LETTERS TO THE EDITOR

Reversible proximal myopathy in epilepsy related Cushing's syndrome

Epilepsy can induce hypercortisolism secondary to altered temporolimbic modulation of the hypothalamopituitary secretion of ACTH.^{1,2} Hypercortisolism can produce a reversible myopathy. Epilepsy, however, has not been recognised to cause a symptomatic Cushing's syndrome. The development of proximal myopathy as part of an epilepsy based Cushing's syndrome, in particular, has not been reported. We report on three such patients as well as their successful treatment with normalisation of serum cortisol using ketoconazole.³

Three women (table) with epilepsy who complained of easy fatigability, had mild to moderate weakness of trunk, neck, and upper and lower limb girdle muscles. All had irregular menses and hirsutism. They had increased serum ACTH concentrations and serum and 24 hour urinary cortisol concentrations. Weakness was persistent in two and intermittent, correlating exclusively with periods of seizure exacerbation and raised cortisol secretion in patient 3. In this patient, seizures would flare up every few months. At such times, she would experience daily to weekly seizures for one to three months with development of fatigability and clinically documented weakness after two or three weeks. EMG showed myopathic changes characterised by normal resting activity, small units, and increased recruitment patterns in all three patients. EMG findings were normal between exacerbations in patient 3 on two out of two occasions. Deltoid muscle biopsy was carried out in patient 2 and showed mild non-specific myopathic changes with type I predominance. Dexamethasone suppressed ACTH and cortisol secretion in all patients. MRI studies of the pituitary and adrenal glands showed no evidence of tumour. Thyroid function tests, and gonadal steroid

and creatine kinase concentrations were normal. All serum concentrations of antiepileptic drugs were in the therapeutic range.

Treatment with ketoconazole (200 mg three to four times a day) normalised the 4 00 pm serum cortisol and 24 hour urinary cortisol concentrations in all three patients. Normalisation of cortisol concentrations was associated with alleviation of the complaint of increased fatigability, normalisation of strength and EMG, and a reduction in seizure frequency in all three patients (table). Discontinuation of ketoconazole for three months in all three patients was associated with a recurrence of the myopathy within two to three weeks with subsequent recovery again within three weeks after reinstitution of ketoconazole.

Proximal muscle weakness in all three patients could be attributed to hypercortisolism. This conclusion is supported by the documentation of hypercortisolism, the failure to find other possible causes, and the reversibility of the myopathy and accompanying EMG features by normalisation of serum cortisol concentrations using ketoconazole treatment.³ Hypercortisolism, in turn, may have been related to abnormal temporolimbic modulation of hypothalamopituitary secretion of ACTH.^{1,2} This possibility was suggested by the presence of active, focal temporal epileptiform discharges in all three patients, the absence of any pituitary or adrenal tumour or hyperplasia, the absence of abdominal striae characteristic of classic Cushing's syndrome, and the absence of emotional depression, clinically and by the Hamilton scale, which can also raise serum cortisol. The intermittent occurrence of this Cushing's myopathy and its relation with antecedent seizure exacerbation in patient 3 offers further support for a possible epileptic causality. The description of this previously unreported epilepsy based Cushing's myopathy is important because it represents a readily treatable cause of fatigability and muscle weakness which may otherwise be underrecognised and attributed to postictal effects or medication toxicity.

Some adrenocorticosteroids, including cortisol, are glutamatergic, as well as bicuculline or picrotoxin-like antagonists of γ -aminobutyric acid A (GABA-A) receptor in the brain and exert potent anxiogenic,

proconvulsant, and convulsant effects.^{4,5} Hypercortisolism, therefore, may potentially exacerbate seizure disorders. The favourable seizure response to normalisation of serum cortisol concentrations in all three patients is consistent with this notion and the possibility that temporolimbic epilepsy may not only induce hypercortisolism but that the hypercortisolism, in turn, may exacerbate temporolimbic discharges leading to a positive feedback loop and a vicious circle.

