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POOR PROGNOSIS DESPITE SUCCESSFUL TREATMENT OF POSTANOXIC GENERALIZED MYOCLONUS



Generalized myoclonus (GM) after cardiopulmonary resuscitation (CPR) implies a poor prognosis.¹ Postanoxic GM is usually classified as one type of convulsive status epilepticus,² which is also reflected by terms like myoclonic status,³ myoclonic status epilepticus,⁴ or postanoxic status epilepticus.⁵ Antiepileptic drugs commonly used in the treatment of status epilepticus such as phenytoin or valproate, however, are ineffective in the majority of these patients.^{3,4,6} Reports of single patients⁷ and our own observations⁶ indicated that propofol may control GM. This prompted us to use propofol as standard treatment of postanoxic GM in 60 consecutive comatose survivors of CPR.

Level of evidence. This is a single observational study without controls (Class IV).

Methods. We included 28 women, aged 26 to 87 years, mean age 58 years, and 32 men, aged 20 to 82 years, mean age 55 years. All were resuscitated due to cardiac arrest or ventricular fibrillation outside the hospital. None of the patients was treated with mild hypothermia. No patient had a history of epilepsy. All developed GM within 24 hours after CPR. GM always involved the facial muscles, shoulder, and proximal arm muscles. More than half of the patients also had jerks of the diaphragm. As there are numerous sources of acoustic stimuli on intensive care units, it is sometimes impossible to differentiate spontaneously occurring myoclonic jerks from those triggered by acoustic stimuli. Keeping this limitation in mind, about half of our patients had spontaneous myoclonic jerks, which increased on acoustic or somatosensory stimuli, and the other half myoclonic jerks on external stimuli (noise, pain, touch, tracheal suctioning).

All patients had bipolar 8-channel EEG recordings with needle electrodes positioned according to the standard 10–20 system (Fp2-T4, T4-O2, Fp2-C4, C4-O2, Fp1-T3, T3-O1, Fp1-C3, C3-O2). Filter setting was 0.53 Hz and 70 Hz. The first EEG (10 minutes) was done 6 to 24 hours

after CPR when the patients had GM. During this recording, IV propofol was started with a single dose (1.5 mg/kg body weight). Efficacy was defined as cessation of GM and epileptiform EEG activity, i.e., absence of spikes and/or sharp waves intermixing the bursts in patients with a burst-suppression pattern (BSEEG), or spikes, polyspikes, sharp waves and sharp-slow waves in patients with continuous generalized epileptiform discharges (CGED).

