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## Guillain-Barré syndrome after heat stroke

Heat stroke is usually not listed among the events triggering Guillain-Barré syndrome. Two cases of a Guillain-Barré syndrome-like polyneuropathy after heat stroke are on record, although without reference to electroneurography.[1] We report on a patient, who developed Guillain-Barré syndrome 10 days after severe heat stroke. He had electrophysiological evidence of demyelination, increased CSF protein, and high anti-GM1 antibodies. Heat stroke activates the immune system by cytokine release,[2] opens the blood-nerve barrier, and exposes peripheral nerve antigens and thus may induce Guillain-Barré syndrome, as suggested by results from our patient.

A 28 year old drug addict was using anticholinergic drugs against sweating during levomethadone withdrawal. He was found unresponsive in a public garden on a hot summer day (ambient temperature 32°C) after ingesting cocaine. His core temperature was 42.5°C at admission. He was in deep coma with wide unreactive pupils and without corneal and pharyngeal reflexes. Tachypnoea had induced hypocapnia. Blood pressure was 85/30 mm Hg and heart rate was 165/min. He developed disseminated intravascular coagulation, thrombopenia below 10 000 MRD/ml, and metabolic acidosis. Creatine kinase rose from 128 to 751 U/l. Leucocytes and C reactive protein remained normal. After 4 days of coma he was transferred to a closed psychiatry ward because of agitation and frightening hallucinations. After 5 more days he complained of fatigue, myalgia, and arthralgia and, 3 days later, developed fever (38.9°C), tetraplegia, and dysphagia. He required intensive care within hours. Vital capacity was 1.5 l. Proximal arm muscles had MRC grades between 2 and 3. All other limb muscles had grades 1 or 2. Facial muscle weakness increased for 2 more days. There was no ophthalmoplegia, but areflexia and stocking glove hypaesthesia for vibratory and cold stimuli. He did not respond to early intravenous immunoglobulin treatment and underwent plasma exchange from day 14 to 18. Bulbar muscles improved on day 15. Head movements improved 1 week later. Minimal hand functions recurred after 4 more weeks. He still required help with dressing and was unable to stand 14 months after disease onset.

Protein comcentration in CSF was 480 mg/l 2 days after onset of tetraparesis, and 7300 mg/l 2 weeks later. Cell count was 6 cells/mm$^3$. He had high IgM (500 U/l; enzyme linked immunosorbent assay (ELISA); normal below 120 U/l) but only moderately increased IgA antibodies against GM1. 0nly one of 20 patients with Guillain-Barré syndrome examined in the same laboratory had higher anti-GM1 IgM antibodies. The anti-GM1 antibodies were normal 8 weeks after plasmapheresis.

Compound motor action potentials were<0.7 mV in all tested nerves from day 2 to day 95. Distal latencies were more than 150% above the upper limit of normal in the left peroneal nerve. Conduction velocities were below 70% of the lower limit of normal in the left peroneal and the left median nerve. F latency was above 150% of the upper limit of normal in the left ulnar nerve. F responses were missing in both median nerves and in the right peroneal nerve. A conduction block was present along the right ulnar nerve (wrist stimulation 0.69 mV; plexus stimulation 0.37 mV). Abnormal temporal dispersion and possible conduction block was present in the left ulnar nerve (wrist stimulation amplitude 0.36 mV; duration 8.6 ms; elbow stimulation amplitude 0.19 mV; duration 10.2 ms). Median sensory nerve conduction was normal and sural nerve conduction was moderately slowed (36 m/s) at day 2. Needle EMG disclosed abundant fibrillations and positive sharp waves in proximal and distal limb muscles at day 95.

