An EEG recording showed a low voltage normal background activity coexisting with low voltage fast rhythms without any paroxysmal activity.

The patient was admitted to hospital and antipsychotic medication with 15 mg/day haloperidol was added to his antiepileptic drug treatment. Biperiden (4 mg/day) was added to reduce extrapyramidal side effects.

After 4 weeks of treatment the patient's symptomatology was reduced to a degree of 50% from the initiation of the treatment and the patient left the hospital. In the follow up, the haloperidol dose was reduced gradually within 4 months to a dose of 5 mg/day (maintenance therapy).

The psychotic reaction in our patient was not an ictal symptom because it occurred in a state of clear consciousness with a normal EEG in a period that was seizure free.

Regarding the involvement of drugs as a causative factor for psychosis, all established antiepileptic drugs have been shown to precipitate psychiatric symptoms. Treatment of the patient consisted of lamotrigine and topiramate, drugs that have been implicated in the provocation of psychotic symptoms⁴ but as he had been already under the same medication for the past 10 months before the vagus nerve stimulator was implanted, the precipitation of psychosis does not seem to be pharmaceutical. Further support to the above hypothesis is provided by the fact that the psychotic symptoms appeared just when seizure control was achieved by vagus nerve stimulation.

The comorbidity of psychosis and epilepsy in our patient could not be excluded. However, the absence of a history of psychosis as well as the lack of a positive family history for any major psychiatric disorder does not render support to the above possibility.

The reduction of seizure frequency and EEG normalisation as a cause of psychotic-like reactions in epileptic patients have been proposed by many authors.¹ In our patient seizure cessation had a temporal sequence with development of psychosis and EEG normalisation.

The term "forced or paradoxical normalisation" is more or less a theoretical concept with an unknown biochemical mechanism. Neurotransmitter hypotheses, kindling the effect of recurrent seizures on the limbic system that facilitate the psychosis have been proposed as the possible underlying mechanism.¹

Our case may differentiate the proposals for the underlying mechanism of psychosis and EEG normalisation in epileptic patients. We suggest that seizure cessation in an epileptic brain seems to play a major part in the development of psychotic symptoms, independent of antiepileptic medications.

As far as we know, this is the first report of a psychotic reaction with a forced normalisation induced by vagus nerve stimulation. Recent studies shows that c-fos expression is increased during vagus nerve action in the posterior cortical amygdala, cingulate retrosplenial cortex, and other areas.⁵ Extensive brain areas seems to be involved and thereby a possible influence on behavioural mechanisms could not be excluded.

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A randomised double blind trial versus placebo does not confirm the benefit of α -interferon in polyneuropathy associated with monoclonal IgM

The peripheral neuropathy associated with a monoclonal anti-MAG IgM is considered as a specific entity.¹⁻³ The clinical features are different from those seen with monoclonal IgG or IgA, with sensory loss and ataxia more often found. A causal link between the monoclonal IgM and the development of neuropathy is suggested by the antibody activity of the IgM to nerve polypeptides or glycolipids,³⁻⁷ the detection of IgM deposits on the myelin sheaths of patients' nerve biopsies,^{2,8,9} and the induction of the neuropathological process through the transfer of the anti-MAG IgM in animal models.^{10,11} The low rate (30%) of clinical improvement with chlorambucil (CLB) or plasma exchange in such patients justifies the search for new therapeutic strategies.^{12,13}

In a previous phase II open clinical trial randomly comparing intravenous immunoglobulins (IVIg) and α -interferon (α -IFN), we concluded that IVIg was inefficient but that α -IFN produced a significant clinical improvement in eight out of 10 patients at 6 months and in seven of them at 12 months.¹⁴ The mechanism of action of α -IFN was unclear as the concentration of the monoclonal IgM as well as the titre of anti-MAG antibody were unchanged. As the improvement with α -IFN was mainly related to an improvement of sensory symptoms, most of them being subjective, we designed a multicentre, prospective, randomised double blind study of α -IFN versus placebo.

