LETTERS TO THE EDITOR

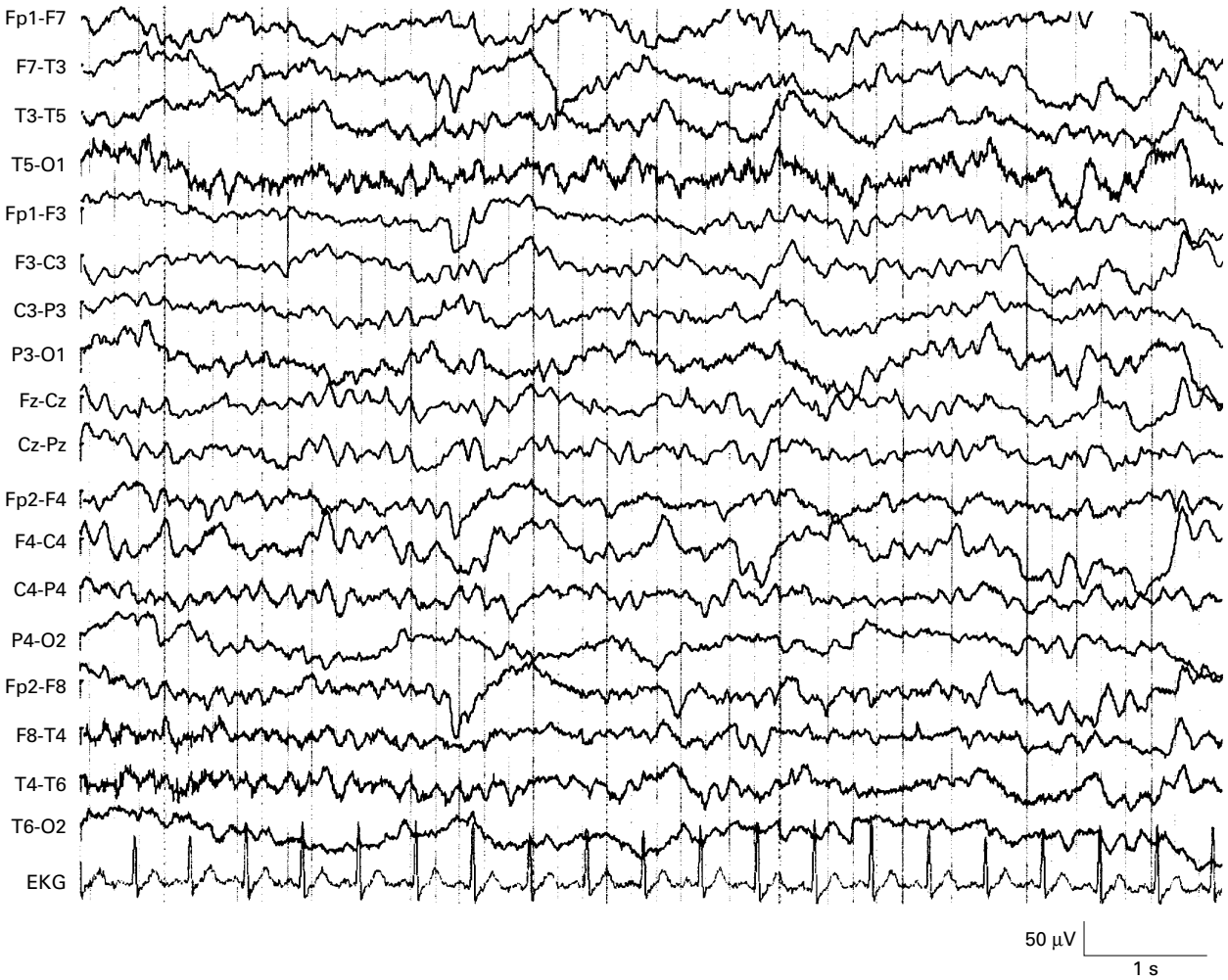
Treatment of paroxysmal sympathetic storm with labetalol

First described by Penfield in 1929, paroxysmal sympathetic storm is characterised by episodic hyperhidrosis, hypertension, hyperthermia, tachypnoea, tachycardia, and posturing. It has commonly been associated with closed head traumatic brain injury, agenesis of the corpus callosum, hydrocephalus, and suprasellar or diencephalic tumours.[1 2] Penfield hypothesised that these sympathetic spells were caused by epileptiform discharges in thalamic nuclei irritated by increased intracranial pressure, thereby leading him to name this entity "diencephalic autonomic seizures".[2] Electroencephalograms obtained on patients during these autonomic attacks, however, have not shown epileptic activity, and anticonvulsant therapies have not proved useful in their treatment.[2 3] Bromocriptine and morphine have been the standard treatments for paroxysmal sympathetic storm, and propranolol has been shown to reduce the hyperpyrexia seen during autonomic spells.[3 4] In this case report, we describe a patient treated successfully with labetalol, but not metoprolol, suggesting that β1 antagonism alone is not sufficient to suppress paroxysmal sympathetic storm.

