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 $0.58 \times 10^9/l$ (normal 0.7-1.1). At this point the granulocyte count was normal at $2.8 \times 10^9/l$. 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 $1.4 \times 10^9/l$, with $0.8 \times 10^9/l$ lymphocytes and $0.5 \times 10^9/l$ 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 anti-convulsant treatment with hypogammaglobulinaemia: this may be due to the sharing of key surface molecules between the lymphoid and nervous systems.

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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 $53 \times 10^9/l$ with abnormal

MRI of the lumbar spine at L3 level (left); enhancement of the cauda equina roots after gadolinium (right). The roots remain discrete.

clotting function which was corrected with fresh frozen plasma. The CSF was turbid with 6000 white cells per mm³, 90% of which were polymorphonuclear cells, and a protein concentration of 0.6 g/l. Antibiotic treatment with cefotaxime and benzylpenicillin was instituted with the benzylpenicillin alone being continued when both blood and CSF cultures showed *Neisseria meningitidis*.

By the fifth day he had persistent headache but was oriented. He complained of lumbar backache and leg pain with unsteadiness, and failed a trial without a urinary catheter because of urinary retention. He was unable to stand for more than a few seconds and could not walk at all; he was also faecally incontinent. Examination on the 12th day of his illness showed him to be confined to bed, afebrile, alert, and fully oriented without signs of meningism. He had no papilloedema and no cranial nerve signs. Apart from a depressed left triceps reflex he had no signs in the arms. There was a severe flaccid asymmetric leg weakness, worse on the left, with all tendon reflexes, except for that at the right knee, being absent even with reinforcement.

Both plantar responses were flexor. There was impaired pinprick sensation from L4 to S5 bilaterally. Proprioception was impaired in the right toes and in the right ankle. Vibration sensation was intact. A urinary catheter remained in situ.

Further investigations showed an erythrocyte sedimentation rate of 85 mm/hour with a C reactive protein concentration of 36 mg/l. Full blood count, urea, electrolytes, clotting screen, liver function tests, calcium, phosphate, complement and HIV-1 antibodies were normal or negative. A repeat CSF examination showed 66 white cells per mm³, of which 58 were monocytes, a protein concentration of 3.8 g/l, and a normal CSF/blood glucose ratio. No oligoclonal IgG was detected in either the serum or CSF. A polymerase chain reaction performed on this CSF was negative for cytomegalovirus, herpes simplex, and varicella zoster. Magnetic resonance imaging of the lumbar spinal canal including the conus showed a minor L4/5 disc protrusion and gadolinium enhancement of the cauda

equina roots which, however, remained discrete (figure). Nerve conduction studies showed reduced compound muscle action potentials distally in the legs with normal conduction velocities, normal F wave latencies, and normal sensory action potentials. Needle EMG showed denervation changes in the extensor digitorum brevis, tibialis anterior and rectus femoris muscles bilaterally. During the next six weeks a gradual improvement occurred on no treatment, and three months later he was continent and walking outdoors.

This patient developed a lower motor weakness of the legs within five days of a meningococcal meningitis, which continued to progress for a week thereafter before plateauing and improving. On both clinical and neurophysiological grounds it seemed likely that this was the result of a lumbosacral radiculopathy. Various neurological sequelae are described after meningococcal infection, occurring in about 10% of cases.¹ The commonest are single palsies of the sixth, seventh, and eighth cranial nerves with either unilateral or bilateral involvement. Third and fourth nerve palsies have been described. More rarely a transient hemiparesis, often with seizures, has been reported to occur in the convalescent phase when the CSF has cleared. Mention is made of flaccid weakness of single muscles or groups of muscles in the review by Banks, but no cases were seen in his series.² There is a single report of lower motor neuron leg weakness which occurred between 8 to 10 days after the onset of the meningococcal meningitis and when the patient had recovered from the acute infection.³ This weakness was attributed to a conus lesion on the grounds of symmetry of both motor and sensory involvement and the combination of tendon areflexia with extensor plantars. Myelography in this case was normal. This patient was treated with a two week course of prednisolone and made an almost total recovery.

The pathogenesis of these sequelae remains uncertain. As most occur in the convalescent phase when the purulent CSF has cleared it is doubtful that they represent a direct infective pathology or the result of the pressure of meningeal exudate on nerve

roots as suggested by Banks.²

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. Gotshall³ suggested an intramedullary 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.⁴ 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 equinitis can occur as a result of cytomegalovirus infection in HIV positive patients and usually leads to death within a few weeks.⁵ 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 equinitis 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.¹ 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.² A great part of this is due to impairment of the motor nucleus of the urethral and anal striated sphincters (Onuf's nucleus).²⁻⁴ Electromyography of either of those two muscles may establish such a neurogenic lesion.^{2,4} 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.

Twenty 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