

LETTERS

Cerebral salt wasting syndrome in meningoencephalitis: a case report

Acute hyponatraemia is a common finding in patients with intracranial pathology. The diagnosis of the syndrome of inappropriate antidiuretic hormone (SIADH) is often made, but it is important to distinguish this from cerebral salt wasting syndrome, which responds to very different management. Cerebral salt wasting is well documented in neurosurgical patients and in patients with space occupying pathology. We present a case of a 26 year old man who developed cerebral salt wasting syndrome during an episode of meningoencephalitis.

Case report

A 26 year old man was admitted through the A&E department to a local district general hospital with four days of episodic confusion. There was no significant past medical or family history. Recreational drug use was denied and a urine screen was negative. A diagnosis of toxic encephalopathy was made. On day 2 he became pyrexial and agitated, and was sedated with haloperidol. Otherwise his examination was unremarkable, and his Glasgow coma scale (GCS) was 15, with no focal neurology. Routine blood tests, chest x ray, and computed tomography (CT) of the head were normal. CSF examination revealed a lymphocytic picture (130 cells/cm) with a protein of 1.9 g/l and a glucose of 2.3 mmol/l. A diagnosis of probable viral meningoencephalitis was made and he was started on intravenous acyclovir, together with benzylpenicillin, clarythromycin, and metronidazole.

On day 4 he remained pyrexial and confused, and he developed respiratory distress with clinical and radiographic consolidation in the right mid/lower zones. He became hypoxic and required intubation.

He was transferred to a tertiary intensive care unit. Repeat routine blood tests, blood cultures, atypical serology, urine, and protected catheter specimens were unremark-

Table 1 Profile of biochemistry results over 30 hours

	Time:	↓100 mg IV hydrocortisone given						
		18:00	00:00	06:00	10:00	11:00	18:00	00:00
<i>Plasma</i>								
Sodium (mmol/l)		129	123	122	122	122	129	131
Urea (mmol/l)		3.3	4.3	3.8	4	4.1	3.6	3.2
Osmolality (mmol/kg)			286				275	
<i>Urine</i>								
Sodium (mmol/l)			148	112	37	117	111	109
Osmolality (mmol/kg)			432	530	651	550	256	348
Output (ml/kg/h)		2.5	3.8	4.25	2.75	1.4	1.0	1.2
<i>Saline infusion (0.9%)</i>								
Rate (ml/kg/h)			3.5	3.75	3.7	2.5	2.25	1.2

↑Saline infusion begun

able. During day 5 he was rapidly weaned off sedation and extubated. His GCS was 15, with no focal neurology. Over the course of 12 hours his gas exchange again deteriorated owing to collapse of his left lung. Following reintubation, bronchoscopy revealed viscid sputum obstructing the left main bronchus. Sedation was again weaned (on day 6) and he developed some complex partial seizures. A repeat CT revealed no intracranial pathology, and repeat lumbar puncture showed a lymphocytosis of 5 cells/cm. On day 8 an EEG revealed anterior delta rhythm activity, consistent with an encephalopathy. Polymerase chain reaction tests for herpes simplex and varicella were negative.

On day 9 his GCS deteriorated to 8 and he needed increased ventilatory support. An acute hyponatraemia was noted (plasma sodium 132 mmol/l, falling to 123 mmol/l over 12 hours). It was also noted that the central venous pressure fell, urine output increased (6 litres in 24 hours), and he lost 1.5 kg in weight. Biochemistry supported the diagnosis of cerebral salt wasting syndrome, with a high urine sodium loss (148 mmol/l), normal serum osmolality (280 mmol/l), a urine osmolality of 432 mmol/l, and normal urea. In the picture of SIADH one would instead see a relatively normal central venous pressure and a low volume of "inappropriately" concentrated urine (urine sodium > 20 mmol/l and urine osmolality greater than plasma osmolality). Biochemically, SIADH would be characterised by a lower serum osmolality (< 260 mmol) and a low or low normal plasma urea, indicating serum dilution with excess water (table 1).