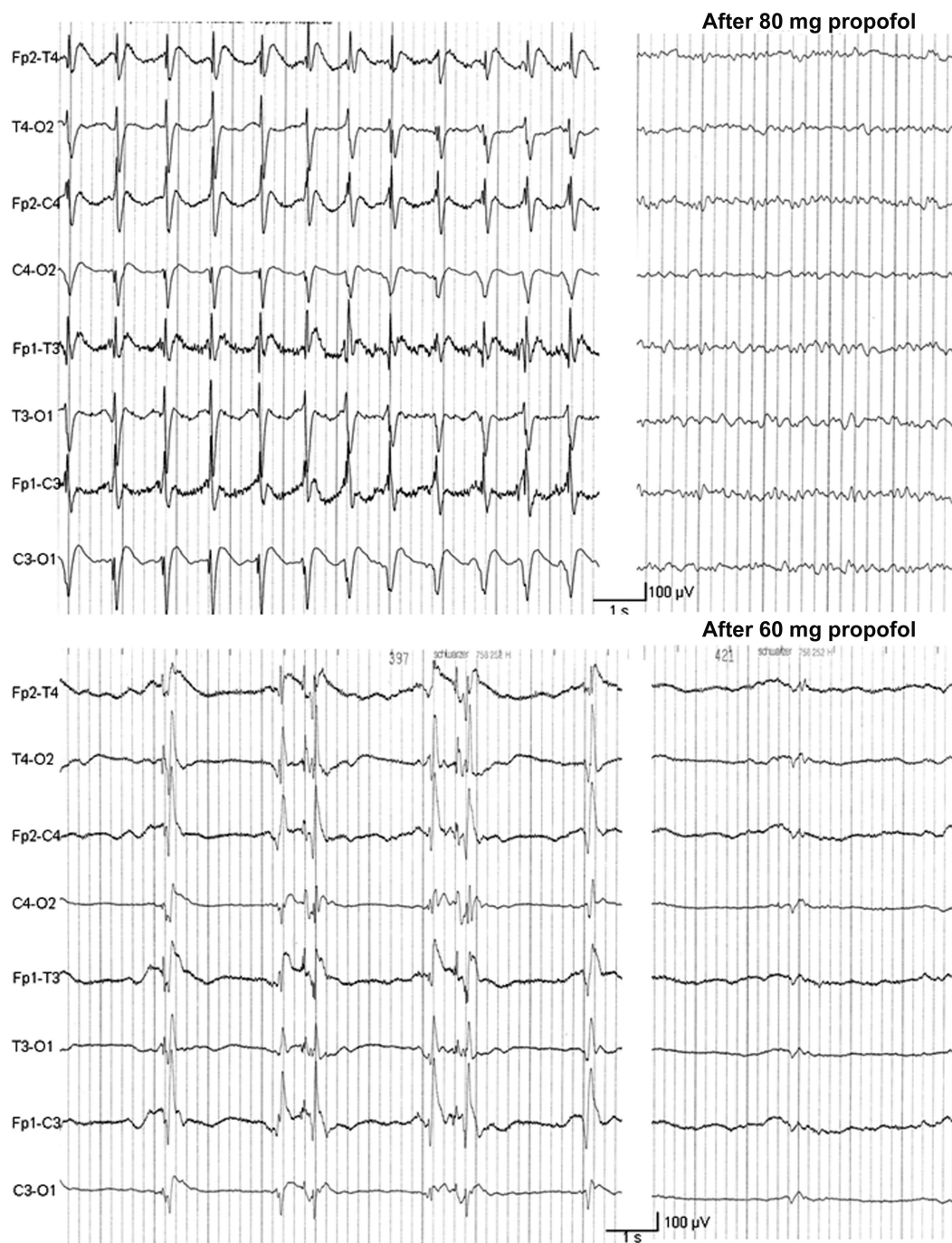
The bolus injection of propofol was followed by continuous infusion (1 mg/kg body weight/h). The dose was individually adjusted to suppress GM; i.e., reappearance of GM prompted another bolus injection of 1 mg/kg body weight and an increase of continuous propofol by 20 mg/h. Necessity of propofol was reevaluated after 1 and 2 other days; i.e., 2 and 3 days after CPR. For that purpose, we discontinued propofol and performed another EEG (for 10 minutes) 1 hour after stopping propofol. The drug was stopped when GM had ceased and when the EEG was without epileptiform activity.

Serum neuron-specific enolase was determined 1, 2, and 3 days after CPR. Determinations regarding the level of care to be provided were made 4 days after CPR in all patients surviving up to this point.

Results. GM was associated with BSEEG ($n = 39$) or CGED ($n = 21$) without intervening background activity and without change on external stimuli (acoustic, pain). GM ceased immediately after a single dose of IV propofol in all patients, which also reliably suppressed epileptiform EEG activity (figure). Cessation of GM was maintained by continuous propofol infusion at individual doses between 80 and 250 mg/h.

Forty-one patients died within 3 days after CPR, leaving 19 surviving patients 4 days after CPR. At that time, each patient had 1) a serum neuron-specific enolase between 35 and 650 ng/mL at days 2 or 3 post-CPR, 2) 3 recordings of an unfavorable EEG pattern, i.e., BSEEG, CGED, flat (below 20 μ V) or isoelectric (at 2 μ V/mm) recordings, and 3) no motor response on painful stimuli. One third also had bilateral absence of the pupil light reaction or of the corneal reflex or both. Each of these findings predicts poor out-

Figure Suppression of epileptiform discharges (and cessation of generalized myoclonus) in comatose survivors of cardiopulmonary resuscitation with generalized myoclonus



Upper recordings: burst-suppression EEG; lower recordings: continuous generalized epileptiform discharges.

come.¹ This was communicated with the families. Treatment was subsequently restricted to mechanical ventilation and IV fluids. Eighteen patients died during the following 10 days, and 1 survived in a persistent vegetative state.

Discussion. Propofol reliably controls postanoxic GM in comatose survivors of CPR. Epileptiform EEG activity of these patients was also suppressed. Successful

treatment of GM, however, does not change the poor prognosis of these patients, which seems to be determined by the severity of the anoxic brain damage. (Preliminary and limited experiences indicate that this is also the case in patients with GM and/or CGED or BSEEG treated with mild hypothermia.)

Our observations do not contradict recent findings that single patients with postanoxic status epilepticus (PSE) may survive with mild or moderate

deficits.⁵ In contrast to our patients, these patients were treated for 24 hours by mild hypothermia, had repetitive (and not continuous) epileptiform discharges during PSE, and EEG background was reactive.⁵ Brainstem reflexes were also preserved.⁵ It also remains unclear whether PSE in these patients matched the state of our patients, as clinical data are sparse, describing “prolonged myoclonic or convulsive seizures” only.⁵

Even though propofol does not change the poor prognosis of patients with postanoxic GM, control of GM justifies its use. Cessation of GM is a relief for the relatives, who are often considerably distracted by the sight of their loved ones shaken by GM. It also eases nursing and ventilation of these patients.

