Table 1 Frequency of relapse of Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) following various immunisations

	GBS		CIDP	
Vaccine	Patients	Relapses	Patients	Relapses
Influenza	211	8 (3.8%)	46	2 (4.3%)
Tetanus	105	6 (5.7%)	23	2 (8.7%)
Typhoid	50	3 (6.0%)	14	0
Polio	42	4 (9.5%)	7	0
Hepatitis A	37	3 (8.1%)	7	0
Hepatitis B	20	1 (5.0%)	2	0
Rabies	1	0	0	0
Pneumococcus	15	0	6	2 (33.3%)
BCG	8	2 (25.0%)	4	0
Yellow fever	12	2 (16.7%)	2	0
Meningococcus	16	1 (6.2%)	4	0
Cholera	5	0	0	0
Rubella	5	0	1	0
Diphtheria	5	2 (40.0%)	1	0
Measles	2	0	0	0
Smallpox	2	0	0	0
Mumps	1	0	0	0

Some patients had received more than one vaccine.

plasma lactate were both 2.1 mmol/l and oligoclonal bands were not found. DNA was extracted from a blood sample and analysed for mtDNA mutations using standard procedures and was negative at positions 3243, 8344, 8993, 3460, and 14484, but with a homoplasmic mutation at position 11778.

Our patient had the mutation most often associated with MS-like CNS lesions and visual loss in women.[1] Brain stem lesions have been previously described in a patient with visual loss, complete ophthalmoplegia, and bilateral tinnitus.[3] However, to our knowledge, this is the first description of LHON in association with brain stem lesions presenting with respiratory arrest and loss of involuntary ventilation (Ondine's curse). The high signal lesions in the pons and medulla involved the nucleus ambiguus and nucleus of the solitary tract, which are part of the ventral and dorsal respiratory groups respectively, and would seem well placed to account for loss of respiratory control during sleep with well preserved capacity for volitional respiratory manoeuvres while awake. Ondine's curse produced by lesions of these structures and their tracts through a variety of causes has been well described.[4 5] However, the exact nature of CNS lesions in patients with mitochondrial cytopathy remains obscure.

Our patient tolerated NIPPV. She improved on this regimen such that 123 days after admission she was able to take a 45 minute daytime nap and maintain an oxygen saturation of >97% throughout, while breathing room air unassisted. Eight months after her respiratory arrest, she was able to take a few steps with a Zimmer frame and had successfully weaned off NIPPV support. This patient provides a further example of the broad manifestations of mitochondrial disease.

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Risk of relapse of Guillain-Barré syndrome or chronic inflammatory demyelinating polyradiculoneuropathy following immunisation

Reports of the rare occurrence of Guillain-Barré syndrome (GBS) or chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) following immunisation[1] and recurrence of symptoms following subsequent immunisation[2] have given rise to concern over the safety of vaccine administration in this patient group. Similar concerns have been addressed and dismissed in patients with multiple sclerosis,[3] but no such information exists for inflammatory neuropathy. To provide more information about vaccine safety in GBS and CIDP we audited the recurrence of neurological symptoms following immunisation.

The Guillain-Barré Syndrome Support Group, a British patient organisation, posted 3000 questionnaires to its members, asking them to identify their illness, record all immunisations administered after their illness, and describe any symptoms within six weeks of immunisation suggestive of recurrence of GBS or worsening of CIDP.

All but one of the patients who reported neurological symptoms after immunisation were contacted by telephone to confirm their history and to grade their symptoms using the modified Rankin scale.[4] For the patient who could not be contacted by telephone, the patient's consultant neurologist provided the information. Questionnaires were sent to the general practitioner for each patient who reported a "relapse" to confirm which vaccine had been administered.

A total of 1114 patients (37.1%) completed the questionnaires, of whom 927 had had GBS, 179 had CIDP, and eight were excluded because they had other diseases. Of the 927 patients with GBS, 311 had received immunisations since having GBS. Eleven (3.5%, 95% confidence limits (CL) 1.8%, 6.2%) reported symptoms including increased fatigue, weakness, numbness, and paraesthesiae, but these were usually mild and no patient required hospitalisation or treatment. In three cases symptoms came on within 24 hours of immunisation and all but one developed symptoms within one week of immunisation. One patient reported symptoms rendering him unable to walk unaided or drive for six weeks, which increased his modified Rankin scale score from grade 2 to 4.