Intravenous 0.9% saline was begun (initially at a rate of 3.5 ml/kg/h), and a single dose of 100 mg of hydrocortisone was given (table 1). Over the next 36 hours the serum sodium normalised and the high renal sodium loss ceased. During treatment the urine osmolality fell from 432 mmol/kg to 256 mmol/kg, which represents a state of "hyperhydration" as a result of the large volume fluid replacement. He was extubated two days later and went on to make a full recovery.

Discussion

Cerebral salt wasting syndrome was first described by Peters *et al.*,¹ seven years before the identification of SIADH. Despite outward similarities, the pathophysiology, biochemistry, and treatment of these two conditions is very different (table 2). In SIADH there is renal conservation of water and dilutional hyponatraemia. Cerebral salt wasting syndrome is defined as a natriuresis with sodium and water loss and a decrease in intravascular

volume.² As a result, SIADH is treated by fluid restriction and cerebral salt wasting responds to sodium and water replacement.

Cerebral salt wasting syndrome has been reported in neurosurgical cases³ and in a case of tuberculous meningitis.⁴ However, there are no reports of this condition in other infective neurological processes. Its mechanism has been linked with natriuretic peptides similar to atrial natriuretic factor. Both brain natriuretic peptide and C-type natriuretic peptide have been implicated, and indeed brain natriuretic peptide has been shown to be increased in early subarachnoid haemorrhage.⁵

This case shows the difference between cerebral salt wasting syndrome and SIADH, and the importance of correct diagnosis and correct treatment. In cerebral salt wasting syndrome, saline infusion under central venous pressure guidance will correct the metabolic deficit, and in our case the mineralocorticoid effect of intravenous hydrocortisone helped to reduce the renal sodium loss. The mineralocorticoid fludrocortisone acetate acts directly on the renal tubule to reduce sodium excretion, and Hasan *et al* have shown that it significantly reduces the negative sodium balance in similar cases.⁶

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Table 2 Differential diagnosis of cerebral salt wasting syndrome and the syndrome of inappropriate antidiuretic hormone secretion

Variable	CSW	SIADH
Weight	↓	↑
CVP	↓*	↑ or N
Postural hypotension	+	-
Serum osmolality	↑ or N	↓
Serum uric acid	N	↓
Plasma urea	N or ↑	↓ or N
PCV	↑	↓ or N
Urine sodium	↑↑	↑
Urine volume	↑↑	↓ or N

*<5 mm Hg.
CSW, cerebral salt wasting syndrome; CVP, central venous pressure; PCV, packed cell volume; SIADH, syndrome of inappropriate antidiuretic hormone secretion.
↑, increased; ↓, decreased; N, within normal limits; +, present; -, absent.

A case of familial inverse Marcus Gunn phenomenon

Inverse Marcus Gunn phenomenon is a rare congenital synkinetic movement presenting as eyelid drooping on jaw opening. It has only rarely been reported.¹ Often this phenomenon follows peripheral facial palsy,² suggesting abnormal synkinesis of the facial nerve. However, the precise mechanism remains uncertain. Only one electromyographic study has been reported in this condition.³ In that case, trigemino-oculomotor synkinesis was the supposed mechanism, rather than trigemino-facial synkinesis. We report a patient with familial inverse Marcus Gunn phenomenon and speculate on the neuronal mechanism with the support of electromyographic results.

A 31 year old woman visited our clinic complaining of involuntary winking of her left eyelid on jaw opening. The symptom was most prominent when she opened her mouth forcefully, such as when eating or yawning. She stated that the symptom had been noticed from birth, and that her mother and uncle were also affected, but not her two sons. She had no history of previous peripheral facial palsy.