A 21 year old white man was an unrestrained passenger in a motor vehicle accident and developed a closed head shear injury. He was admitted to a hospital where a head CT showed hydrocephalus necessitating a ventriculoperitoneal shunt placement. A head MRI showed abnormal T2 signal in the corpus callosum and the dorsal midbrain consistent with shear injury. Although initially comatose, he improved to near baseline over the next few months. He was admitted to our hospital 15 months later with a shunt infection, necessitating treatment with vancomycin, shunt externalisation, and, eventually, replacement. During and after resolution of the shunt complications, he developed episodes of sympathetic hyperactivity while under continuous monitoring in an intensive care unit. These attacks were characterised by (1) diaphoresis throughout the entire body, (2) tachycardia (heart rate 140–160 bpm) measured by automated pulse oximetry or by ECG, (3) hypertension (blood pressure 170–180/100 mm Hg) measured by arterial line pressure transducers or by sphygmomanometer, (4) fevers to 39.1 °C orally, and (5) flexor posturing. He was alert during these episodes, and responded to questions appropriately with denial of any acute onset of discomfort or pain. Furthermore, these attacks were not correlated with periods of bladder distension (Foley catheter in place) or impaction (radiograph not suggestive of retained stool). Individual episodes lasted 5–10 minutes and recurred at 5–10 minute intervals. Clusters of these spells would last 1 to 2 hours with more than three clusters a day.

Multiple CSF and blood cultures were negative. Serial head CT showed marked reduction of hydrocephalus and no brain stem abnormalities after shunt correction. No other intracranial pathology was noted. Plain films and MRI of the spine showed no myelopathic findings suggesting autonomic dysreflexia. Abdominal and pelvic CT did not show any hidden masses or lesions. Toxicology screen at onset of symptoms was negative. Electroencephalograms obtained during these episodes of dysautonomia disclosed theta and delta slowing with some sharply contoured waves, but no definite ictal or interictal epileptiform activity (figure).

Although initially treated successfully with bromocriptine (5 mg twice daily) and morphine (15 mg every 6 hours), he was withdrawn from morphine with a methadone taper at the request of his parents secondary to concerns over addiction. He was then started on metoprolol (25 mg thrice daily) with little effect on the frequency or severity



EEG obtained during episodes of paroxysmal sympathetic storm (tachycardia with heart rate of 120 bpm) shows predominant delta and theta waves (greater on the right than on the left) with no clear epileptiform activity, indicating that these attacks are not of seizure origin.

of the hyperautonomic episodes. Replacement with 100 mg labetalol twice daily led to reduction in the frequency of events to about one a day. Subsequent increase of the medication to 200 mg twice daily resulted in a marked decrease to less than one paroxysmal sympathetic storm over several days. At the time of discharge, the patient had returned to his preadmission baseline.

The current observations lend support to the prevailing view that paroxysmal sympathetic storm may represent disruption of autonomic function in the diencephalon and brainstem. Bullard has proposed that the clinical syndrome may be the result of a release phenomenon within the brainstem and/or diencephalon from loss of overriding cortical or subcortical inhibition.[3] More recent case studies suggest localisation to the central sympathoexcitatory regions including the paraventricular hypothalamic nucleus, lateral periaqueductal grey matter, lateral parabrachial nucleus, or rostral ventrolateral medulla.[3] Compromised autonomic neuronal integrity centrally is not surprising in the setting of infection after traumatic brain injury.

Various medications can potentially be used in managing central sympathetic storm. Imidazoline agonists and specific α2 adrenoceptor antagonists, such as clonidine and methyldopa,[5] have recently been shown to have sympathoinhibitory actions centrally within the rostral ventrolateral medulla. These agents have so far been used in the treatment of essential hypertension, tetanus, or autonomic dysreflexia. β Blockers such as propranolol however, have long been the mainstay of treatment of the hypertension, tachycardia, and hyperpyrexia associated with paroxysmal sympathetic storm.[6 7] This non-selective β adrenergic antagonist acts through inhibition of peripheral catecholamine activity, and being highly lipophilic, may also exert central effects through membrane stabilisation or receptor blockade. Moreover, propranolol may reduce sustained muscle contraction.[7] Taken together, these findings suggest that non-selective β receptor antagonism is sufficient to inhibit the clinical manifestations of diencephalic seizures.

The present case suggests that β1 receptor antagonism alone is not sufficient to treat hyperautonomia during paroxysmal sympathetic storm. This patient was initially placed on starting doses of metoprolol, a selective β1 antagonist, with little clinical effect in controlling the frequency of the autonomic attacks; however, labetalol, an α1 and β1-β2 adrenergic receptor antagonist did lead to an observable decline in symptoms. Both sympatholytic agents were given at doses typically used in initiating treatment of systemic hypertension, suggesting that the observed response seen with labetalol could not be explained solely by a dosage phenomenon. Prior studies also demonstrate that small amounts of propranolol (20 mg four times a day) can achieve similar responses to those seen with labetalol,[6 7] further arguing against a dose dependent effect. Thus, at a minimum, either α1 or β2 receptor blockade, likely in addition to β1 blockade, is necessary in the treatment of paroxysmal sympathetic storm.

