rodenticide. As he became acutely disturbed and violent in the ward he was given several injections of intramuscular haloperidol, and he received no further antipsychotic medication. On the next day he developed severe rigidity associated with profuse sweating and marked autonomic instability. His heart rate was 120 beats per minute and was irregular. His blood pressure showed wide fluctuations and there was urinary incontinence. He then became confused and went into a state of semiconsciousness. There was no increase in body temperature. The creatine phosphokinase concentration was 1575 IU on the 2nd day and 6771 IU on the 4th day of his illness, and the white cell count was 17 000/mm^3 (neutrophils 60%, leucocytes 30%, eosinophils 6%, macrophages 4%). As the patient did not have any increase in body temperature there was doubt as to the diagnosis. In standard medical texts fever was recorded as a necessary finding in NMS. However, a medline search contained reports of three patients with NMS in the absence of fever. The patient was immediately started on bromocriptine at a dose of 2.5 mg three times a day. By the 5th day of treatment his condition improved with the autonomic disturbances disappearing and the rigidity subsiding. His creatine phosphokinase concentration became normal after 5 days of treatment.

A 20 year old man was started on 10 mg trifluperazine twice a day for schizophrenia with catatonic features and discharged after being given a depot injection of 40 mg flupenthixol intramuscularly. Five days later he was readmitted due to progressively increasing stiffness of his body, difficulty in swallowing, drowsiness, and incontinence of urine. On examination he was very rigid and semiconscious, but opened his eyes to deep pain, and had severe diaphoresis which drenched the bed clothes. However, he had no rise in body temperature. His heart rate was 130 beats per minute, respiratory rate 28 per minute, and his blood pressure showed marked fluctuations. The creatine phosphokinase assay done on the 2nd day gave 2109 IU/l and the white blood cell count was 12 400/mm^3 (neutrophils 93%). Other investigations including analysis of his CSF was normal. We made a tentative diagnosis of NMS, even though the patient did not have fever, as we had treated a patient with NMS presenting without fever previously. The neuroleptic medication was stopped and he was started on 2.5 mg bromocriptine three times a day. As the response was poor the dose was gradually increased to 10 mg three times a day. He made a relatively slow recovery and came out of the comatose state after 1 week of treatment and autonomic disturbances and rigidity disappeared after 10 days of treatment. On discharge from hospital on the 14th day after starting bromocriptine his creatine phosphokinase was 230 IU/l.

An 18 year old boy with schizophrenia was on long term antipsychotic drugs. He was admitted with increasing stiffness of the body, drowsiness, and urinary incontinence. On examination he was rigid, had a tachycardia (pulse rate 130 beats per minute) alternating with a bradycardia (pulse rate 50 beats per minute) and his blood pressure showed wide fluctuations. There was no increase in body temperature at admission or during the course of his illness. The creatine phosphokinase concentration was 1450 IU/l on the 2nd day of his illness and the white cell count was 15 000/mm^3 (neutrophils 85%). Antipsychotic medication was stopped and he was started on 2.5 mg bromocriptine three times a day. He made a complete recovery, with the autonomic disturbances and rigidity subsiding within 5 days of treatment. One week later his creatine phosphokinase was 100 IU/l.

The neuroleptic malignant syndrome usually occurs with the use of therapeutic doses of neuroleptic drugs and commonly develops during the initial phases of treatment, when the drug dose is being stepped up, or when a second drug is introduced. However, it can occur at any time during long term neuroleptic treatment with factors such as exhaustion, agitation, and dehydration acting as triggers.[1] The above point is noteworthy especially given the possibility of the occurrence of a variant and uncommon clinical picture such as that described in our paper. There are no specific laboratory findings, but neutrophil leucocytosis and raised creatine phosphokinase concentrations lend weight to the diagnosis.[9]

These three cases illustrate the point that NMS can occur without fever. Our patients had all the features of NMS apart from fever and the response to bromocriptine can be taken as strong evidence that the diagnosis was accurate. Being familiar with this fact and other different ways in which this syndrome can present plus a high degree of suspicion are important in making an early and accurate diagnosis of NMS. In fact, the appearance of muscle rigidity and clouding of consciousness in any patient receiving antipsychotic medication should prompt clinicians to suspect NMS and immediately initiate appropriate investigation and management. A failure to do so may lead to delay or failure to withdraw neuroleptic medication, and thus lead to potentially irreversible sequelae and even death. The first case also illustrates that at times of doubt about the diagnosis of an uncommon presentation of a well described illness, reference to the literature including an immediate Medline search could help in making decisions about appropriate patient management.

