

## LETTERS TO THE EDITOR

### Comparison of the handling of neurological outpatient referrals by general physicians and a neurologist

Physicians in the United Kingdom see many patients with neurological disease both as outpatients, and as inpatients where about 20% of admissions to general medical wards may be neurological.<sup>1</sup> The process by which general practitioners (GPs) refer patients with neurological symptoms to hospital for a specialist opinion is not uniform throughout the UK. In some areas GPs may refer directly to the neurologist but in others there is no such open access and patients must first be referred to a local physician who may or may not refer the patient to a neurologist. This method of practice occurs frequently in the UK and Ireland because there are fewer neurologists per head of population than in most other countries of Western Europe. These two methods of patient management have never been compared. It is difficult to measure the effectiveness of an outpatient consultation, but efficiency and the use of resources are easy to measure. This is the subject of the following study.

Altnagelvin Hospital in Londonderry and Tyrone County Hospital (TCH) in Omagh are the District General Hospitals for two adjacent populations within the area of the Western Health and Social Services Board for Northern Ireland. Londonderry had four consultant general physicians and two neurological sessions per month which were closed to GPs. Omagh had two consultant general physicians, and two consultant neurologist sessions per month which were open to GPs.

Between 1 November 1987 and 31 May 1988 all patients with neurological symptoms seen by physicians in Londonderry were identified after scrutiny of all referral letters by one of the authors (TE). During this time, all patients seen in the neurology clinic in Omagh were identified. After each patient was seen a specially designed form was completed (by TE in Londonderry and by VP in Omagh); this included information on symptoms, diagnosis, investigations, referrals, drugs prescribed or stopped and

whether the patient was to be followed up, admitted or discharged. Twelve months after the first clinic visit, the medical records of each patient were obtained and the above information was updated.

During the six month period a total of 104 patients with neurological symptoms were referred by GPs to physicians in Londonderry and 39 to the neurologist in Omagh (to whom a further 36 patients were referred by other consultants). The groups were remarkably similar in easily measurable features (table). Referral patterns were long-established at each hospital. In Londonderry there was no convenient alternative destination for patients with neurological symptoms. In Omagh there was an alternative, namely the local physicians; although the exact number referred to them during this period is not known, there was little discrepancy in the referral rates per 1000 population—0.74 to the physicians in Londonderry, and 0.70 to the neurologist in Omagh. The mean interval between the referral letter being sent and the patient being seen was 14 weeks for the physicians, and 10 weeks for the neurologist.

Twenty one different diagnoses were made by the physicians and 20 by the neurologist. Tension headache was the commonest diagnosis accounting for 21% in both groups. Diagnoses after the first visit were divided into four categories: epilepsy, structural disease, (such as, transient ischaemic attacks, multiple sclerosis, myelopathy), non-structural disease, (such as, tension headaches, migraine, hysteria, faints), and uncertain/not made. The notable difference between the two groups is the number of uncertain diagnoses in the physicians' group.

The age range of the patients was remarkably similar although there was an excess of males seen by the neurologist. The presenting symptoms were similar, headache and blackout combined accounting for 53% in the physicians' group, and 64% in the neurologist's group. The proportions in each of the four diagnostic groups at one year were remarkably similar. More than 90% of patients were seen by a consultant in both hospitals.

The management of patients showed marked differences between the groups. The neurologist discharged more patients, had fewer uncertain diagnoses, caused fewer admission days, instituted fewer investigations, prescribed fewer drugs, and arranged fewer paramedical and consultant referrals. These outcomes suggest more effi-

cient management by the neurologist. This of course is a relatively small study from a single area and it may be important to establish similar findings from elsewhere.

If these differences in managing neurological outpatients were found elsewhere in the British Isles, there are a number of ways whereby the situation might be improved. GPs might refer fewer patients with neurological symptoms to hospital and physicians might be encouraged to perform fewer investigations, discharge more patients at the first visit, prescribe fewer drugs, and shorten hospital admissions. All this may be possible but is unlikely to occur unless the neurological training which non-neurologists receive is increased. All neurologists might run open clinics. This is not done at present for two reasons: first, many neurologists prefer closed clinics because they then do not have to see as many patients with non-structural disease, and second, and more importantly, there are quite simply not enough neurologists.

In the United Kingdom there is one full time neurologist for every 370 000 population<sup>2</sup>; this compares unfavourably with most other European countries, and the USA has ten times as many neurologists per unit of population.<sup>3</sup> The recommendations of the Association of British Neurologists of one neurologist per 200 000 population<sup>2</sup> would require a doubling of present neurologist numbers. This solution might be more achievable than reforming the neurological practice of GPs and physicians. If neurologists do provide more efficient management of GP referrals than physicians, then increasing the number of neurologists should be self-funding.