On neurological examination, her extraocular movements were normal and ptosis was not noted. There was no facial paralysis or sensory changes. Masticatory movement or forced mouth opening induced closure of the left eye. Her mother showed the same feature on neurological examination. Brain MRI showed no abnormal findings. Facial nerve conduction studies and the blink reflex were normal. Two channel electromyography showed co-contraction of the left lateral pterygoid muscle and the orbicularis oculi muscle on repetitive masticatory movements (fig 1).

Inverse Marcus Gunn phenomenon, the opposite of the Marcus Gunn phenomenon, is characterised by eyelid closure on jaw opening. Few cases have been reported, most following peripheral facial paralysis. Only one case of congenital inverse Marcus Gunn phenomenon was reported by Lubkin.³ He observed that on electromyography the levator palpebrae muscle was inhibited or inactivated during jaw opening, without any movement of the orbicularis oculi muscle, and concluded that his patient's symptom was limited to interactions at the level of the third and fifth cranial nerve complexes. Because the Marcus Gunn phenomenon is a pterygoid-levator synkinesis between the pterygoid and the levator palpebrae muscles, Lubkin's case may be the true inverse Marcus Gunn phenomenon. However, our patient's electromyographic studies showed that the ipsilateral orbicularis oculi muscle co-contracted with the lateral pterygoid muscle when she opened her mouth. Because these findings were consistently reproducible, we think this phenomenon is caused by synkinesis of the trigeminal and facial nerves in our case.

Most cases of inverse Marcus Gunn phenomenon appear to follow peripheral facial nerve paralysis,^{2,4} with contraction of the orbicularis oculi on jaw opening. However, our patient had no history of peripheral facial paralysis and surprisingly her mother and uncle showed the same phenomenon. We therefore conclude that our patient has a congenital trigemino-facial synkinesis with partial autosomal dominant inheritance. The orbicularis oculi muscle is supplied by the facial nerve connected to maxillary and buccal branches of the trigeminal nerve. As Rana pointed out,² ascending proprioceptive impulses from muscle stretch during full

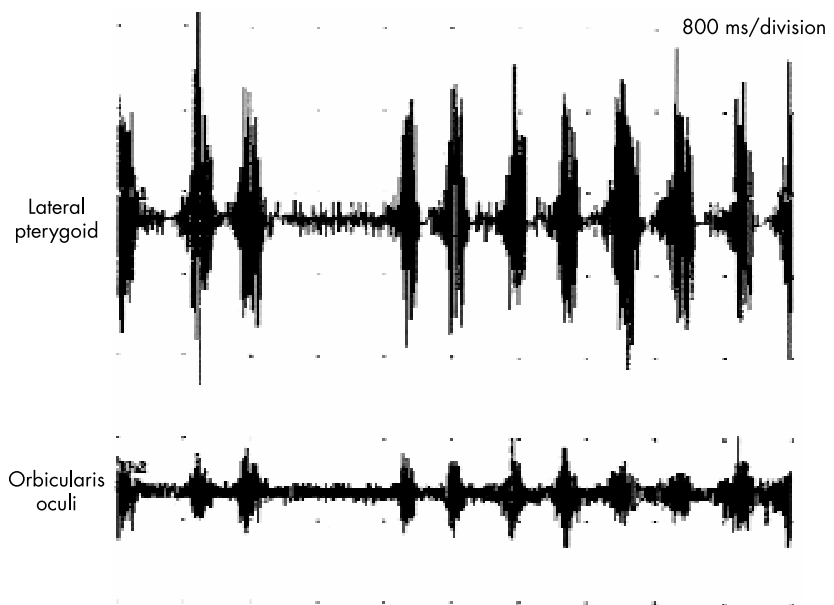


Figure 1 Electromyography showing co-contraction of ipsilateral lateral pterygoid and orbicularis oculi muscles. The orbicularis oculi muscle contracted simultaneously with repetitive masticatory movement.

mouth opening that are carried in the facial nerve could then trigger contraction of the orbicularis oculi muscle owing to faulty regeneration after a traumatic nerve injury. More recently there has been a tendency to explain these synkinetic movements in terms of plastic change in the central nervous system following deafferentiation. As our patient's symptom is congenital, we suppose that the trigemino-facial synkinesis is the result of an abnormal partial connection between the motor neurones of the trigeminal and facial nerves.

