MATTERS ARISING

Early diagnosis and intravenous immune globulin therapy in paraneoplastic cerebellar degeneration

Moll et al, 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 possible explanation which may explain the course of events.

In their report a 44-year-old woman developed severe dysarthria 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. Although this complication was originally reported with higher doses, lower ones can also cause a milder ataxia 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 then after enough time had elapsed she did 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 titers.

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 the titers for these antibodies is now readily available through commercial laboratories, it seems a opportune time for developing more rigid inclusion and exclusion criteria for these unusual CNS syndromes.

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4 Horton D, Olsen KB, Sullivan J, et al. 5-Fluorouracil (5-FU) can indeed induce a transient cerebellar syndrome, usually together with a diffuse toxin 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, day 8). At the time 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. After a further 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 Reith 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 colleagues' provides a much-needed update on the epidemiologic and clinical relevance of abnormalities of the corpus callosum, and in particular their implications for the pathobiology of schizophrenia. The advent of MRI has generally made it possible to use modern imaging to detect these and other midline developmental abnormalities and, as alluded to by David et al, 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 striking1 and needs to be considered with current perspectives on schizophrenia as a neurodevelopmental disorder. The corpus callosum develops in intimate association with the hippocampus and other limbic structures and (developmental) abnormalities of these latter regions have been one of the most consistent neuroimaging and neuro-pathological findings in schizophrenia.4 Therefore, such abnormalities should not be dismissed lightly as incidental neuroradiological findings, but rather provide an unique opportunity to explore the clinical and neurodevelopmental correlates of cerebral morphology in schizophrenia and other CNS disorders (Buckley et al, in preparation). These abnormalities complement other findings of a greater prevalence of obstetric complications, minor physical anomalies, neurotological 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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Brachial plexopathy after botulinum toxin administration for cervical dystonia

Sampaio et al 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 neural elements or/and an immune-mediated mechanism similar to serogeneric 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 they 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, lacrimation, or ptosis, are not 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 immuno-logical studies into account to provide a unique immune-mediated mechanism similar to serogeneric peripheral neuropathy. The report raises questions of general interest.


reported tongue sores or lip oedema as a putative side effect following BT injection, nor have we ourselves observed similar nervous reactions in any of our cases. On the other hand, many viruses, predominately herpes simplex types, varicella zoster and various coxsackie types produce oral manifestations resulting in vesicles or ulcers, but without muscle pain or weakness. Such changes may or may not be pathogenic for a number of other infectious agents. Without further information, appearance of tongue sores and lip oedema in this case cannot further be clarified. It seems possible that they had appeared unrelated to a drug reaction as a common or uncommon stomatological infection, with or without upper pharyngeal/respiratory infection.

The authors use the sequence of clinical events and the neurophysiological findings as their main argument for a relationship between a brachial plexopathy and the BT injections. From this sequence, however, the plexopathy could be considered unrelated to the BT injections as well. The following two arguments, however, do not preclude an immune-mediated mechanism for its occurrence.

Firstly, plexopathy started with irradiating neck pain that, after a free interval of 23 days, was followed by weakness of selected shoulder and arm muscles. Despite this the generally assumed clinical similarity of immune-to-nonimmune forms of brachial plexopathy, this interval between pain and onset of weakness is frequently significantly longer in BT than in non-BT patients. Persistence of pain at the onset of weakness, on the other hand, is seen more frequently in the serogenous forms.

Secondly, the haemaggulatin-toxin complex of the Clostridium botulinum type A administered has strong antigenic and biochemical similarities to the toxoid of C. tetani. In accordance with everyday neurology experience, host vaccine-induced plexopathies from the toxoid form of C. tetani are extremely rare. Given the worldwide, billion-fold application of tetanus toxoid for many decades, it seems improbable that vaccine-induced complications following BT injections at the peripheral nervous system will occur at a conspicuously higher rate than with tetanus toxoid.

