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,¹ chronic inflammatory polyneuropathy² and other immune related disorders of the nervous system.³ 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.^{4,5} Failure of therapy is commonly explained by the development of irreversible neuronal cell loss before therapy was started.^{4,6}

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.^{4,6}

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 cyclophosphamide, 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.⁷ 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.^{4,5} 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.⁷ Although an anti-neuronal nuclear antibody reactivity is uncommon in paraneoplastic cerebellar disease associated with breast carcinoma, this has been observed previously.⁸

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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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.¹ A missense (Val->Ile) mutation in codon 717 of the amyloid precursor protein (APP) gene on chromosome 21 has been described in two families,² and in four other unrelated families of different geographical origins with early onset AD.³ The absence of this mutation in the general population, verified in at least 436 normal individuals,⁴⁻⁶ 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-

Figure

ignated β -amyloidopathy (APP 717).³ We screened 85 cases of early onset AD to estimate the frequency of this mutation.

The patients were collected from an ongoing genetic study on early onset AD. The clinical diagnosis was based on a standardised protocol, fulfilling NINCDS-ADRDA criteria.⁷ The age of onset of patients was < 60 years, with a mean (SD) of 54.0(4.9). Sixty four cases had no affected first or second degree relatives, 21 were familial with at least one first or second degree relative with AD.

DNA was extracted from blood leucocytes, and exon 17 of APP gene was amplified by the polymerase chain reaction (PCR), according to Goate *et al.*² Since the (APP 717: Val->Ile) mutation creates a BclI restriction site allowing its direct detection,² the PCR product was digested with the BclI restriction enzyme and analysed on a 2% agarose gel. The enzyme did not recognise the mutant BclI site in any of our cases, whereas it digested the PCR product of an in vitro generated exon 17 with the (APP717: Val->Ile) mutation. This agrees with the studies of Van Duijn *et al.*⁸ and Schellenberg *et al.*⁶ including patients with a higher age of onset. Combining the results of all studies on early onset patients of Caucasian origin,^{2,4,6,8} it may be concluded that for a confidence interval of 95%, less than 2.6% of isolated cases, and between 0.3 and 5.3% of familial cases, would have this mutation.

Two other missense mutations have, however, also been found in the same codon of APP gene^{9,10} supporting the hypothesis of allelic heterogeneity in early onset AD. We cannot therefore exclude the presence of another APP gene mutation in our sample. Even if the (APP 717: Val->Ile) mutation is of poor diagnostic value, the identification of other mutations within the same gene will establish a clear molecular classification and contribute to the understanding of the pathogenesis of the disease.

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Palatopharyngolaryngeal myokymia resembling "palatal myoclonus"

"Palatal myoclonus" consists of rhythmic movement of pharyngeal, laryngeal and palatal muscles at the average rate of 100 jerks/minute.¹ Usually seen in association with brain stem lesions, the hypertrophically degenerated inferior olive seems to serve as the central oscillator. Some patients with "palatal myoclonus", however, have no organic lesions in the posterior fossa.¹

We report a patient with palatopharyngolaryngeal involuntary movement resembling "palatal myoclonus" in synchrony with myokymic discharges recorded on needle EMG.

A 57 year old housewife complained of hearing ear clicks and experienced an involuntary twitch in the throat. Beginning insidiously, the symptoms have neither worsened nor remitted for 18 months. She also noted occasional muscle cramps in lower extremities. She had no history of cerebrovascular disease, encephalitis or trauma. None of her family had neurological disorders.

Neurological examination revealed "palatal myoclonus" consisting of involuntary up and down movements of the uvula at a rate of 40-80 beats/minute. Clicking sounds in association with the movements was audible by the examiner. Incessant rippling of the skin in the anterior neck reflecting the contraction of the pharyngeal and outer laryngeal muscles was observed. Laryngoscopic examination

Figure Surface EMG in successive sweeps recorded from a pair of electrodes placed on the right lateral part of the soft palate (A) showing nonrhythmic spontaneous group discharges. Needle EMG recorded from the right palatal (B) and mylohyoid (C) muscle showing myokymic discharges.

showed twitches of the inner laryngeal muscles. These movements, showing no temporal relationship with either respiration or heart beat, did not change with posture, sleep or when the patient held her breath. She had normal costoabdominal respiration without disturbance of phonation or swallowing. Ocular movements were full without pendular nystagmus. There was no spontaneous contraction in facial, masseter, tongue, sternocleidomastoid, diaphragmatic or limb muscles. Examination of the muscles revealed normal tonus without atrophy or weakness. She had intact sensation and normal reflexes and had no ataxia, hyper-sweating, myotonia, or Trousseau or Chvostek signs.

Normal laboratory data included total and ionised serum calcium and magnesium, thyroid and parathyroid functions, and immunological studies. Brain MRI showed no abnormalities. Surface EMG recorded from the right lateral part of the soft palate showed nonrhythmic group discharges of varying durations (fig A). Simultaneous recording from different sites of the anterior neck revealed asynchronous firing. Studies with a concentric needle electrode placed in the palatal and mylohyoid muscles confirmed the presence of single or grouped fasciculation potentials or myokymic discharges (fig B, C), firing at 60-120 beats/minute. Careful search disclosed neither fibrillation potentials nor positive sharp waves. The facial, masseter, sternocleidomastoid and limb muscles were normal with no evidence of myokymic discharges at rest or even after hyperventilation. Motor and sensory nerve