

## LETTERS TO THE EDITOR

### Early diagnosis and intravenous immune globulin therapy in paraneoplastic cerebellar degeneration

Effective therapy with intravenous immune globulin (IVIg) has been reported in Guillain-Barré syndrome,<sup>1</sup> chronic inflammatory polyneuropathy<sup>2</sup> and other immune related disorders of the nervous system.<sup>3</sup> Paraneoplastic neurological disease includes limbic encephalitis, subacute cerebellar degeneration and sensory neuronopathy and usually leads to severe handicap. Although individual successful cases have been reported, therapy including plasmapheresis, immunosuppressive or anti-tumour therapy, has rarely been of benefit in this group of incapacitating disorders.<sup>4,5</sup> Failure of therapy is commonly explained by the development of irreversible neuronal cell loss before therapy was started.<sup>4</sup>

An autoimmune mechanism is probably involved in paraneoplastic disorders of the CNS and specific anti-neuronal autoantibodies have been identified in serum of these patients.<sup>4,6</sup>

We present the first case of complete recovery following IVIg therapy in a patient with a paraneoplastic neurological syndrome, in which therapy was started within two weeks after onset of neurological symptoms.

A 44 year old woman with bilateral adenocarcinoma of the breast had radical mastectomy with axillary node dissection at the left and partial mastectomy with axillary node dissection at the right. Pathological examination revealed radical excision of an undifferentiated ductal adenocarcinoma, classification T1N1MX (right) and T2N1MX (left). At day 15 (figure), surgery was followed by adjuvant chemotherapy consisting of three courses of cyclofosfamide, methotrexate and 5-fluoro-uracil over a period of two months. During this treatment, she developed severe dysequilibrium. She was unable to walk by herself or to sit up

because of vigorous orthostatic tremor. There was also severe intentional tremor of the hands and feet. CSF and CT scan of the brain revealed no abnormalities. Serological viral studies were negative. An anti-neuronal antibody was found which reacted with a neuronal nuclear protein with a titre in serum of 1:1600 and in spinal fluid of 1:8, using an indirect immunofluorescent immunohistochemical detection method.<sup>7</sup> Antibodies stained the nuclei of Purkinje cells, granular cells and cells in the molecular layer of the cerebellum. The observed staining pattern was the same as described for anti-Hu antibodies associated with small cell lung cancer and paraneoplastic neurological disease. However, on immunoblots of cerebellar neuronal protein extracts serum did not react with the characteristic anti-Hu 38-40 kD band. Anti-Purkinje cell antibodies of the anti-Yo type were not detected. A diagnosis of paraneoplastic cerebellar degeneration was made. Plasma exchange was started 10 days after onset of neurological symptoms. A total of 6 courses of 2.4 litre plasma exchange each, was given over a two week period. Over this period neurological symptoms continued to deteriorate. Twenty six days after onset of neurological symptoms, we started immune globulin in a dose of 0.4 g/kg for 5 consecutive days. Four days after starting IVIg, signs of cerebellar ataxia began to improve and the patient was able to sit up independently. One week later she was able to walk by herself. In the weeks following, further improvement was seen and the patient became able to resume her work. Continuation of chemotherapy was well tolerated. During plasma exchange, anti-neuronal antibody titre in serum decreased from 1:1600 to below 1:200 and in spinal fluid from 1:8 to below detection level (figure). Serum antibody titres remained below 1:200 during and after IVIg therapy. During a follow up of 8 months after therapy her neurological symptoms did not return.

These data cannot prove that the positive effect was either due to plasmapheresis or to IVIg, although they do suggest a response to IVIg rather than to plasma exchange in spite of a rapid initial drop of antibody titre following plasma exchange. For this condition plasma exchange has usually been unsuccessful.<sup>4,5</sup> We believe that the combination of early diagnosis by detection of specific

antineuronal antibodies followed by early IVIg administration before irreversible neurological damage has developed, explains the complete recovery of this patient. This stresses the importance of making an early diagnosis in patients suspected of a PNS not only for early tumour detection and its therapy but also for the possibility of reversing neurological symptoms. The use of specific anti-neuronal antibodies in these cases can be of great help and lead to an early and specific diagnosis, while other investigations are usually negative or non-specific.<sup>7</sup> Although an anti-neuronal nuclear antibody reactivity is uncommon in paraneoplastic cerebellar disease associated with breast carcinoma, this has been observed previously.<sup>8</sup>