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The study was made possible by the help and cooperation of the physicians at Altnagelvin Hospital, Londonderry and the secretaries and medical records staff there and at Tyrone County Hospital. We thank Dr Anthony Hopkins and Dr Jo Lyttle for helpful comments on the manuscript, and Miss Hazel McClurg for typing it.

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Table Comparison of patients seen by physicians and neurologist

	Physician's group n = 104	Neurologist's group n = 39
Referral rate	0.74	0.70
Sex M/F	52/52	23/16
Mean age (SD)	35.3 (16.6)	34.5 (15.0)
Symptoms		
Headache	30%	38%
Blackout	23%	26%
Dizziness	10%	8%
Other	37%	28%
Diagnoses at 1 year		
Epilepsy	15%	10%
Structural	20%	21%
Non-structural	45%	61%
Uncertain	20%	8%
Discharged at 1st visit	37%	64%
Mean investigations/patient	3.80	0.67
Referred to other consultant	26%	5%
Admission rate (days/pt seen)	0.7	0.1
Drug balance/patient	+ 0.38	-0.02
Follow up visits/patient	0.94	0.62

### Aseptic meningitis as complication of intravenous immunoglobulin therapy for myasthenia gravis

In 1991 Waston *et al*<sup>1</sup> described two cases of aseptic meningitis associated with intravenous immunoglobulin (IVIg) therapy in two patients with immune thrombocytopenic purpura (ITP). In both cases there was temporal correlation between the treatment and the outburst of the meningitis but no challenge was performed. Two other cases of recurrent meningitis associated with IVIg was reported in children with ITP.<sup>2,3</sup> We report a patient suffering from myasthenia gravis (MG) who developed aseptic meningitis after IVIg therapy and relapsed after challenge.

A 20 year old woman had a four year history of MG. The disease manifested itself with horizontal diplopia, ptosis and fluctuating proximal weakness. (Osserman grade - II).<sup>4</sup> Diagnosis of MG was supported by high levels of antiacetylcholine receptor antibodies of 22.8 pmol/ml (normal range 0-5 pmol/l), and decremental response on repetitive nerve stimulation with improvement after Edrophonium chloride (Tensilon). The patient had thymectomy in 1988 due to thymic hyperplasia and since then was treated with anticholinesterase medication with a partial response. Due to progressive weakness in the last months, she was admitted to hospital in October 1992 for IVIg treatment.

On admission her general examination was normal, neurological examination revealed mild ptosis, proximal muscle weakness without bulbar signs or respiratory difficulties. ESR, anti nuclear factor, rheumatoid factor, immunoglobulin levels, thyroid function, and chest x ray were normal.

The patient was treated with IVIg (Gamimune, Miles Inc, USA) 4.5%-5.5% solution in 9%-11% maltose without preservative in dosage of 0.4 gr/kg/day. On the third day of treatment her temperature rose to 37.8°C and she complained of severe headache with photophobia, nausea and she vomited once. She had nuchal rigidity, positive Brudzinsky sign, normal fundi and no focal neurological signs. Lumbar puncture revealed clear CSF, with a pressure of 200 mm H<sub>2</sub>O. Cell count was 80  $\mu$ l, 50% lymphocytes and 50% neutrophils. CSF protein was 0.97 g/l and glucose 2.5 mM/l (blood glucose 3.9 mM/l). Gram stain, bacterial and viral cultures, cryptococcal antigen, and acid fast staining were negative. IVIg infusion was discontinued and the patient recovered after 72 hours without antibiotics or any specific treatment. Lumbar puncture was repeated after 10 days and showed 10  $\mu$ l lymphocytes, normal protein (0.19 g/l) and glucose (3.1 mM/l) levels.

As IVIg therapy was considered an important mode of therapy in this young patient, it was necessary to establish whether the meningitis was associated with IVIg or coincidental.

We therefore obtained informed consent and started a challenge with IVIg infusion increasing the dose from 0.1 gr/kg/day to 0.4 gr/kg/day. On the fifth day her temperature rose to 38.6°C and she developed severe headache with photophobia. Nuchal rigidity with positive Brudzinsky and Kernig's signs were again noted. IVIg treatment was discontinued and after 48 hours the fever, headache and signs of meningeal irritation disappeared. The patient refused a third CSF examination. Side effects of IVIg treatment are usually mild, consisting mainly of allergic reactions in IgA deficient patients, hepatitis, and transient vasomotor symptoms with chills, nausea, flushing, chest tightness and wheezing.<sup>5</sup> Transient headache, vomiting, altered consciousness associated with fever had been described in several patients.<sup>6</sup>

Drug induced meningitis has been reported with trimethoprim-sulfamethoxazole, nonsteroidal anti-inflammatory agents, azathioprine, isoniazide, OKT3 and others.<sup>7</sup> Most reports were in patients with underlying connective tissue diseases such as systemic lupus erythematosus, but not in MG patients.