Decreased sweating due to anticholinergic medication, cocaine induced increased heat production, and high ambient temperature precipitated heat stroke in our patient. Ten days afterwards he developed an acute neuropathy that met clinical and neurophysiological criteria for Guillain-Barré syndrome. Similar time delays have been seen in two other patients with Guillain-Barré syndrome-like neuropathies after heat stroke[1] and in the second of two patients reported as critical illness neuropathy after extreme hyperpyrexia.[3] This patient had increased CSF protein and fasciculations which are unusual in critical illness neuropathy. He may have had Guillain-Barré syndrome as well. Weakness evolved with delay in these four patients with Guillain-Barré syndrome-like neuropathies, whereas it was present immediately after hyperpyrexia in five more patients, who probably did not have Guillain-Barré syndrome. One patient with heat stroke was tetraparetic when he regained consciousness.[4] He had pyramidal and cerebellar signs and persistent atrophic weakness due to axonal or motor neuron loss and no neurophysiological evidence for demyelination. Four of 14 patients with cancer exposed to whole body hyperthermia and chemotherapy complained of weakness immediately after hyperthermia.[5] Their nerve conduction abnormalities are reported as "compatible with scattered demyelination".

Our patient had chronic HCV infection which may be associated with vasculitic neuropathy and cryoglobulinaemia, both absent in our patient. A connection between Guillain-Barré syndrome and non-A non-B hepatitis has been suggested,[6] but the close temporal relation makes heat stroke a more probable cause of the disease in our patient. His high anti-GM1 antibodies suggested immune mediation. Anti-GM1 IgA is increased after *Campylobacter jejuni* infection, whereas IgM dominated in our patient who had no evidence of *Campylobacter jejuni* infection. Heat stroke disrupts the gastrointestinal mucosal wall. Endotoxins enter circulation and stimulate macrophages, which release TNF-α, Il-1, Il-6, and IFN-γ. All these cytokines are raised after heat stroke[2] and open the blood-nerve barrier. This may have exposed the GM1 epitope in our patient. IFN-γ induces Schwann cells to express MHC class II gene product, inviting T cell attack. TNF-α is proinflammatory, myelinotoxic, and increased in Guillain-Barré syndrome.

Guillain-Barré syndrome-like neuropathies have been reported from Saudia Arabia,[1] where heat stroke is common, but they were not noted in connection with epidemic heat stroke in North America.[7] Our patient had all features associated with fatal heat stroke: long lasting coma, shock requiring intravenous catecholamines, metabolic acidosis, and disseminated intravascular coagulation.[7] Guillain-Barré syndrome may occur more often after heat stroke, if more patients survive extreme hyperthermia thanks to intensive care.

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## Hydrodynamic performance of a new siphon preventing device: the SiphonGuard

Around 10% to 30% of shunt revisions may be attributed to posture related overdrainage. Of the various siphon preventing devices available at present, two construction types are the most prominent: those using a gravitational mechanism and those using a subcutaneous membrane. Gravitational devices such as Elekta-Cordis Horizontal-Vertical Valve, Chhabra Valve, Fuji Valve, or Miethke Dual-Switch Valve are widely used.[1] Their main drawback is susceptibility to malfunction when the shunt becomes displaced from its vertical axis after implantation and unpredictable operation during persistent bodily movements. The membrane devices: the Anti-Siphon Device (ASD, Heyer Schulte) or Siphon Control Device (SCD, Medtronik PS Medical) have generally proved clinically effective,[2 3] although in some cases these devices may obstruct the CSF drainage when the subcutaneous pressure increases or the scar tissue isolates the device from atmospheric pressure. The flow regulat-

ing Orbis-Sigma Valve (Elekta-Cordis) may also reduce clinical complications related to overdrainage in the upright body position.[4] It prevents excessive CSF drainage by instantaneously increasing its hydrodynamic resistance when the drainage rate rises.

The new Codman SiphonGuard device is intended to reduce the drainage rate when the flow dramatically increases during transition from a horizontal to vertical body position. It consists of two passages for the CSF drainage. In the central, wide channel a ball on spring valve is inserted. The valve, unlike in all hydrocephalus shunts, is normally open and closes when the flow rate exceeds the specific threshold level. Then the drainage of CSF is diverted to a much thinner channel, which constitutes a high hydrodynamic resistance. This action may help to prevent posture related overdrainage.