The discrepancy in response between metoprolol and labetalol could result from their different effects on the cardiovascular system or CNS. The β1-β2 adrenergic receptor blockade by labetalol decreases blood pressure and heart rate through negative inotropic and chronotropic effects, and by inhibiting renin release. In addition, labetalol has vasodilator properties resulting from α1 blockade and partial β2 agonism. These reduce peripheral vascular resistance, blood pressure, and coronary vascular resistance, a potential advantage over other β blockers. Alternatively, differences in central activity may explain the increased efficacy of labetalol over metoprolol. As both agents are lipophilic, their central access should not differ significantly; rather, differences in receptor antagonism (β1 versus α1, β1, β2) would more likely explain the therapeutic discrepancy. As proposed with propranolol,[4] inhibition of β2 receptors by labetalol may exert a stabilising effect within the CNS through indirect inhibition of sympathetic nerve activity.

In the present case, we report the use of labetalol as an alternative agent in the treatment of paroxysmal sympathetic storm. It likely exerts both a central and peripheral blockade of α1 and β adrenergic receptors to produce inhibition of autonomic dysregulation. The clinical ineffectiveness of metoprolol further suggests a necessary role for β2 and/or α1 receptors in the clinical presentation of paroxysmal sympathetic storm. Labetalol may prove an alternative equal to or better than morphine in the treatment of these spells, especially when addiction and dependency are of concern.

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Moyamoya disease presenting with singing induced chorea

Moyamoya disease is a relatively uncommon, chronic cerebral vasculopathy of unknown aetiology that is characterised by unilateral or bilateral stenosis or occlusion of the proximal portion of the carotid arteries, together with an abnormal vascular network at the base of the brain. Most childhood cases manifest with the signs and symptoms of cerebral ischaemia or infarction, whereas intracerebral haemorrhage prevails in adults.[1 2] We describe here a case of moyamoya disease in a 29 year old multiparous woman, who presented with involuntary limb movements induced by singing.

A 29 year old woman, gravida two, para two, presented to the neurological outpatient clinic at Chungbuk National University Hospital with recurrent episodes of brief involuntary movements affecting her left hand and arm. The movements were characterised as unilateral, brief, coarse, irregular, and wavering. There was no history of neuroleptic drug therapy, or family history of involuntary movement.

General physical, neurological, and neuropsychological examinations were unremarkable. Baseline blood tests, ECG, and chest radiography all yielded normal results. The episodes of the patient's involuntary movements were unique, in that they usually appeared while she was opera type singing in a choir at church. They were also occasionally provoked by some conditions of hyperventilation such as blowing to cool hot soup, or blowing the dust off a table. This suggested an underlying ischaemic pathophysiology and prompted us to investigate changes in brain vasculature and parenchyma. The short lived choreiform movements were usually preceded by a tingling sensation in her left hand, which occasionally extended to the left leg.

An EEG between ischaemic episodes disclosed diffuse slow waves bilaterally over the hemispheres; these slow waves increased as "build up" with the appearance of delta waves during hyperventilation. Magnetic resonance imaging showed areas of high signal intensity in both frontal subcortical regions, suggestive of focal ischaemic lesions (fig A and B). We determined the patient's cerebral vascular reserve using technetium-99m-HMPAO brain SPECT with acetazolamide challenge. This demonstrated a decreased vascular reserve in both frontal and temporal lobes, as well as in the basal ganglia. Magnetic resonance angiography and subsequent four vessel angiography showed nearly complete obstruction of the terminal portion of each internal carotid artery and the outline of a moyamoya network (fig C and D). Staged encephaloduroarteriosynangiosis was performed on the left and right sides, 1 week apart, resulting in an eventual amelioration of the patient's involuntary movements.

Chorea is one of the rarer, although acknowledged, presenting features of moyamoya disease; chorea is usually observed in children.[3 4] It is suggested that about 6% of patients with moyamoya disease have chorea.[5] Other types of involuntary movements have been described in patients with moyamoya disease: Valsalva related seizures,[6] recurrent episodes of carpopedal spasm,[7] recurrent torticollis,[8] and limb shaking transient ischaemic attack.[9] Hemichorea is characterised by unilateral, brief, coarse, irregular, wavering, involuntary movements, and is usually caused by some asymmetric, focal brain lesion. The clinical presentation of our patient was associated with opera type singing.

Singing requires both hyperventilation and the breath holding Valsalva's manoeuvre. Hyperventilation causes an increase in arterial oxygen tension, which subsequently causes vasoconstriction, which, in turn, reduces blood flow. In addition, Valsalva's manoeuvre increases cerebral venous pressure, which then increases intracranial blood volume and intracranial pressure, thereby reducing the arterial perfusion pressure. Thus, in those regions of the basal ganglia and cortex that are already critically perfused, hyperventilation and Valsalva's manoeuvre can easily lead to transient ischaemic insult, which may be clinically manifested by involuntary movements. It seems likely that hyperventilation and breath holding act synergistically to reduce brain perfusion. In this patient, the hemichoreic episodes were attributed to hypoperfusion of the contralateral cerebral hemisphere, and not to epilep-