MATTERS ARISING

Early diagnosis and intravenous immune globulin therapy in paraneoplastic cerebellar degeneration

Moll *et al.*¹ present what appears to be a well documented case of paraneoplastic cerebellar degeneration which responded differentially to plasmapheresis and IVIg. Although their synthesis of the data is consistent with the available data, another possibility exists which may explain the course of events.

In their report a 44-year-old woman developed severe dysequilibrium soon after being diagnosed and treated for breast cancer. It is clearly stated that she received 5-fluorouracil (5-FU) just before this syndrome started. In fact, 5-FU has well documented neurotoxicity characterised by gait and appendicular ataxia, dysarthria and hypotonia and its onset may be subacute.² Although this complication was originally reported with higher doses, lower ones can also cause a milder ataxia³ which in most cases is completely reversible. Based on clinical and serological studies, Moll *et al.* conclude that plasmapheresis was ineffective but immune globulin effective in this patient; it seems just as possible that the patient received 5-FU on day 20, developed an unusually severe cerebellar syndrome for the dose administered, was given plasmapheresis, received more 5-FU on day 61 while still symptomatic and only after enough time had elapsed did she finally recover. I think this situation is just as likely as the one outlined by the authors and explains why the patient's clinical course did not correlate with her antibody titres.

Although recent studies on CNS paraneoplastic syndromes have generated much interest in the correlation between CNS reactive antibodies and neurological syndromes, it is unclear whether their presence clinches the diagnosis. Since screening for these antibodies is now readily available through commercial laboratories, it seems an opportune time for developing more rigid inclusion and exclusion criteria for these unusual CNS syndromes.

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- 1 Moll JW, Henzen-Logmans SC, van der Meche FGA, Vecht CH. Early diagnosis and intravenous immune globulin therapy in paraneoplastic cerebellar degeneration. *J Neurol Neurosurg Psychiatry* 1993;56:112.
- 2 Riehl JL, Brown WJ. Acute cerebellar syndrome secondary to 5FU therapy. *Neurology* 1964;14:961-7.
- 3 Horton J, Olson KB, Sullivan J, *et al.* 5-Fluorouracil in cancer: an improved regimen. *Ann Int Med* 1970;73:897-900.

Moll *et al.* reply:

Dr Recht makes a valuable point. 5-Fluorouracil (5-FU) can indeed induce a transient cerebellar syndrome, usually together with a diffuse toxic encephalopathy leading to associated mental changes. As

the medical oncologist felt it very important to continue chemotherapy in our patient, she received her third cycle of CMF three weeks after onset of symptoms: cyclophosphamide (100 mg/m², days 1-14), methotrexate (40 mg/m², days 1 and 8) and 5-FU (600 mg/m², days 1 and 8). As we were aware that her cerebellar symptoms which had not yet fully recovered at that time, might deteriorate, we watched her carefully and observed an increase in ataxia and titubation a few days following administration of CMF. These symptoms recovered to baseline abnormalities within a few days, with ongoing improvement later. Further chemotherapy was continued uneventfully, with cyclophosphamide (500 mg/m²), epirubicin (50 mg/m²) and prednisone (40 mg, days 1-10).

Thus for clinical reasons alone we consider it unlikely that 5-FU induced the cerebellar symptoms. Two other reasons make it also improbable. First, this complication has usually been observed with doses of 1000 mg/m² or higher which is occasionally administered to patients with colorectal carcinoma. Our patient received 600 mg/m² 5-FU, which is the standard dose for adjuvant chemotherapy in breast cancer. Second, the finding of auto-antibodies in paraneoplastic neurological syndromes (PNS) is a very specific finding. The titres of these antibodies, however, do not often correlate with the clinical course. This non-correlation does not contradict a pathogenic role for these auto-antibodies at the time the paraneoplastic syndrome develops. The detection of specific antineuronal auto-antibodies is often the only finding enabling the clinician to make a reliable diagnosis of PNS during life. Dr Recht hints at the necessity of rigid inclusion criteria in designing treatment protocols for PNS. We suggest that requirements should include an early diagnosis before irreversible neurological damage has developed together with initiating new modes of therapy within four weeks after onset of neurological symptoms.

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Neuroradiological anomalies and schizophrenia

The recent informative review by David and colleagues¹ provides a much-needed update on the epidemiology and clinical relevance of anomalies of the corpus callosum, and in particular their implications for the pathobiology of schizophrenia. The advent of MRI has generally resulted in more frequent detection of these and other midline developmental abnormalities and, as alluded to by David *et al.*¹ this refinement has been responsible for wide variations in reported prevalence and definition of "caseness". Nevertheless, the over-representation of such anomalies in recent neuroimaging studies of patients with schizophrenia is striking^{2,3} and is consonant with current perspectives on schizophrenia as a neurodevelopmental disorder. The corpus callosum develops in intimate association with the hippocampus and other limbic struc-

tures and (developmental) abnormalities of these latter regions have been one of the most consistent neuroimaging and neuropathological findings in schizophrenia.⁴ Therefore, such anomalies should not be dismissed lightly as incidental neuroradiological findings, but rather provide a unique opportunity to explore the clinical and neurodevelopmental correlates of cerebral morphology in schizophrenia and other CNS disorders (Buckley *et al.*, in preparation). These anomalies complement recent findings of a greater prevalence of obstetric complications, minor physical anomalies, neurological soft signs, and abnormal dermatoglyphics in patients with schizophrenia,⁴ and collectively point to the importance of early fetal maldevelopment in the later expression of at least some forms of this disorder.

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- 1 David AS, Wacharasindhu A, Lishman WA. Severe psychiatric disturbance and abnormalities of the corpus callosum: review and case series. *J Neurol Neurosurg Psychiatry* 1993;56:85-93.
- 2 O'Callaghan E, Buckley P, Redmond O, *et al.* Abnormalities of cerebral structure in schizophrenia on magnetic resonance imaging: interpretation in relation to the neurodevelopmental hypothesis. *J R Soc Med* 1992;85:227-31.
- 3 Degreaf G, Lantos G, Bogerts B, Ashtari M, Lieberman J. Abnormalities of the septum pellucidum on MR scans in first-episode schizophrenic patients. *Am J Neuroradiol* 1992;13:835-40.
- 4 Waddington JL. Schizophrenia: developmental neuroscience and pathobiology. *Lancet* 1993;341:531-36.

Brachial plexopathy after botulinum toxin administration for cervical dystonia

Sampaio *et al.*¹ favour "a causal relationship" between the local administration of botulinum toxin (BT) in distinct cervical regions and a bilateral brachial plexopathy in a 32-year-old woman, and propose either a direct effect of BT on the brachial plexus or an immune-mediated mechanism similar to serogenic peripheral neuropathy. The report raises questions of general interest.

The paper does not mention whether the BT injections were successful in those muscles into which they were injected, or whether there were side effects, local or general, other than those discussed, which could be attributed to the BT injections.

The fluid in which the BT was dissolved is not stated, and the volumes administered at the single injection sites are not given. Local side effects following BT injections, such as dry mouth or dysphagia, seem to be at least partially related to the concentration of toxin and the total fluid volume injected.² Consideration of a direct effect of BT injections on the brachial plexus would have to take into account these factors.

The report also does not state whether the laboratory investigations before, or those after, the plexopathy took immunological studies into consideration.

Since its first use, possible side effects of BT treatment have been vigorously monitored by many authors.^{2,4} None of them, to our knowledge, has ever systematically