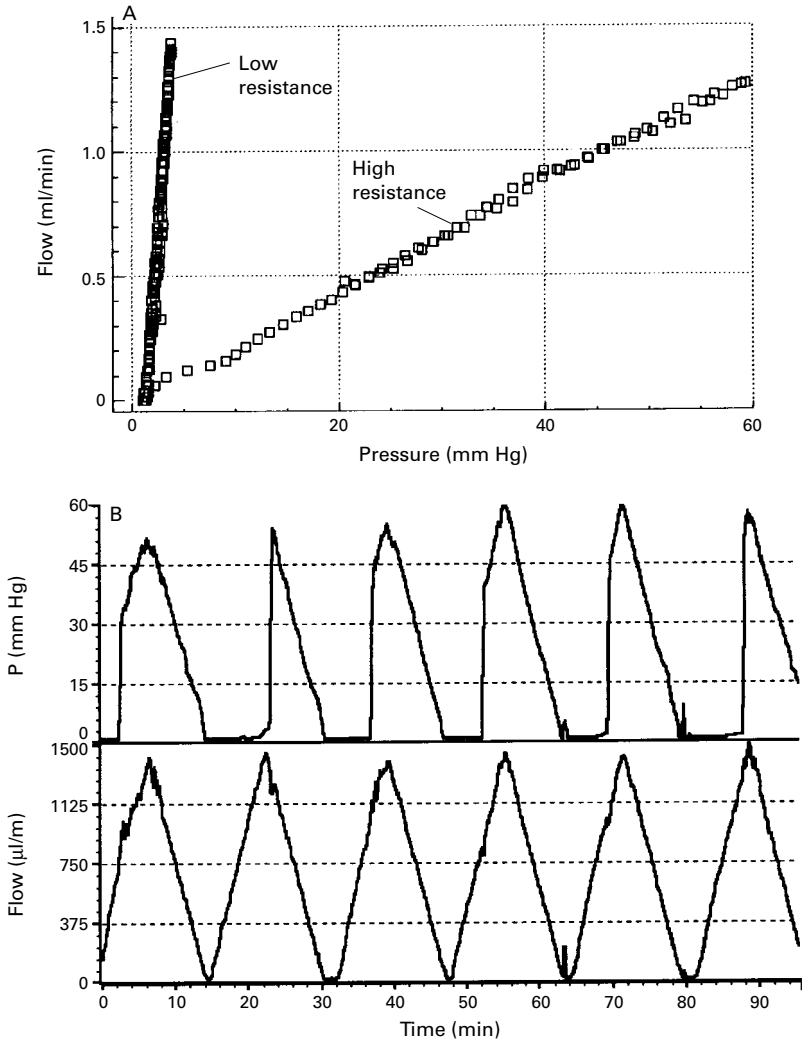
We tested a sample of three SiphonGuards (kindly provided by Johnson and Johnson) in the United Kingdom Shunt Evaluation Laboratory[5] to characterise the hydrodynamic performance of the device and its ability to reduce posture related overdrainage.

The pressure flow performance curve consisted of two straight lines of different slopes, both crossing the origin. They represent the two possible states of the SiphonGuard—low resistance ( mean of 1.5 mm Hg/ml/min) and high resistance (mean of 42 mm Hg/ml/min, figure A). The differential pressures resulting from the above values, providing the CSF flow is on average 0.3 ml/min in the horizontal body position, would be 0.45 mm Hg and 12.6 mm Hg respectively.

Switching between low and high resistance was initiated by a flow rate, the threshold of which varied between 0.7 and 1.8 ml/min (figure B).

Switching from the high to low resistance was initiated by the differential pressure decreasing below the threshold from 4 to 6 mm Hg.

Overall, the mechanism of the SiphonGuard seemed to work according to the designers' intention. It is supported by the concept that, during rapid transition from horizontal to vertical body position, initial flow rate increases above 2–3 ml/min. This is enough to switch the valve to the high resistance state, limiting overdrainage. However, in practice, it may not always be the case. In patients with small or slit ventricles previously having overdrainage, CSF may not be available to produce the flow at such a high rate. Moreover, because reliable switching occurs above 1.8 ml/min, in shorter persons or in patients resting persistently in a semisitting position (for example, elderly patients watching TV or reading books) the drainage rate of 1 ml-1.5 ml may cause clinical deterioration without initiating the antisiphon action of the SiphonGuard. Another possible drawback concerns the reverse change—that is, switching back from high to low resistance, to be expected when a patient moves from a vertical to a horizontal position. The device may not return to its state of low resistance. If the resistance switching mechanism is indeed triggered by a differential pressure (with a threshold of around 5 mm Hg) the SiphonGuard may stay in the high resistance state permanently. Its high hydrodynamic resistance may force the differential pressure to persist higher than 9–16 mm Hg, under conditions when the CSF drainage rate should equal its formation rate (0.2–0.4 ml/min). Hence, it is possible that the device may remain "locked" in the high resistance state, causing underdrainage in the horizontal body position.