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Moderate hypoglycaemia obliterates working memory in humans with and without insulin treated diabetes

Moderate hypoglycaemia is common in people with insulin treated diabetes, and some mental functions deteriorate during this state. Working memory is a crucial cognitive process, necessary for many everyday tasks, but its integrity during hypoglycaemia is not

known. We examined the effect of moderate hypoglycaemia on working memory in 32 young adults (16 with type 1 (insulin dependent) diabetes). Mean performance on working memory was reduced almost to levels of chance. During hypoglycaemia, therefore, this important mental ability is almost obliterated though the subjects remain fully conscious.

Working memory is the mental capacity simultaneously to store and manipulate information.¹ It supports human capabilities in composing spoken language and in negotiating the environment. Individual differences in working memory correlate very highly with measures of reasoning and general intelligence.² Glucose is the brain's principal fuel, and mental function deteriorates when arterial plasma glucose falls below 3.0 mmol/l. Mental functions that are complex and performed under time pressure are particularly affected, the usual finding being a modest reduction in performance.³ To date, working memory has not been studied during hypoglycaemia. Here we examine the effect of controlled, moderate hypoglycaemia on performance of a challenging working memory task.

Working memory performance was studied in 32 young adults. Sixteen (nine men, seven women) were healthy, non-diabetic subjects aged between 26 and 34 years (mean (SD), 29.6 (1.7) years); a further 16 (nine men, seven women) were otherwise healthy individuals with type 1 diabetes, aged between 20 and 38 years (28.5 (5.4) years). Those with diabetes had a mean HbA1c of 8.3 (0.5)%. The mean number of correct items in the national adult reading test was 36.9 (6.1) for the non-diabetic group and 34.6 (5.6) for the diabetic group. Thus both groups comprised people of above average cognitive ability, with an overall mean intelligence quotient of about 113. They were examined under conditions of euglycaemia (4.5 mmol/l) and hypoglycaemia (2.5 mmol/l). The hyperinsulinaemic glucose clamp technique was used to achieve precise control of arterialised plasma glucose.

Permission to conduct the study was given by Lothian Health medical research ethics committee. Written, informed consent was obtained from all subjects.

Table 1 Working memory and other mental test scores during euglycaemia and hypoglycaemia (n=32)

	Euglycaemia	Hypoglycaemia	p Value for mean difference	Eta squared	p Value for variance difference
Four term order (working memory; number correct)	12.4 (4.3)	3.7 (2.3)	<0.001	0.86	<0.001
Digit symbol (number correct)	71.8 (12.1)	61.3 (15.5)	<0.001	0.57	0.08
Trail making B (seconds)	37.6 (8.4)	58.3 (11.6)	<0.001	0.74	0.08

Values are mean (SD). Eta squared is the proportion of the variance in the test scores accounted for by study condition (Euglycaemia v hypoglycaemia).

The experiment had a repeated measures, counterbalanced design with glycaemic condition as a within subjects factor (repeated measure); between subjects factors were whether or not subjects had diabetes and the order of conditions (euglycaemia-hypoglycaemia and hypoglycaemia-euglycaemia). Data, presented as mean (SD), were analysed using general linear modelling (repeated measures) on SPSS version 10.1. There were no significant order effects.