Patients included in this study had to fulfill all the following criteria: (1) have had stable or progressive neuropathy for at least 3 months; (2) show the presence of a serum monoclonal IgM with anti-MAG antibody activity as detected by immunoblotting on delipidated human myelin⁶; (3) have a clinical neuropathy disability score (CNDS) above 10 (see below); (4) have no other causes of peripheral neuropathy, especially diabetes, alcohol, cryoglobulinaemia, and amyloidosis; (5) not have had treatment in the past 3 months.

The study was designed to be a multicentre, prospective, randomised, double blind clinical trial comparing α -IFN and placebo.

The protocol was approved by the Hôpital Pitié-Salpêtrière ethics committee. After providing written informed consent, patients underwent stratified randomisation according to the existence of a previous treatment, through a blind telephone assignment procedure. The patients were randomly allocated to receive either α -IFN or placebo. α -Interferon (Roferon, Roche) was given at 4.5 MU three times a week for 6 months. Placebo consisted of sodium chloride, benzyl alcohol, polysorbate 80, and glacial acetic acid diluted in sterile water. The reconstituted vials of α -IFN or placebo were delivered by the pharmacy of each centre and appeared identical.

The clinical neuropathy disability score (CNDS) was the same as that used in our preliminary study.¹⁴ The score in a normal subject was 0. It could range from 0 to 93, summing 0 to 28 points for the motor component, 0 to 12 for the reflexes component, and 0 to 53 points for the sensory component. In addition, the patient was asked to appreciate the change in five symptoms: paraesthesia, dysaesthesia, ground perception, striction, and walking in major improvement (-2), slight improvement (-1), stability (0), slight worsening (+1), major worsening (+2). This score termed "subjective assessment" ranged from -10 to +10 and was added to the previous one except for the initial examination. Follow up examinations were performed by the same physician for each patient every 3 months.

The main end point was defined by the absolute difference in the CNDS from baseline to the 6th month (or to the time of withdrawal of treatment if the treatment was stopped before the 6th month). The number of patients in each group who experienced an improvement of the CNDS of more than 20% defined a secondary end point.

Estimation of sample size was based on the main criterion, using a two sample *t* test. We were expecting a difference of CNDS between treatment groups of 10 with SD 10, using the estimates derived from a previous trial.¹⁴ Specifying a type I error of 0.05, a power of 0.90, a two sided test required 22 patients per group. Given the low incidence of this disease, the protocol planned one interim analysis to minimise the sample size, using repeated significance tests with a nominal significance level of 0.029.

Statistical analysis was made on an intention to treat basis. Comparisons used a Kruskal and Wallis test for continuous variables, Fisher's exact test for binary variables. Relations between continuous variables were studied by the Spearman coefficient. All tests were two sided. The SAS (SAS Institute, Cary, NC) software package was used.

After the inclusion of 24 patients, Roche laboratory decided not to provide placebo any more because of trade difficulties. The promotor of the study (AP-HP) decided to carry out the interim analysis which led to stopping the accrual of patients because of the absence of benefit of α -IFN versus placebo.

Twenty four patients were enrolled from five hospitals, 12 being assigned to α -IFN and 12 to placebo. Eleven patients (five in the α -IFN group, six in the placebo group) had been previously treated with CLB without improvement of the neuropathy. In 10 of them, plasma exchanges had also been unsuccessful. The mean duration (SD) of the peripheral neuropathy was 3.6 (3.9) years.

Patients' characteristics according to treatment group

	α -IFN (n=12)	Placebo (n=12)
Age (y)	67.5 (61.5-74.5)	67.5 (66-73.5)
Male sex	6 (50)	10 (83)
Patients never previously treated	7 (58)	6 (50)
Duration of neuropathy (y)	3 (2-10)	3.5 (1-9.5)
Patients with bone marrow lymphoid infiltrate	2 (17)	1 (8)
Clinical score:		
M0	34 (25.5-35.5)	30 (25.5-36.5)
M3	28 (21-35)	28 (21.5-33)
M6	31 (27.5-35)	28 (24-31)

Values are median (25th-75th percentiles) or n (%).

The randomisation procedure resulted in balanced treatment groups for patient characteristics and neurological abnormalities (table).

Three patients in the α -IFN group withdrew from treatment, two because of side effects (one at day 30 for diarrhoea and one at day 60 for influenza symptoms) and one at day 60 because of worsening of the neuropathy. No patients had to stop treatment because of haematological toxicity.