These findings raise the possibility that epilepsy may be the basis for a hypercortisolism induced proximal myopathy that is readily reversible by normalisation of cortisol concentrations using ketoconazole. Normalisation of cortisol may benefit epilepsy as well.

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Serial magnetic resonance imaging shows separate medial and lateral medullary infarctions resulting in the hemimedullary syndrome

There have been several reports on MRI of the classic medullary vascular syndromes such as dorsolateral infarction and medial infarction.¹⁻⁴ The syndrome with both dorsolateral and

Summary of patients

	Patient 1	Patient 2	Patient 3
Age (y)	32	43	31
Epilepsy	CPS/SGS	CPS/SGS	CPS
EEG	L and R temp foci	R temp focus	L temp focus
Medications	Carbamazepine	Phenytoin phenobarbitone	Carbamazepine phenytoin
Irregular menses	+	+	+
Hirsutism	+	+	+
Obesity	Mild	-	Moderate
Striae	-	-	-
Weakness	Mild persistent	Moderate persistent	Moderate intermittent
Cortisol:			
Serum (pm) (1.4-10.7 µg/dl)	19.8-31.0	11.0-15.0	25.1-29.9
Urinary (20-90 µg/24h)	70.3-106.0	57-102	123-183
ACTH (20-90 pg/ml)	57-124	72-120	76.5-142.5
Dex supp (<1 µg/dl)	+	+	+
EMG	Myopathic	Myopathic	Myopathic
Biopsy	Not done	Non-specific myopathic	Not done
Treatment	Ketoconazole 200 mg four times daily	Ketoconazole 200 mg three times daily	Ketoconazole 200 mg three times daily
Outcome:			
Follow up (y)	3	2	5
Myopathy	Absent	Absent	Absent
Sz freqn	92%	Seizure free	32%
Menses	Regular	Hysterectomy for fibroids	Regular

CPS=complex partial seizures; SGS=secondary generalised seizures; L=left; R=right; temp=temporal; irregular menses=irregular or <25 or >32 day interval menstrual cycles; weakness: mild= >4/5 strength, moderate= >4/5 strength; Dex supp=dexamethasone suppression test; sz freqn=seizure frequency during follow up period compared with baseline.

medial infarctions is known as hemimedullary (Babinski-Nageotte) syndrome.⁵ However, because of the separate arterial topography supplying the medulla, the simultaneous occurrence of ischaemic lesions of its medial and lateral parts would be extremely rare.^{6,7} We report MRI of a patient with an ipsilateral lateral medullary infarction (Wallenberg's syndrome) followed by a medial medullary infarction with a 6 month interval. The initial stroke event on the central facial weakness of this patient was previously reported.⁸

A 40 year old man noted weakness of the right limbs and dysarthria. Since the age of 38, the patient had been on an antihypertensive drug regimen. He was conscious, and his blood pressure was 134/80 mm Hg. Neurologically, there were noted right supranuclear facial weakness, paralysis of the left hypoglossal nerve, paralytic dysarthria, and right hemiparesis with prominent weakness of the arm. Deep tendon reflexes were exaggerated in the right limbs and Babinski's sign was positive on the right side. Light touch and vibratory sensations were slightly decreased in the right leg, but temperature and pain sensations were well preserved. There was no diabetes mellitus or hyperlipidaemia. No abnormalities were noted on ECG, transthoracic echocardiogram, and Holter monitoring. Brain MRI at 10 days after the onset showed a high signal intensity area (T2 weighted image) in the left ventromedial part of the upper medulla, which was diagnosed as an infarct (figure A). Cerebral angiography performed at 12 days after onset showed mild atherosclerotic changes of the vertebralbasilar artery. The right facial weakness and left tongue paralysis were gradually improved and the patient was discharged with persisting mild right hemiparesis after one month.

Six months later, however, he suddenly experienced a floating sensation and gait difficulty. At that time he was alert and had a blood pressure of 160/106 mm Hg.