The “four term order” working memory test is from Kyllonen’s well validated cognitive battery of tests which is based on a model of human information processing.⁴ The task involves storing rules and stimuli in working memory and mentally manipulating the order of the stimuli so that they fit the rules. For each item of the task, subjects listen to three rules read aloud by the experimenter and then choose which of eight response options correctly accords with the rules. For example, the rules in one item are: “The animals come after the furniture; the horse comes before the dog; the desk does not come before the rug.” Eight response alternatives are then displayed on a card. The subject would score correctly by choosing the sequence “rug-desk-horse-dog.” Twenty four different items were used in each study condition. Subjects also performed the digit symbol test from the Wechsler adult intelligence scales—revised, and the trail making B test from the Halstead Reitan neuropsychological test battery. Performance on these latter two tasks is known to deteriorate during hypoglycaemia.

As expected, mean scores on the digit symbol and the trail making B tasks were significantly poorer during moderate hypoglycaemia (table 1). The hypoglycaemia induced deterioration involved a fall in the mean scores overall, with considerable overlap in scores between the two conditions. The variance of these two tests did not differ significantly between the euglycaemia and hypoglycaemia conditions (Pitman’s test for variance difference in non-independent measures, NS). Scores on the four term order task declined from a mean of 12.4 (4.3) during euglycaemia to 3.7 (2.3) during hypoglycaemia ($p < 0.0001$). Two further aspects of this result are notable. First, a score of 3.0 represents chance responding on the four term order test, which is close to the mean score during hypoglycaemia. Second, the variance in the four term order test scores fell significantly from hypoglycaemia to euglycaemia ($p < 0.001$, using Pitman’s test; table 1). Thus a range of individual differences in working memory scores during euglycaemia—from chance to near perfect performance—was reduced to near uniform chance responding during hypoglycaemia. There was no significant association in the diabetes group between HbA1c and the decline in working memory induced by hypoglycaemia. There was no difference in the effect of hypoglycaemia between the diabetic and non-diabetic

groups on any of the three mental tests (that is, there was no group by condition interaction for any test).

Unlike other mental functions, working memory—as indexed by the four term order task—was almost obliterated during moderate hypoglycaemia in young adult humans, with and without type 1 diabetes. Working memory is a pillar of human mental performance, its variance in humans being almost indistinguishable from differences in reasoning and general intelligence.² It is likely that, whereas other working memory tasks might also deteriorate during hypoglycaemia, those that were less complex than the four term order task would not be reduced to chance levels of performance. Animal studies suggest that performing difficult working memory tasks makes especially high demands on brain extracellular glucose, specifically in the hippocampus.⁵ However, the comparability of human and animal studies of working memory is limited because of the different tasks used, and the different meaning that the concept of working memory may have when applied to human versus other species. The hippocampus and other medial temporal lobe structures and the frontal lobes are especially sensitive to the effects of neuroglycopenia.⁶ A possible basis for the special vulnerability of working memory to the effects of hypoglycaemia is therefore the interaction of local brain energy demands and the regional density of the cerebral glucose transporters GLUT1 and GLUT3. The degree of hypoglycaemia induced here, which often occurs in people with type 1 (insulin dependent) diabetes, does not affect conscious level. Though many mental tasks show some deterioration in this state, it is remarkable to find a core mental function that the brain is almost totally unable to support.

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Parainfectious opsoclonus-myoclonus syndrome: high dose intravenous immunoglobulins are effective