*(A) Pressure-flow performance curves for the SiphonGuard for the low and high resistance states. (B) Switching between low and high resistance states was monitored by repetition of triangularly increasing and decreasing perfusion rate (lower plot in µl/min) controlled by computer controlled infusion pump. Switching point may be demonstrated by an abrupt increase in the pressure measured across the device (upper plot). The same device changed the resistance state at variable flow rate from 0.7 to 1.5 µl/min.*

In vivo, the device may contribute to the significant fluctuations of pressure resulting from the difference between the operating pressures for low and high resistance—similar to that described for the Orbis-Sigma Valve. Moreover, it may not prevent the overdrainage related to nocturnal vasomotor pressure waves,[5] as often reported in paediatric cases.

These reservations, based on our short laboratory study, should be taken into consideration both by neurosurgeons and the manufacturer. Whether they cause system malfunction under specific clinical conditions remains to be shown. We advocate a well controlled multicentre study on this new and interesting device together with in vivo measurements of shunt function using a CSF infusion test during tilting.[6]

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### Convulsions induced by donepezil

Donepezil, a centrally acting acetylcholinesterase inhibitor, has been recently introduced for the symptomatic relief of cognitive impairment in patients with mild to moderate Alzheimer's disease. Several adverse events thought to be related to donepezil have been reported so far, the most common ones being gastrointestinal disturbances due to cholinomimetic effects of donepezil.[1] Convulsions have not been reported for donepezil to date. We report on a patient with mild Alzheimer's disease who presented with convulsions during treatment with donepezil.

The patient was a highly educated, ApoE4 homozygous, 72 year old man, who was diagnosed with dementia of probable Alzheimer's type (NINCDS-ADRND criteria) 14 months previously. His medical history, with the exemption of non-familiar dementia, was unremarkable and his only medication was 100 mg aspirin daily. His mini mental state examination score was 22 points. He was treated with 5 mg donepezil once daily for 2 weeks, and then 10 mg a day for 23 days when he was admitted due to convulsions. The patient was unconscious for 40 minutes with urinary incontinence and bitten tongue. Blood analyses were normal. A contrast brain CT showed a mild degree of cortical atrophy with no structural lesions. EEG showed mild and diffuse neuronal dysfunction with the absence of grafoelements indicative of epilepsy. Donepezil was discontinued and no other therapy was instituted. Six weeks later 5 mg donepezil once daily was restarted. On day 52 of donepezil treatment the patient's caregiver had reported loss of consciousness and convulsions in our patient. The donepezil was discontinued and 100 mg indomethacin a day was prescribed. For the subsequent 8 months the patient has been convulsion free and his current mini mental state examination score is 19.

Convulsions in Alzheimer's disease are rare until late in the illness, when up to 5% of patients reportedly have infrequent seizures.[2] We think that convulsions reported in our patient could be due to donepezil. It has already reported that some centrally acting cholinesterase inhibitors—that is, tacrine, velnacrine, and physostigmine[3–5] might induce convulsions in patients with Alzheimer's disease. The mechanism of convulsive action of acetylcolinesterase inhibitors is not clear. As donepezil seems a useful drug in some of the carefully selected patients with mild to moderate dementia of Alzheimer's type we think that this report will extend our knowledge of donepezil's safety profile.

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### Severe toxic neuropathy due to fibrates

The main adverse effects of lipid lowering agents in the fibrate family involve the gut, the skin, the liver, the blood, and the muscular system. Some of these complications are more frequent when renal failure exists.[1] Here we report a case of neuropathy secondary to long term treatment with fenofibrate in a patient without renal failure taking recommended doses.

