impairment of the motor control of the external and anal striated sphincters (Onuf's nucleus). Electromyography of either of those two muscles may establish such a neurogenic lesion. We evaluated the usefulness of EMG assessment of the external anal sphincter in disclosing the neurogenic lesion, thus helping to differentiate multiple system atrophy from idiopathic Parkinson's disease.

Twoty four patients presenting with parkinsonian features underwent clinical assessment and external anal sphincter EMG. They had no other disease that could lead to neuropathy. A clinical diagnosis of
Postmeningococcal lumbosacral radiculopathy.

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