Axial T2 weighted MRI (5000/96, TR/TE). High signal intensity areas (arrows) are noted in the left ventromedial part of the upper medulla (A) and the left dorsolateral part of the upper to middle medulla (B) 6 months after the first stroke.

Neurological examination showed left Horner's syndrome, skew deviation with slight downward position of the left eyeball, clockwise rotatory nystagmus, impairment of temperature and pain sensations of the left face, paralysis of the left soft palate, hoarseness, slight dysphagia, cerebellar ataxia of the left limbs, decreased temperature and pain sensations of the neck and all parts of the right side, and hypohidrosis of the left half of the body. Slight right hemiparesis was present. Brain MRI performed on the next day showed a high signal intensity area (T2 weighted image) in the left dorsolateral portion of the upper to middle medulla. A repeat MRI study at one month after this second attack clearly showed an infarct in a left dorsolateral portion of the medulla with a reduction of oedema, and showed a reduction of an infarct in the left ventromedial part from the first stroke (figure B).

The patient presented here developed a left dorsolateral medullary infarction 6 months after the onset of an infarction involving the left ventromedial part of the upper medulla. Both were clearly seen on MRI. The dorsolateral part and medial part of the medulla are supplied by separate branches from the posterior inferior cerebellar artery and the anterior spinal artery, both of which are indirectly supplied by the vertebral artery. Hence the occlusion of the vertebral artery could produce simultaneous hemimedullary syndrome.^{2,6} However, serial infarctions of the separate topographic areas of the medulla resulting in a hemimedullary syndrome have been suggested,^{3,5} serial events documented by MRI—such as in the present patient—have not been reported. The present case provided unequivocal evidence that the hemimedullary syndrome can occur as serial events of the medial and lateral medullary infarctions.

With the advent of MRI, it has recently become possible to see microvascular lesions in the brain stem that would in the past have been detected only by postmortem examination. In patients where such multiple ischaemic lesions occur at separate sites and times so as to form a certain distinct syndrome, serial observations with MRI will certainly prove the pathogenic background of this syndrome and be of great clinical interest.

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Oculo-auriculo-vertebral spectrum disorder (Goldenhar "syndrome") coexisting with schizophreniform disorder

Oculo-auriculo-vertebral spectrum disorder is a complex and heterogeneous inborn condition affecting primarily aural, oral, and mandibular development with an estimated incidence of between 1/3500 and 1/26 000 births. It is thought to be connected to the development of the first and second branchial arch. It may additionally affect the skeletal system, kidneys, heart, gastrointestinal tract, and eye. Familial occurrence has been reported, but most cases seem to be sporadic.¹ Structural CNS and neurological abnormalities occur often, but with great variability.² Mental retardation seems to be a common feature,¹ but other relevant psychiatric disorders have not been reported.

We present what seems to be the first published case of a patient with an organic schizophreniform disorder and oculo-auriculo-vertebral spectrum disorder.

A 27 year old man was referred for psychiatric treatment by his general practitioner. The patient reported intermittent speech problems since the age of 9 which, he was unshakably convinced, were the effect of "electromog". He would often smell strange and sickening odours originating in his mother's kitchen that nobody else would notice and were causing his problems. Officially he was studying business administration, but had not passed any of the necessary exams in the past 3 years. Mentally he thought he was absolutely sane.

From birth he showed facial asymmetry, right thumb dysplasia, and dysplasia of the right auricle. Neither the patient nor his mother knew of a relevant family history of psychiatric disorders or dysplasias of any kind. There were no further psychiatric treatments except for one short admission for somatisation disorder 2 years previously. No prenatal or perinatal abnormalities were known. The patient's school performance had been average to good. He had first successfully trained and worked as a chemical laboratory assistant, but he had discontinued a subsequent polytechnic engineering course for no obvious reason.

On psychiatric examination the patient was suspicious and reserved. Thought contents were restricted to his complaints; formal thought showed a loosening of associations and often tended to be illogical. Attention, comprehension, and concentration were mildly impaired. There were olfactory hallucinations (kitchen smells), but no other