BT is a new therapeutic agent with a high level of medical surveillance. Medical observation, therefore, will link any evidence of a possible adverse event to the administration of such an agent; this is even more likely, if the event represents a condition with a generally ill-defined etiology, such as the non-serogenous or non-vaccine-induced forms of "idiopathic" brachial plexopathy. Analyses of such cases must take into account selection bias before further conclusions are drawn.

In our opinion, the above documentation does not sufficiently rule out the mere coincidence between BT injections and the bilateral brachial plexopathy. As BT is one of the most important novelties of neurological treatment in recent years, possible adverse effects in its use merit close attention, but should be documented as completely as possible.


Sampaio et al. reply: In our patient we used 200 LD 50 U/ml in the first treatment, we injected 4 ml saline distributed in eight points: two in the right sternomastoid; three in the right posterior cervical region (splenium capitis and trapezius); and three in the left posterior cervical region (splenium capitis and trapezius).

After this first treatment there was no clinical improvement in the cervical dystonia; a booster injection was therefore performed 15 days later. At that time, 2 ml of a solution of 200 LD 50 U/ml of saline were injected in both posterior cervical regions.

Tongue sores and lip oedema are conspicuous adverse events. The causality between the use of a drug and their appearance is difficult to establish. Although there are an long list of drugs that may cause these events, other aetiologies cannot be excluded. We admit that tongue sores would not be mentioned if not actively sought. Only when the patient confirmed their presence. Their tongue sores were discrete but in our patient the complaints were severe.

We admit that it is impossible to be sure of a causal relation between the use of BT and the development of brachial plexopathy but the possibility does exist.


Delirium and quantitative EEG
In the recent report by Jacobson et al. on conventional and quantitative EEG in the diagnosis of delirium among the elderly, the authors report that there are variables which distinguish normal from encephalopathic records (mini-mental State Examination and relative power in delta and an index of EEG slowing). Jacobson et al. stated that EEG with quantitative analysis has the potential to provide important information to supplement the clinical examination, in making an appropriate and timely diagnosis. Our experiences generally agree with studies by Koponen et al. and Jacobson et al. to our knowledge, the only supportive reports of quantitative EEG in delirium. Nevertheless, we wish to stress some points.

Firstly, in 1990, Inouye et al. reported a valid and reliable instrument in the detection of delirium—conventional EEG (CAM). This consists of nine criteria from DSM-III-R and can be completed in less than five minutes.

Secondly, qualitative changes seen in "EEG" (triphasic waves and focal and diffuse epileptic discharges) may not be recognised if we used the quantitative EEG alone. In particular, specific EEG patterns, including periodic lateralised epileptiform discharges suggestive of focal intracranial causes of ACS, and diffuse abnormal EEG activity (triphasic waves, spikes, sharp waves, and spike and wave complexes) may not be recognised by using automated frequency analysis alone.

Thirdly, quantitative EEGs followed serially over time seem to show that delirium is less transient than currently believed: in our preliminary study, six of 14 patients had focal or diffuse increase of the alpha power, or both, after the resolution of clinical features of ACS.

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Diagnosis by axilla skin biopsy in an early case of Lafora's disease
Rubio et al. reported a young girl with a family history of Lafora's disease, myoclonus affecting the upper limbs and head, EEG abnormalities, no evidence of dementia and the presence of Lafora bodies in skin axillar tissue. We describe two siblings with Lafora's disease: one with epilepsy, myoclonus, EEG abnormalities, severe dementia and numerous Lafora bodies in the muscle and skin tissue; the other without dementia complained of one myoclonic seizure of the upper arms, and had EEG abnormalities and Lafora bodies in the muscle and skin tissues. We concluded that the diagnosis of Lafora's disease by skin and muscle biopsy is possible in the early stages of the disease, when there are myoclonic epilepsy and EEG abnormalities, and before the onset of dementia.

In our case of Lafora's disease the diagnosis was made in an earlier clinical stage.
Brachial plexopathy after botulinum toxin administration for cervical dystonia.

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