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Recurrent herpes simplex virus encephalitis secondary to carbamazepine induced hypogammaglobulinaemia

Herpes simplex encephalitis (HSE) is frequently complicated by seizures. Immunosuppression is a recognised side effect of anticonvulsant therapy. We present a case of recurrent HSE where host immunocompetence was impaired because of hypogammaglobulinaemia, most likely induced by carbamazepine therapy.

A 40-year-old man presented to his local hospital with a 5 day history of rigors, nausea, vomiting and photophobia. He reported formed visual hallucinations and his wife complained that over the preceding week he had been uncharacteristically short tempered. A tonic–clonic seizure was witnessed in the accident and emergency department. A cranial CT scan was normal. CSF analysis showed 120 white cells/mm^3 (lymphocytes 100%), 3 red cells/mm^3 and no organisms on gram stain. The CSF opening pressure was 36 cm water and protein concentration 770 mg/l (150–450). He was treated with intravenous cefotaxime, aciclovir (10 mg/kg) and phenytoin, with a presumptive diagnosis of encephalitis. Increased signal in the right medial temporal lobe was noted on an MRI scan. An EEG revealed abnormal excess theta/delta waves over both hemispheres, consistent with diffuse cerebral dysfunction. Dexamethasone (4 mg three times daily) was started on day 2 of admission. Subsequently, herpes simplex virus (HSV) DNA type 1 was detected by PCR analysis of CSF. Serum immunoglobulin levels were normal: IgA 2.47 g/l (1.0–5.0), IgG 12.5 g/l (6.8–15.6) and IgM 0.74 g/l (0.5–2.8), as was serum electrophoresis. He completed 3 weeks of intravenous aciclovir therapy and was discharged on oral phenytoin.

One month after discharge, he re-presented with a maculopapular rash and mouth ulcers. A skin biopsy confirmed erythema multiforme and carbamazepine was substituted for phenytoin.

Seven months after his initial presentation, he was admitted to our hospital following a tonic–clonic seizure. His wife reported that he had been increasingly agitated over the preceding 10 days. He was pyrexial, confused and non-compliant with anticonvulsant drug therapy. A cranial CT scan demonstrated atrophic changes in the right temporal lobe. The CSF opening pressure was 38 cm water, white cell count 20 cells/mm^3 (82% lymphocytes, 18% polymorphs), protein concentration 600 mg/l and glucose 3.9 mmol/l (blood glucose 7.9 mmol/l). He was restarted on intravenous aciclovir (10 mg/kg) and cefotaxime. An MRI scan confirmed an area of scarring in the right medial temporal lobe. EEG findings were consistent with viral encephalitis. Immunoglobulin levels revealed profound hypogammaglobulinaemia; IgA 0.85 g/l (0.8–2.8), IgG 1.1 g/l (6–16) and IgM 0.16 g/l (0.5–1.9). (The immunoglobulin reference ranges vary between the two hospitals.) A full blood count demonstrated lymphopenia; total lymphocyte count 0.9×10^9/l. Lymphocyte subsets were normal on immunophenotyping. CSF PCR detected the presence of HSV DNA type 1.

Hypogammaglobulinaemia was attributed to carbamazepine therapy; this was cautiously withdrawn and substituted with sodium valproate. Antibiotic prophylaxis and twice weekly intravenous pooled human immunoglobulin replacement therapy (Flebogamma 0.4 g/kg) (IVIg) were commenced. He completed 3 weeks of intravenous aciclovir therapy (10 mg/kg). Regular immunoglobulin was continued for 6 months. The IgM level was monitored during this time as a marker of immune recovery (IVIg contains negligible levels of IgA and IgM). Immunoglobulin levels were normal 6 weeks after starting IVIg therapy (IgA 1.29 g/l, IgG 11.0 g/l and IgM 0.39 g/l). However, after 8 months (when IVIg replacement had been discontinued), immunoglobulin levels fell again (IgG 3.6 g/l, IgM 0.32 g/l with normal IgA) and he received two further infusions of IVIg (0.4 g/kg) over a 6 month period. It is now 9 months since he was last treated with IVIg and his immunoglobulin levels remain normal off treatment (IgG 7.05 g/l). No alternative cause for hypogammaglobulinaemia has since emerged. He has been seizure free for 2 years. Psychometric testing highlights difficulty with tasks requiring complex attention skills and significant anterograde memory impairment. He has returned to part-time employment.