The mechanism of drug induced meningitis is presumed to be an acute hypersensitivity reaction limited to the leptomeninges without systemic anaphylaxis. Our case adds to the previous four cases of aseptic meningitis associated with IVIg, it is the first described in an MG patient and proved with challenge. As the use of IVIg in the treatment of neurological disorders will increase in the future, the phenomenon of associated aseptic meningitis should be anticipated.

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#### Paraneoplastic opsoclonus-myoclonus in Hodgkin's disease

Opsoclonus is rapid, irregular, chaotic and conjugate eye movements that occur in all directions. It may be part of a syndrome with myoclonus of the trunk and limbs, and may also be associated with cerebellar dysfunction.

A 22 year old female presented with a three month history of shortness of breath, left-sided pleuritic chest pain, weight loss, pruritus and night sweats. On examination there was a lymph node mass in the left supraclavicular region, hepatosplenomegaly and a left-sided pleural effusion. A biopsied lymph node showed lymphocyte depleted Hodgkin's disease (BNLI Grade II). CT scan of the chest and abdomen showed a large mediastinal mass, left-sided pleural effusion and marked hepatosplenomegaly, and she was staged IV B Hodgkin's disease. Treatment consisted of alternating courses of LOPP (chlorambucil, vincristine, procarbazine, prednisolone) and EVAP (etoposide, vinblastine, adriamycin, prednisolone). After 8 courses of chemotherapy she continued to have generalised itching, persistent mediastinal widening and elevated erythrocyte sedimentation rate. Bilateral posterior iliac marrow trephines were disease-free, and it was decided to treat her with high dose BEAM chemotherapy (BCNU, etoposide, cytarabine, melphalan) and autologous bone marrow transplant (ABMT), 18 months after presentation. During the subsequent pancytopenic phase she required support with antibiotics (piperacillin, gentamicin, ceftazidime, vancomycin), platelets and parenteral nutrition.

Seven weeks after BEAM chemotherapy she developed tremors, headaches and an unsteady gait. On examination she had severe opsoclonus, and myoclonic movements of the head and limbs. There were no cerebellar signs. Blood glucose, electrolytes, urea, creatinine, bilirubin, haemoglobin, white cell count and immunoglobulins were normal. There was no increase of CSF pressure, and normal CSF total protein, glucose, cell counts and immunoglobulins. CT and MRI scans of the head were normal. A CT scan of the chest showed persisting but decreased mediastinal lymphadenopathy. She received 1g methylprednisolone intravenously daily for 3 days and localised radiotherapy to the mediastinal mass.

Her neurological symptoms improved gradually over the next 3-4 weeks and she remains well and free from any neurological symptoms approximately 12 months after BEAM chemotherapy and ABMT.

The term opsoclonus was first used by Orzechowski<sup>1</sup> in 1927 to describe rapid irregular conjugate eye movements in several patients with non-epidemic encephalitis. Opsoclonus can be diagnosed at the bedside by the presence of spontaneous, large-amplitude conjugate saccades occurring in all directions of gaze without a saccadic interval. The combination of opsoclonus and myoclonic movements of the head and upper limbs without evidence of cerebellar dysfunction found in our patient are typical of previously reported cases of the OM syndrome.<sup>2</sup> These patients differ from those with paraneoplastic cerebellar degeneration by more rapid onset, predominance of truncal over appendicular ataxia, presence of myoclonus, a tendency for remission, and preservation of cerebellar Purkinje's cells.<sup>3</sup>

Opsoclonus occurs in association with a wide variety of aetiological factors,<sup>4</sup> including viral and bacterial infections of the CNS, intracranial tumours (for example, glioblastoma), thalamic haemorrhage, hydrocephalus, multiple sclerosis, intoxication with lithium and amitriptyline, and in non-ketotic hyperosmolar diabetic coma.<sup>5</sup> Most published cases of OM syndrome have been described in children as a paraneoplastic manifestation of neuroblastoma.<sup>6</sup> OM as a "remote effect" of cancer in adults is much less common and has been described as a series of single case reports over many years<sup>4</sup> and the associated tumours have included carcinoma of the uterus, bladder, breast, lung and thymus. Our report is the first of OM in a patient with Hodgkin's disease.

The site of the lesions causing opsoclonus is unknown. It may occur as a result of an abnormality in the tonic inhibitory control of horizontal and vertical saccadic burst-neurons by "pause cells" in the pontine paramedian reticular formation (PPRF). The most likely site of the lesion is the pretectal region of the midbrain.<sup>7</sup> In our case, CT and MRI scans did not reveal any abnormality in this or any other region.

The pathogenesis of opsoclonus, with or without an associated neoplasm is also unclear. There has been the occasional report linking viral infection of the CNS to OM.<sup>8</sup> This is unlikely in our case as there was no clinical evidence of viral infection, and CSF/MRI examination was normal. Gentamicin administration during the pancytopenic phase was a possibility since streptomycin, a similar aminoglycoside, has