Opsoclonus-myoclonus syndrome (OMS) is a rare neuro-ophthalmical disorder that affects children more often than adults. Opsoclonus is characterised by involuntary, irregular, but conjugate saccadic eye movements either multidirectional or horizontal (“ocular flutter”) precipitated by change of fixation.¹ Pathophysiologically, a disordered interaction of “burst” and “omnipause” cells located in the brain stem has been suggested.² The associated myoclonus is typically exacerbated by muscle activation and predominantly involves the face, limbs, and trunk. Among various aetiologies of OMS, paraneoplastic, paraviral or idiopathic encephalitis are the most common causes and an autoimmune mediated brain stem dysfunction is the suggested underlying pathomechanism.³ Tumour related childhood OMS occurs predominantly in association with neuroblastoma and gangli- onneuroblastoma. Paraneoplastic OMS in adults may evolve with lung, breast or uterus cancer, or neuroblastoma.² Parainfectious and idiopathic forms account for about 50% of cases.¹ As OMS is rare there is no standard treatment recommendation. Some cases resolve spontaneously or with symptomatic treatment including clonazepam, valproic acid, piracetam, thiamine, reserpine, chlormethiazole. ACTH seems to be the treatment of choice in children with paraneoplastic OMS whereas in adult onset OMS the role of immunotherapy is less well established.² Here we report a patient with parainfectious OMS whose symptoms were well controlled with repeated administration of high dose intravenous immunoglobulin (Ig).

Case report

A few days after recovery from flu-like symptoms a 36 year old computer specialist experienced subacute evolution of jerking involving his arms and legs that exacerbated while moving his limbs. His gait became increasingly unsteady. He noticed visual instability and reported severe oscillopsia interfering with reading. He also felt irritable. Neurological examination, performed four weeks after the onset of symptoms showed brief and small amplitude horizontal eye oscillations,

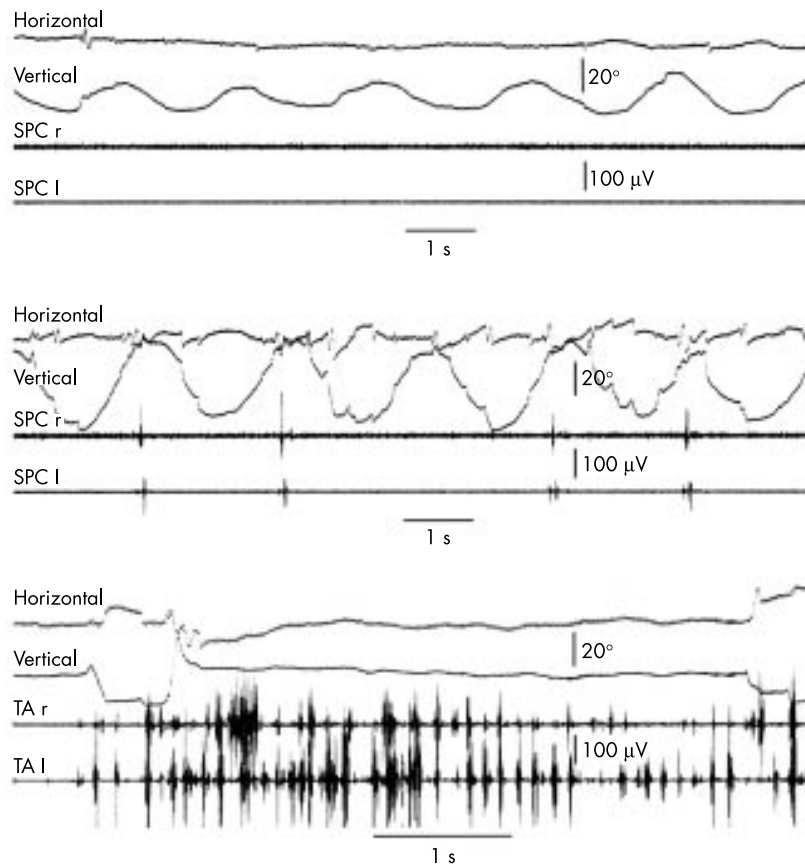


Figure 1 Polygraph recordings of horizontal and vertical eye movements (top two registrations in each panel, AC recording, time constant 1.6 s) from the splenius capitis muscles on the right and left (SPC r, SPC l). Top and middle, both, the frequency of horizontal ocular oscillations and the myoclonus irradiation into the neck muscles depend on the amplitude of vertical eye movements. Bottom, with feet closed while standing (artefact in the electrooculogram), irregular myoclonus occurred simultaneously in the right and left tibialis anterior (TA) muscles without, however, associated myoclonic eye movements (50 Hz artefact in the horizontal eye recording).