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GIANT URTICARIA AND PERSISTENT NEUTRALIZING ANTIBODIES AFTER THE FIRST NATALIZUMAB INFUSION



Natalizumab (NTZ) (Biogen Idec/Elan) is a monoclonal immunoglobulin G antibody against alpha-4-integrin that is prescribed in France for patients with multiple sclerosis (MS) who have experienced at least one relapse during a 1-year therapy with interferon- β and an increase in the T2 lesion load, or in naïve patients who have experienced at least 2 relapses and have MRI evidence of active disease defined by more than 9 T2 lesions and gadolinium enhancement. Common adverse events described with NTZ include infusion-induced reactions in 15% of patients and hypersensitivity reactions in 4% of patients during or within 1 hour after infusion.^{1,2} Hypersensitivity reactions commonly occur at the beginning of the treatment with a peak during the second and third infusion. Development of persistent anti-NTZ antibodies is reported in 6% of patients.³

We report the case of a patient who presented with a severe hypersensitivity reaction 8 days after the first infusion. She developed early and persistent anti-NTZ antibodies.

Level of evidence. This article provides Class IV evidence that natalizumab is able to produce hypersensitivity

reactions such as giant urticaria, laryngeal edema, dyspnea, and fever. This is a single observational study without controls.

Case report. A 37-year-old patient was treated with NTZ for active relapsing remitting MS. She had previously been treated with IM interferon β 1a, glatiramer acetate, and finally subcutaneous interferon β 1a. Cerebral MRI showed an increase in the T2 lesion load and 1 gadolinium-enhanced lesion. She had no history of allergy. The first infusion was well-tolerated. Eight days later, she presented with a severe systemic hypersensitivity reaction including urticarian eruption, sensation of dyspnea, abdominal pain, and fever (figure).

The symptoms were treated with antihistaminic therapy and oral prednisone during 10 days. We found positive anti-NTZ antibodies on 2 analyses performed 20 and 60 days after the beginning of the symptoms. NTZ treatment was stopped. The patient observed an antihistaminic therapy with good outcome after 2 months. Prick test with NTZ was negative.

Discussion. Type I hypersensitivity reactions induced by NTZ can present with cutaneous reactions (urticaria), respiratory symptoms, and edema. There are also cases of a drop in blood pressure and cardiovascular shock. They typically occur shortly after treatment initiation, during or within 1 hour after infusion and mainly after the second and the third infusion.

Figure Giant urticarian eruption



Some type I hypersensitivity reactions have been described after several infusions and are strongly associated with the presence of persisting anti-NTZ antibodies.³ Recently, delayed hypersensitivity reactions (type III) have been described with NTZ; several publications reported 6 cases with a hypersensitivity reaction several days after infusion.⁴⁻⁶ Reported symptoms included rash, arthralgia, edema, and fever. The events occurred several hours to days after the first infusion in one case, mainly after the second infusion. Positive anti-NTZ antibodies were identified in such cases as early as after the second infusion.⁵

Our case may be similar. Presented symptoms, chronology, and negative prick test were compatible with delayed hypersensitivity. The patient also developed persistent anti-NTZ antibodies, identified after the first infusion and confirmed 6 weeks later. She had not been previously exposed to NTZ. To our knowledge, a delayed hypersensitivity reaction with persistent anti-NTZ antibodies has never been reported after a single infusion.

The hypersensitivity mechanism requires a period of sensitization to the antigen, and our case is surprising.

NTZ has a long half-life; pharmacokinetic studies found detectable concentrations of natalizumab in the serum of patients for 8 weeks after a single infusion. The presence of anti-NTZ antibodies has been detected as early as 4 weeks after a single infusion. However, in our case, the time to first symptoms seems to be too short to permit anti-NTZ production antibodies.

Hypersensitivity reactions to a monoclonal antibody (mAb) after a single infusion have been reported for cetuximab; in these cases, the anti-mAb antibody was already present before the first infusion, and induced natural preexposure to an oligosaccharide present on the Fab cetuximab portion.⁷ Hence, we suppose that such a cross-reaction occurred in the present case.

Our case highlights the risk of a delayed hypersensitivity reaction to natalizumab and the risk of early persistent anti-NTZ antibody production. Some immunologic effects of NTZ are unknown and need to be investigated.

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