Influenza, tetanus, and typhoid were the most common immunisations associated with a relapse after GBS but the number of patients who reported symptoms was small compared with the total numbers receiving each of these vaccines (table 1). Although the results suggest that some vaccines that are administered less frequently (such as diphtheria) may be associated with a higher relapse risk, the numbers were small and most of these vaccines were administered at the same time as other vaccines.

Of the 311 patients with GBS who had received vaccines after having GBS, 29 had also received a vaccine in the six weeks before the onset of their initial illness. Two of these patients (6.9%, 95% CL 0.85%, 22.8%) had a recurrence of symptoms after a second, different, vaccine was subsequently administered.

Of the 179 patients with CIDP, 65 had been immunised after disease onset. Five reported worsening of neurological symptoms following immunisation. In three the symptoms were similar to a typical relapse of their CIDP, but only one of these patients required treatment within two months of immunisation. The other two patients with CIDP were immunised
when already experiencing mild neurological symptoms, which then worsened, so that their modified Rankin scale score increased from 1 to 4 and they became dependent on a walking stick and unable to drive.

Of the patients with CIDP who experienced a relapse after immunisation, two relapses occurred among 23 patients who received the tetanus vaccine, giving a risk of relapse of 8.7%. Two of 46 (4.3%) patients with CIDP had relapses after influenza vaccine, of whom one had simultaneous pneumococcus vaccine. Two of six (33%) patients, including the last mentioned, experienced relapses after pneumococcus vaccine. Fourteen patients with CIDP had no symptoms of relapse following immunisation with typhoid vaccine. Between one and seven patients with CIDP had no

symptoms after yellow fever, diphtheria, meningococcus, oral polio, BCG, hepatitis A, hepatitis B, cholera, or rubella vaccine.

This audit of patients with GBS and CIDP who have received vaccines suggests that the risk of relapse following immunisation is low. The response rate to the questionnaire was small as a proportion of the membership of the GBS Support Group. This is partly because an unknown but large proportion of members are relatives or friends and not former GBS or CIDP patients.

Only 11 of 311 patients with GBS (3.5%, 95% CL 1.8%, 6.2%) who had been immunised after having the disease reported a recurrence of symptoms. All of the vaccines that were associated with neurological symptom recurrence had also been received by many more patients who remained well. Some of the patients who reported symptoms after receiving vaccines had also received the same or other vaccines on other occasions without experiencing any problems. Only one respondent experienced symptoms that increased their modified Rankin scale score. The risk of relapse severe enough to alter the modified Rankin scale score is 0.3% (95% CL 0.01%, 1.78%) while the risk of a relapse requiring treatment or hospitalisation is at most 1.18% (95% CL).

It is more difficult to draw conclusions about the risk of immunisation for relapse in CIDP because our sample size was smaller. Five (7.7%, 95% CL 2.5%, 17.0%) of 65 patients noted a return of symptoms following immunisation. The reports of minor symptoms or acceleration of deterioration following influenza and pneumococcus vaccines merit caution in recommending these immunisations in patients with CIDP, although the risk of infection in immunosuppressed patients may outweigh any potential risk. Of greatest concern is the risk of relapse following tetanus toxoid, which was 8.7% (95% CL 1.7%, 28.0%) in our patient sample. In view of these figures and previous reports of relapse of CIDP following tetanus toxoid[2 5] patients may wish to avoid routine tetanus toxoid immunisation.

Finally, it is important to acknowledge the difficulties in drawing conclusions from a questionnaire in which the patients reported their diagnostic classification and relapses. It is intuitively likely that more patients who experienced symptoms following immunisation responded to the questionnaire, which would overestimate the frequency of relapses. Consequently the true risks of relapse following immunisations after GBS or in CIDP may be less than those discovered in this audit.

