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Chronic enteroviral meningo-encephalitis in X-linked agammaglobulinaemia: favourable response to anti-enteroviral treatment

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Sir: Human enteroviruses can cause persistent CNS infection in B-cell-deficient patients. Before the introduction of intravenous immunoglobulin (IVIG) therapy this complication was considered to be fatal [1, 2, 3]. Today, the deleterious course of the disease can be controlled by regular IVIG substitution. Nevertheless, despite ongoing IVIG therapy there is evidence of viral persistence as detected by PCR leading to progressive neurological deterioration in many patients [2, 3]. Efficient anti-enteroviral drugs were not available, until recently when Pleconaril (VP63843, ViroPharma Incorporated, USA) was introduced, a drug able to prevent enteroviral uncoating and replication with proven anti-enteroviral efficacy in immunologically uncompromised patients [4].

We describe a 26-year-old man with proven X-linked agammaglobulinaemia (XLA) who was treated with Pleconaril because of chronic enteroviral meningo-encephalitis. He had been regularly treated with IVIG (0.4 g/kg/4 weeks) since early childhood. At the age of 23, 1 month after a bout of gastro-enteritis, he developed fever, paresthesia, spastic hemiplegia, hypoglossus paresis, ataxia, anisokoria, hemianopsia, and somnolence during a 24 h period. CSF examination showed high leucocyte and protein counts (Fig. 1). PCR analysis demonstrated the presence of enteroviral RNA. A slow replicating cytopathic enterovirus was detected by cell culture. Unfortunately, the serotype of the enterovirus could not be determined by the national and European enteroviral reference centres. After 1 week of therapy with corticosteroids (2 mg/kg/day for 3 days) and high dose IVIG (0.4 g/kg/day for 6 days) he continuously improved. Weekly IVIG (0.4 g/kg/week) treatment was administered for 4 months and then switched to every other week. Residual neurological observations after 18 months included weakness, intention tremor and positive left-sided Babinski sign. Three lumbar punctures performed 15, 16 and 19 months after the initial symptoms revealed excessive elevations of CSF protein (up to 11.9 g/l; CSF/serum albumin ratio 0.34; normal: 0.007), pleocytosis (maximum 2236 cells/μl) and high levels of CSF IgG (up to 2.32 g/l). Enteroviral cultures were negative but PCR examinations remained positive in CSF and blood (Fig. 1). After informed consent, a compassionate treatment with Pleconaril was initiated (5 mg/kg body weight, orally every 8 h for 10 days). No adverse effects were seen during and after drug therapy.

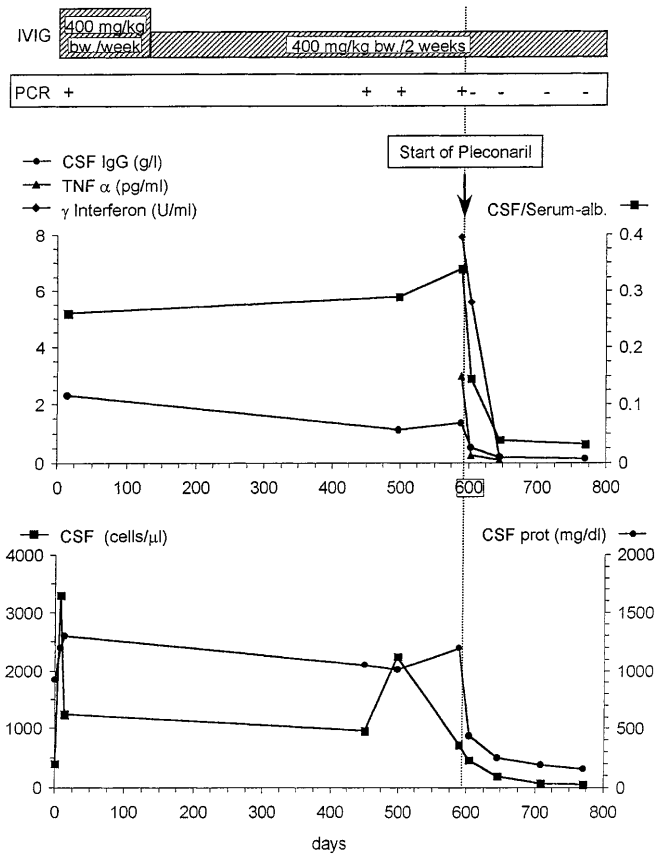

Fig. 1 Results of CSF examination before and after treatment with Pleconaril

Examinations at 2, 44, 107, 169 and 310 days after completion of Pleconaril therapy revealed negative enteroviral PCRs and cultures in blood and CSF (total observation period 11 months). CSF cell count became normal (5 cells/ml). The CSF protein level (0.51g/l, normal <0.45 g/l) and CSF/serum albumin ratio (0.01) were almost normalized 11 months after therapy. CSF levels of γ-interferon had dropped significantly 2 months after treatment (Fig. 1). The positive Babinski sign disappeared at 3 months and intention tremor at 6 months after treatment. According to our experience and that of others, in many patients immunoglobulins can only ameliorate the clinical course, but cannot eliminate enterovirus even with direct intrathecal instillation [1, 2, 3]. In our patient the discrepancy between the markedly abnormal CSF

findings and the mild residual neurological symptoms was striking. We suggest that due to the intensity of the previous IVIG substitution (resulting in serum IgG trough levels >11 g/l), high amounts of immunoglobulins could have penetrated a damaged blood-brain barrier causing a reduction of viral replication. After initiation of Pleconaril treatment, CSF pleocytosis and the disturbed blood-brain barrier progressively improved and became normal 11 months after treatment. All PCR analyses in CSF and peripheral blood were negative. A local reduction of CSF pro-inflammatory cytokines (γ-interferon) was noted (Fig. 1).

Our data suggest successful virus eradication. No new batches of immunoglobulin had been introduced during and after anti-enteroviral treatment which could have contained high titres of specific neutralizing antibodies. However, on rare occasions, PCR results may intermittently be negative during the course of chronic enterovirus encephalitis [1, 2]. Therefore, only further long-term follow up can unequivocally prove sustained virus eradication. In an ongoing study of the European Society of Immunodeficiency, preliminary results with Pleconaril have been promising [5, 6].

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Hyperinsulinism and weight loss in obese children

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Sir: We read with great interest the paper by Alikasifoglu et al. [1] describing the metabolic parameters in obese children and the relationship between the plasma level of insulin and the success of weight reduction after weight loss treatment. The authors conclude that hyperinsulinemia may not consistently cause resistance to weight reduction because they found the reduction in excess weight was no different in NIO (normoinsulinemic obese) and HIO (hyperinsulinemic obese) groups. Although this may be true, it cannot be substantiated by the findings of their study. The two groups studied were not comparable (neither age- nor sex-matched) and there may well have been differences in pubertal status.

The authors state that hyperinsulinemia in childhood obesity seems reversible after weight loss because they found an important decrease in serum insulin levels after a six-month weight-reduction program. However, apart from weight loss other factors may have influenced insulin levels considerably. First, it is possible that the physical exercise included in the weight-reduction program influenced plasma insulin levels considerably [2, 3]. Second, it is possible that dietary changes included in the treatment (the dietary protocol is not specified in the paper) may have affected insulin levels as well [3].

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