The incidence of recurrent HSE following aciclovir therapy has been reported as up to 5%.[1] Low levels of antibody generally predispose to extracellular bacterial infection but susceptibility to viral infection,[2] including enteroviral meningo-encephalitis, is recognised.

Anticonvulsants have been reported to cause immunosuppression, typically IgA deficiency, although carbamazepine has also been associated with low levels of IgG.[3–5] There are insufficient data to be sure of the mechanism underlying hypogammaglobulinaemia induced by carbamazepine, but the majority of the few reported cases cite low levels of circulating B cells with normal cell mediated immunity.[3 5 6] Fortunately, immunosuppression attributed to anticonvulsants is generally reversible following drug withdrawal.

The true prevalence of immunosuppression secondary to anticonvulsant therapy is difficult to estimate. One study reported that 60% of general hospital patients on phenytoin and 47% of those on carbamazepine fail to mount delayed hypersensitivity reactions to antigens or make antibodies to *Salmonella typhi* and tetanus toxoid.[4] Both visceral leishmaniasis[6] and reactivation of human herpes virus 6[7] have been reported in patients with hypogammaglobulinaemia secondary to carbamazepine therapy but, to our knowledge, recurrent HSE has not been previously attributed to anticonvulsants.

Erythema multiforme is a recognised side effect of phenytoin,[8] thought to be the causative agent in this case. However, erythema multiforme is associated with HSV[9] and recurrent erythema multiforme with hypogammaglobulinaemia has also been reported.[10] Other clinical signs of HSE and immunoglobulin levels were not recorded when this patient presented with erythema multiforme.

Given that seizure activity is a frequent complication of encephalitis and that many of these patients require long term anticonvulsant treatment, our finding of recurrent HSE associated with hypogammaglobulinaemia due to carbamazepine has treatment and monitoring implications. It may be prudent to consider monitoring for hypogammaglobulinaemia in these patients for whom viral reactivation can have such potentially disastrous consequences. In the absence of routine monitoring, recurrent viral or bacterial infection certainly necessitates measurement of immunoglobulin levels.

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Treatment of Guillain–Barré syndrome with mycophenolate mofetil: a pilot study

Guillain–Barré syndrome (GBS) is a severe, acute, immune mediated polyneuropathy. Intravenous immunoglobulin (IVIg) is the preferred treatment.[1] The combination of methylprednisolone (MP) and IVIg does not provide significantly better improvement after 4 weeks if not adjusted for important prognostic factors.[2] GBS is associated with many longlasting residual deficits. Autoantibodies, and B and T cells are likely to play a role in the different stages of GBS.[3] Mycophenolate mofetil (MM) is a relatively new immune suppressive agent, suppressing mainly B and T lymphocytes, and is thought to be of additional value in immune mediated neurological conditions.[4–6]

We conducted an open label pilot study to assess the additional effect of MM, administered simultaneously with IVIg and MP. The aim was to investigate whether additional treatment with MM is safe in patients with GBS and, secondly, whether there is a tendency to improved outcome.

Patients and methods

The study was approved by the ethics committees of Erasmus Medical Centre and the nine participating centres. All patients fulfilled the criteria for GBS.[7] Eligibility criteria were onset of weakness within 2 weeks before inclusion and inability to walk independently for 10 m (GBS disability score ≥ 3). Exclusion criteria were age less than 18 years, GBS in the past, pregnancy, breast feeding, immunosuppressive treatment, antacids treatment, use of drugs interfering with the enterohepatic recirculation, suffering from immune mediated disease other than well regulated diabetes mellitus and severe concurrent disease.[2] The group of patients treated with IVIg and MP in the Dutch IVIg-MP trial was used as the historical control group.[2]

Treatment

All patients were simultaneously treated with 0.4 g IVIg/kg/day (Gammagard/S; Baxter BioScience, Westlake Village, California, USA) and 500 mg intravenous MP for 5 consecutive days. In addition, patients were treated with MM (Cellcept; Roche, Welwyn, UK), administered orally twice a day (1000 mg/ day), for 6 consecutive weeks. Treatment with MM had to start within 2 weeks after the onset of weakness and within 72 h after the start of IVIg and MP.