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Hypoglycaemia induced by phenytoin treatment for partial status epilepticus

A 22 year old woman was admitted at our epilepsy unit in status epilepticus. On examination, seizures were characterised by a confusional state with little response to external stimuli, and recurrent, brief, tonic motor manifestations lateralised to the left side. Family history was negative for epilepsy and metabolic disorders. Full term birth was uncomplicated and first psychomotor developmental milestones were normal. In the past medical history there was no sign of any metabolic diseases. There were no reports of cognitive dysfunction or personality disturbances. At the age of 16, the patient presented with epilepsy, which was characterised by two types of seizures: global tonic seizures, which occurred yearly, and brief episodes of loss of contact without any other manifestations, which were rare. The patient was treated for many years with 20 mg of clobazam twice daily. The awake EEGs that were performed routinely during the years of treatment with clobazam showed normal background rhythm with rare epileptiform discharges, characterised by irregular 2–3 Hz spike and wave complexes and localised over both frontal-central regions. Magnetic resonance imaging of the brain, which was performed at the age of 18 years, showed no abnormalities.

On the day of admission at the epilepsy unit, the patient had an urgent EEG that revealed continuous, rhythmic spikes or spike and wave complexes over both frontal-central regions with right predominance. Emergency drug treatment with intravenous lorazepam 4 mg was performed twice with a 15 minute interval, but there was no change in the clinical status. Therefore, after 30 minutes, intravenous phenytoin 1000 mg was given by infusion over a period of 20 minutes, and then an infusion of 750 mg of phenytoin was set up for a period of 24 hours. Clinical symptoms and EEG abnormalities rapidly improved and completely resolved after 40 minutes from the start of the administration of phenytoin.

Nine hours later, while the medical observation was still ongoing, the patient developed an episode of clouding of consciousness, which was preceded by prodromal symptoms, including tachycardia, sweating, light headedness, and irritability. On examination, there was reduction of alertness, confusion, and tachycardia. Pupils were of intermediate diameter and reactive to the light. No focal neurological signs were observed. EEG monitoring did not show any abnormalities. Emergency blood tests revealed severe hypoglycaemia (<20 mg/dl). Prompt correction of the hypoglycaemia was obtained by the intravenous infusion of 50 ml of 50% glucose, and a consequent recovery of consciousness occurred. Phenytoin infusion was then withdrawn and oxcarbamazepine was titrated. In the following days no further episodes of hypoglycaemia were noticed. The patient was therefore investigated with the oral glucose tolerance test, which showed normal levels of plasma glucose, immunoreactive insulin, and immunoreactive insulin/plasma glucose, and with an abdominal CT scan, which did not show evidence of pancreatic insulinoma.

Comment

We have described a patient who experienced a severe episode of hypoglycaemia induced by intravenous phenytoin, which was administrated at the doses recommended for the treatment of status epilepticus.[1] It is known that phenytoin interferes with carbohydrate metabolism.[2] Indeed, it may inhibit the release of glucose stimulated insulin and induce a consequent hyperglycaemia. The ability of phenytoin to inhibit insulin release has been suggested to be related to the blockage of Ca2+ uptake via voltage dependent Ca2+ channels.[3] For this hyperglycaemic propriety, phenytoin has been often used in the treatment of hypoglycaemia induced by inoperable insulinomas.[4]

Beside the well known hyperglycaemic effect of phenytoin, it has been reported that high doses of the drug can induce hypoglycaemia. In particular, a recent study reported a case of hypoglycaemia secondary to an acute voluntary intoxication with 20 g of phenytoin. The authors suggested that the hypoglycaemic episode might be attributable either to an escape from the inhibitory effects of phenitoin on insulin secretion or an increased sensitivity of the tissues to insulin.[5] The striking finding of our case is that the hypoglycaemia is induced by a therapeutical dose of phenytoin, and, to our knowledge, this is the first case of severe hypoglycaemia during treatment with phenytoin for status epilepticus. In this case we have indeed excluded a different aetiology of the hypoglycaemia. In particular, a possible effect on glycaemia produced by status epilepticus,[6] has been considered not relevant, because the status epilepticus was partial and resolved nine hours before the onset of hypoglycaemia. However, what caused hypoglicaemia when a therapeutical dose of phenytoin was administrated is unclear, and further studies are needed to fully investigate the effects of phenytoin on charboidrate metabolism.

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