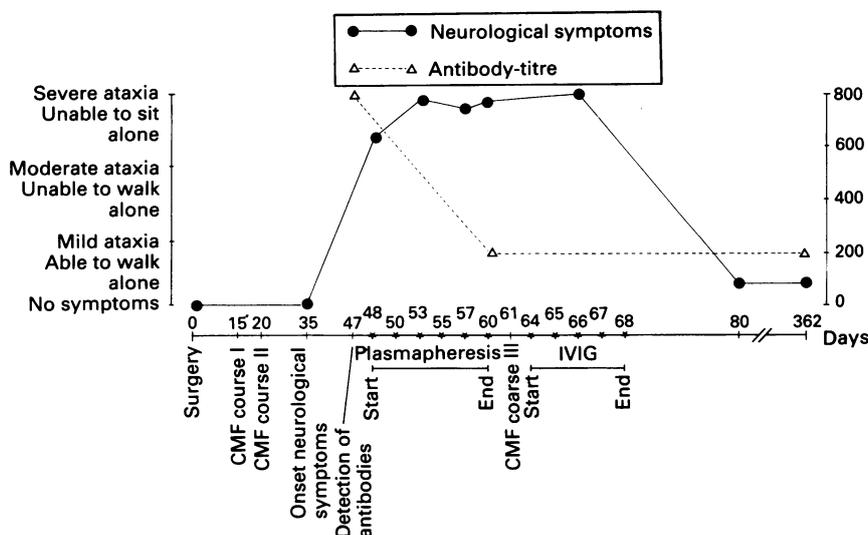
The successful recovery of this case of paraneoplastic cerebellar disease may possibly indicate another group of neurological diseases which may benefit from IVIg therapy and offers a model for studying the therapeutic mechanism. Further study of IVIg therapy for paraneoplastic neurological disorders at an early stage of disease seems warranted.

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- 1 Van der Meché FGA, Schmitz PIM, and the Dutch Guillain-Barré Study Group. A randomized trial comparing intravenous immune globulin and plasma exchange in Guillain-Barré syndrome. *N Engl J Med* 1992;326:1123-9.
- 2 Vermeulen M, van der Meché FGA, Speelman JD, Weber A, Busch HFM. Plasma and gamma-globulin infusion in chronic inflammatory polyneuropathy. *J Neurol Sci* 1985;70:317-26.
- 3 Dwyer JM. Manipulating the immune system with immune globulin. *N Engl J Med* 1992;326:107-116.
- 4 Waterhouse DM, Natale RB, Cody RL. Breast cancer and paraneoplastic cerebellar degeneration. *Cancer* 1991;68:1835-41.
- 5 Graus F, Vega F, Delattre JY, Bonaventura I, Rene R, Arbaiza D, Tolosa E. Plasmapheresis and antineoplastic treatment in CNS paraneoplastic syndromes with antineuronal antibodies. *Neurology* 1992;42:536-40.
- 6 Furneaux HF, Reich L, Posner JB. Auto-antibody synthesis in the central nervous system with patients with paraneoplastic syndromes. *Neurology* 1990;40:1085-91.
- 7 Moll JWB, Henzen-Logmans SC, Splinter TAW, Van der Burg MEL, Vecht ChJ. Diagnostic value of anti-neuronal antibodies for paraneoplastic disorders of the nervous system. *J Neurol Neurosurg Psychiatry* 1990;53:940-3.
- 8 Anderson NE, Rosenblum MK, Posner JB. Paraneoplastic cerebellar degeneration: Clinical-immunological correlations. *Ann Neurol* 1988;24:559-67.

### Absence of the amyloid precursor protein gene mutation (APP717 : Val->Ile) in 85 cases of early onset Alzheimer's disease

Linkage studies suggest that Alzheimer's disease (AD) is genetically heterogeneous.<sup>1</sup> A missense (Val->Ile) mutation in codon 717 of the amyloid precursor protein (APP) gene on chromosome 21 has been described in two families,<sup>2</sup> and in four other unrelated families of different geographical origins with early onset AD.<sup>3</sup> The absence of this mutation in the general population, verified in at least 436 normal individuals,<sup>4-6</sup> suggests that it may be pathogenic. As a result, the Alzheimer's Disease Research Group has proposed that this particular form of the disease be des-



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