Outcome measures

The primary end point was improvement by one or more grades on the GBS disability score after 4 weeks. Secondary end points included the percentage of patients able to walk independently after 8 weeks, median time to independent walking, median time to improvement by ≥ 1 disability grade, improvement by ≥ 1disability grade after 6 months and need for artificial respiration. Adverse events were monitored daily and evaluated every next visit.

Analyses

Percentages in the group of patients treated with IVIg-MP-MM were compared with the group of 112 patients treated with IVIg-MP using the χ^2 test (without correction for continuity), the method of Kaplan and Meier and the log rank test.[2] Two important secondary end points (the proportion of patients that improved by 1 or more grades on the GBS disability score and the proportion of patients that improved to independent walking (GBS disability ≤ 2) over 52 weeks of follow-up) were also compared with the group of 113 patients treated with IVIg alone in the Dutch IVIg-MP trial.[2] Analyses were performed using STATA version 8.0.

Results

Between July 2002 and January 2005, 26 GBS patients were included in the study.

There were no significant differences in baseline characteristics, including age, GBS disability score, onset of weakness until randomisation and antecedent infections between this group of patients and the historical control group (table 1).

Primary end point

In the IVIg-MP-MM treatment group, 16 (62%) of the 26 patients reached the primary end point compared with 76 (68%) of the 112 control patients treated with IVIg-MP (OR 1.3, 95% CI 0.6–3.2, p = 0.54).[2]

Secondary end points

No significant differences between the two treatment groups were found for the secondary end points (see fig 1A, 1B and table 2; fig 1 and table 2 can be viewed on the *J Neurol Neurosurg Psychiatry* website at http://www.jnnp.com/supplemental). To further assess possible differences in treatment modalities, we compared the results of two important secondary end points with the results of the group of 113 patients who received IVIg only in the Dutch IVIg-MP trial (fig 1A, 1B; fig 1 can be viewed on the *J Neurol Neurosurg Psychiatry* website at http://www.jnnp.com/supplemental).[2] No significant differences between the three groups were found for both end points. A comparison of the differences in MRC sum scores and sensory signs between the treatment groups also did not show significant differences.

Adverse events

None of the reported side effects, including urinary or respiratory tract infections, thrombosis, gastrointestinal bleeding and renal failure, differed significantly between the groups. One patient interrupted MM treatment because of abdominal complaints. Two (8%) of 26 patients treated with IVIg-MP-MM died compared with 6 (5%) of 112 patients treated with the combination IVIg and MP. There is no indication that the two patients in the IVIg-MP-MM died of drug related complications (see table 3; table 3 can be viewed on the *J Neurol Neurosurg Psychiatry* website at http://www.jnnp.com/supplemental).

Table 1 Baseline characteristics

Characteristic	IVIg+MP+MM (n = 26)	IVIg+MP[2] (n = 112)
Male (%)	19 (73%)	73 (65%)
Age (y) (median (95% CI))	46 (23–76)	58 (50–61)
Age ≥50 y (%)	12 (46%)	68 (61%)
GBS disability score (F score) at baseline (%)		
F = 3	4 (15%)	26 (23%)
F = 4	21 (81%)	77 (69%)
F = 5	1 (4%)	9 (8%)
Onset weakness–randomisation ≤4 days	13 (50%)	64 (57%)
Diarrhoea (%)	10 (39%)	30 (27%)
Upper respiratory tract infection (%)	7 (27%)	39 (35%)
Positive *C jejuni* serology (%)	6 (23%)	29 (28%)

GBS, Guillain–Barré syndrome; IVIg, intravenous immunoglobulin; MM, mycophenolate mofetil; MP, methylprednisolone.