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1 Bristow MF, Kohen D. Neuroleoptic malignant syndrome. *Br J Hosp Med* 1996;**55**:517–20.
2 Haddad PM. Neuroleptic malignant syndrome may be caused by other drugs. *BMJ* 1994;**308**: 200–1.
3 American Psychiatric Association. *Diagnostic and statistical manual of mental disorders.* 4th ed. Washington, DC: American Psychiatric Association, 1994.
4 Caroff SN, Mann SC. Neuroleptic malignant syndrome. *Med Clin North Am* 1993;77:185–202.
5 Adityanjee, Singh S, Singh G, *et al*. Spectrum concept of neuroleptic malignant syndrome. *Br J Psychiatry* 1988;**153**:107–11.
6 Sullivan CF. A possible variant of the neuroleptic malignant syndrome. *Br J Psychiatry* 1987; **151**:689–90.
7 Dalkin T, Lee AS. Carbamazepine and forme fruste neuroleptic malignant syndrome. *Br J Psychiatry* 1990;**157**:437–8.
8 Hynes AF, Vickar EL. Case study: neuroleptic malignant syndrome without pyrexia. *J Am Acad Child Adolesc Psychiatry* 1996;**35**:959–62.
9 Schrader GD. The neuroleptic malignant syndrome. *Med J Aust* 1991;**154**:301–2.

Acute psychosis and EEG normalisation after vagus nerve stimulation

The acute appearance of psychosis on achievement of seizure control and normalisation of a previously abnormal EEG has long been recognised as a clinical entity termed "forced normalisation".[1] Focal and generalised epilepsies are both implicated.[1] Most of the old and new antiepileptic drugs have been implicated in the emergence of psychosis with EEG normalisation.[1 2]

Chronic vagus nerve stimulation has been proposed as an effective and safe treatment of medically intractable epilepsy, although the mechanism of action and the specific indications of this treatment remain unknown. Side effects are limited and no serious or life threatening damage has been reported.[3]

The case of a patient with medically intractable epilepsy who developed a schizophrenia-like psychosis when control of seizures and scalp EEG normalisation were achieved through vagus nerve stimulation is presented.

A 35 year old man had had intractable left frontotemporal epileptic seizures since the age of 10 years. He is right handed and left language dominant. Up to the age of 25 years he was almost free of seizures under treatment with carbamazepine and phenobarbital. After that the number of seizures gradually increased and secondary generalised seizures appeared. Phenytoin, carbamazepine, valproic acid, phenobarbital, vigabatrin, lamotrigine, and clonazepam were used in different combinations without an acceptable seizure control. Repeated EEG recordings during the past few years were abnormal with prominent slow activity, long intervals of voltage attenuation, and common bursts of high voltage spike wave complexes recorded mainly at the left frontotemporal area. A high resolution MRI was normal.

In October 1997, a vagus nerve stimulator was implanted because of poor seizure control. During a 12 week baseline preceding the implantation, more than 40 complex partial and one to two secondary generalised seizures every 4 weeks were noted. The patient also experienced bursts of uncounted short lasting complex partial seizures on a few days every month. At the time of implantation medical treatment consisted of 500 mg topiramate and 475 mg lamotrigine daily. The patient had been on this daily dose for 6 months before implantation.

The stimulator output was progressively increased over 1 month from implantation. The final parameters were: pulse rate 30 Hz, 5 minutes off, 30 seconds on, 1.5 mA intensity, and 500 ms pulse width. During the subsequent 2 months, seizure frequency dramatically reduced even though medication remained unchanged. For the last 2 weeks of the second month he had noted only one short lasting complex partial seizure; at the same time the family had noted a change in the patient's behaviour. Psychiatric evaluation disclosed a schizophrenia-like syndrome with auditory hallucinations, delusions of persecution, thought broadcasting, psychomotor agitation, and complete lack of insight.

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 symptoms[4] 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 underling 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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1 Pakalnis A, Drake ME, Kuruvilla J, *et al*. Forced normalization. *Ann Neurol* 1988;**44**:289–92.
2 Sander JWAS, Hart YM, Trimble MR, *et al*. Vigabatrin and psychosis. *J Neurol Neurosur Psychiatry* 1991;**54**:435–9.
3 Fisher RS, Krauss GL, Ramsay E, *et al*. Assessment of vagus nerve stimulation for epilepsy. *Neurology* 1997;**49**:293–7.
4 Crawford P. An audit of topiramate use in a general neurologic clinic. *Seizure* 1998;**7**:207–11.
5 Naritoku DK, Torry WJ, Helfert RH. Regional induction of fos immunoreactivity in the brain by anticonvulsant stimulation of the vagus nerve. *Epilepsy Res* 1995;**22**:53–62.

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 myelin[6]; (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 Pitiè-Salpétrière 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 unsucessful. The mean duration (SD) of the peripheral neuropathy was 3.6 (3.9) years.