A 60 year old man was seen in September 1996 complaining of leg pain for 6 months. His relevant medical history included coronary artery disease treated for 10 years with 6 mg molsidomine/ day and 60 mg isosorbide dinitrate/ day, high blood pressure and hyperlipidaemia treated respectively with 100 mg atenolol/ day and 200 mg fenofibrate/day for the past 5 years. He complained of paresthesias along the posterior aspect of both thighs, later complicated by progressive muscle weakness.

The physical examination disclosed a patient incapable of standing on his toes or heels. No proximal muscle weakness was present. The deep tendon reflexes were reduced in all limbs. There was no sensory loss to light touch, vibration sense, pain perception, and joint position sense. There was no disturbance of sphincter control or postural fainting and no impairment of potency to suggest dysautonomia. The rest of the physical examination was within normal limits. The EMG suggested an axonal sensorimotor neuropathy with reduced amplitude of nerve action potentials without any significant slowing of conduction velocity. There were spontaneous fibrillations in the right tibial anterior muscle. The complete blood cell count, erythrocyte sedimentation rate, fibrinogen, C reactive protein, and serum protein electrophoresis were normal. Muscle enzymes were normal and immunological studies (antinuclear factor, serum and urinary immunoelectrophoresis, circulating immune complexes, serum complement, ANCA) were negative. Antiparaneoplastic antibodies and antiglycolipid antibodies were not detected. Two CSF examinations were performed: the CSF contained 1 white cell/mm$^3$, the protein concentration was 65 mg/dl, the glucose concentration was 2.5 mmol/l. Accessory salivary gland biopsy eliminated amyloidosis, sarcoidosis, and Gougerot-Sjögren's syndrome. Nerve biopsy confirmed axonal disease and disclosed a focal perivascular inflammatory lymphocytic infiltrate without vasculitis. No ultrastructural study was performed. An adverse drug effect was suggested in May 1997 and fenofibrate was discontinued. Three months later the patient indicated an improvement in the distance he could walk. In December 1997, he no longer complained of myalgia. Improvement in motor function was apparent; the patient could now stand on his toes and heels without help.

Axonal sensorimotor neuropathy was confirmed in this case by electrophysiological and histological findings. Other common causes of axonal neuropathy were excluded and a toxic cause was considered.[2] Because the patient had been receiving all of his medications well before the beginning of the clinical manifestations, there was no chronological argument targeting any one drug in particular. However, a review of the literature suggested fenofibrate as the causative agent as neuropathies have been described after treatment with clofibrate and bezafibrate.[3–5] In addition, none of the other drugs he was taking have been associated with neuropathy. The role of fenobritate was confirmed by regression of the symptoms after discontinuation of this drug without the addition of any other treatment. There are no previous reports of histological findings in neuropathy due to fibrates. The delay between initial treatment with fenofibrate and the appearance of the symptoms as well as the time required for them to regress, suggest a cumulative toxic effect but no other predisposing risk factor such as high dosage or renal failure was present.

In conclusion, fibrates can be responsible for neuropathies even when given in approved doses and in the absence of renal failure.

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# CORRESPONDENCE

### Macs with multiple sclerosis

Rothwell and Charlton[1] have suggested that Scottish ancestry is associated with an increased susceptibility to multiple sclerosis. They make the novel observation that a higher than expected proportion of patients with multiple sclerosis had Scottish surnames as defined by the prefix Mc or Mac. They quote that the percentage of the population in the Highlands and Islands with a surname of Mc or Mac is 22.6%. They then suggest that this is the percentage with Mc or Mac in Orkney and Shetland but these islands are not part of the Highlands and Islands. In Orkney and Shetland, in fact, only 3.5% of the population have a surname beginning with Mc or Mac, which is much lower than the percentage in north east Scotland—namely 7.5%.

Rothwell and Charlton do make the point, however, that an increase in the proportion of surnames prefixed with Mc or Mac with latitude within Scotland is not associated with an increase in the prevalence of multiple sclero-