The mean CNDS did not change significantly in either group: in the α -IFN group, it moved from 31.4 at baseline to 28.5 at 6 months, in the placebo group from 30.3 at baseline to 27.8 at 6 months. The absolute differences were close in the two randomised groups—namely, 1.8 in the α -IFN group and -2.5 in the placebo group ($p=0.84$) and the relative differences were also close (-6% v -6.5% respectively, $p=0.79$). In both groups, three out of 12 patients (25%) had improvement in CNDS of more than 20% ($p=1.00$). Electrophysiological data were available in nine patients treated with α -IFN and in 11 patients treated with placebo and did not detect significant improvement (data not shown).

In this double blind study of α -IFN versus placebo, we did not confirm the efficacy of α -IFN in peripheral neuropathy associated with a monoclonal anti-MAG IgM as suggested in a preliminary phase II open study.¹⁴ This discrepancy is not easy to explain. The mean baseline neurological scores, the number of patients previously treated, and the disease duration were the same in the two studies. However, both studies dealt with small cohorts. We think that the effect found in our preliminary study could have been amplified by the enthusiasm of physicians and patients in favour of interferon, a new therapeutic strategy at that time in neurological diseases, given that the trial was not blind. Both physicians and patients knew that it was not a placebo group. Interestingly, in our preliminary study, the decrease of the CNDS was mainly due to improvement in sensory symptoms (most of them subjective) and to subjective assessment by the patient. Moreover, we could not elucidate the potential mechanism of action of α -IFN as neither the level of monoclonal IgM, nor the anti-MAG antibody activity was modified.

In conclusion, these disappointing results of α -IFN in monoclonal IgM associated neuropathy point out to the need of double blind randomised studies versus placebo in neurological diseases where sensory symptoms are predominant. In monoclonal IgM associated neuropathy, new strategies leading to eradication of the B cell clone secreting monoclonal IgM, such as the use of fludarabine¹⁵ or anti-B cell monoclonal antibodies,¹⁶ should be tested in further studies.

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Reversible posterior leukoencephalopathy syndrome induced by granulocyte stimulating factor filgrastim

Posterior leukoencephalopathy syndrome is characterised by visual disturbances, altered mental status, drowsiness, seizures, headache, and occasionally focal neurological signs. It is usually associated with severe hypertension and has most often been seen in patients treated with immunosuppressive drugs such as cyclosporin A, tacrolimus, and interferon- α .^{1,2}

The granulocyte and granulocyte macrophage stimulating factor filgrastim (Neupogen®) is used in chemotherapy induced bone marrow suppression. By contrast with molgramostim (Leukomax®) filgrastim is supposed to have fewer CNS side effects. Intracranial hypertension and convulsions have been reported after molgramostim therapy. Only one case of recurring encephalopathy and focal status epilepticus due to filgrastim is published.³ In that case the contrast enhanced CT was normal.

We report a case of reversible posterior leukoencephalopathy syndrome with transient bilateral changes in the occipital and parietal regions involving the white matter on MRI induced by filgrastim. This is to our knowledge the first with reversible changes on MRI to be reported after filgrastim therapy.

A 45 year old previously healthy woman was diagnosed with centrocytic centroblastic non-Hodgkin's lymphoma with intermediate to high malignancy in August 1999. The first cycle of chemotherapy with vincristin, ifosfamide, and etoposid was well tolerated. Two days after termination of chemotherapy she received subcutaneously 300 μ g filgrastim (Neupogen) daily because of bone marrow suppression with leukopenia for 9 days. After 3 days the dose was increased to 600 μ g/day. One day after termination of filgrastim and almost 2 weeks after chemotherapy, she developed acute cortical blindness within 30 minutes. On the next day simple partial and complex partial seizures, non-convulsive status, agitation, and desorientation followed. Brain MRI obtained 1 day later showed bilateral hyperintensities in the parietal and occipital regions involving white matter with some involvement of the overlying grey matter on proton density images (figure). Non-convulsive status with somnolence and disorientation were documented by EEG, which showed a bilateral parieto-occipital focus with continuous rhythmic delta