sometimes associated with jerky horizontal head movements. Vertical, but not horizontal smooth pursuit eye movements over an increasing angle progressively increased the frequency of both horizontal eye oscillations and jerky head movements. While resting or in action he showed non-rhythmic myoclonic jerks involving neck, arm, and leg muscles. There was moderate dysmetria on finger-nose testing and mild truncal ataxia. The remaining neurological and physical examinations were unremarkable. Routine laboratory testing, including full blood count, electrolytes, liver function tests was normal as were serum electrophoresis and complement studies. The cerebrospinal fluid (CSF) had 48 white cells/ μ l with 84% lymphocytes, 3% monocytes, and 14% plasma cells, a protein content of 63 mg/dl (normal <50 mg/dl) and intrathecal production of IgM and positive oligoclonal bands. Serum titres of antibodies against Purkinje cells (anti-Yo) and neuronal nuclear antigens (anti-Hu/Ri) as well as glutamic acid decarboxylase (anti-GAD) were negative as were antinuclear antibodies (ANA) and antibodies against cytoplasmic granuloocyte antigens (ANCA). Serological tests for infectious pathogens (borrelia burgdorferi, chlamydia, HSV, VZV, EBV, HHV6, HTLV-1) were unremarkable and tumour markers (carcinoembryonic antigen, α fetoprotein, CA 19-9, neuron specific enolase and prostatic acid

phosphatase) were not detectable. Serum and CSF angiotensin converting enzyme activities were not increased. Combined electro-oculography and electromyography showed high frequency conjugate ocular oscillations occasionally associated with myoclonic neck muscle activity (fig 1). Visual, sensory, and motor evoked potentials as well as EEG were normal. Cranial magnetic resonance imaging (MRI) was unremarkable. Radiological studies included normal chest roentgenogram as well as chest and abdominal computed tomography. Abdominal and thyroid ultrasonography were unremarkable. The patient received valproic acid 1800 mg per day and methylprednisolone 500 mg for five consecutive days, followed by oral tapering off. OMS remained unchanged for seven days. Therefore, on hospital day nine a five day course of 30 g/d intravenous Ig was started. Within two days clinical symptoms improved considerably and rapidly. At two month follow up the patient had mild residual opsoclonus and some myoclonic jerking on the left. Repeated administration of 5 \times 30 g intravenous Ig led to a complete clinical recovery with no recurrence of OMS since then.

Comment

The patient reported here developed opsoclonus, myoclonus, and moderate ataxia in close temporal association with a flu-like

illness. Intensive diagnostic assessment revealed no evidence of a remote neoplasm and thus, parainfectious OMS was the most probable diagnosis. As serological tests did not confirm a recent infection, classification as idiopathic OMS would also be appropriate.¹ The disabling symptoms responded dramatically to treatment with high dose intravenous Ig. Resolution of opsoclonus, myoclonus, and cerebellar signs coincided closely with intravenous Ig administration suggesting that intravenous Ig and not the preceding corticosteroid pulse therapy accelerated recovery. However, corticosteroids may be beneficial in some cases and a delayed corticosteroid effect cannot be excluded in our case. Consistent with our observation, a response to intravenous Ig was previously reported in some children and adults with idiopathic or parainfectious OMS, among them some whose symptoms did not respond to corticosteroids.^{3,4} In a recent retrospective analysis, Bataller *et al*⁵ observed a more benign clinical evolution and a better response to immunotherapy in adults with idiopathic as compared with patients with paraneoplastic OMS. In this series 8 of 10 patients with idiopathic OMS were treated with either intravenous Ig (n=4), corticosteroids (n=2), combined intravenous Ig and corticosteroids (n=1), or azathioprine (n=1). Accelerated recovery was observed in all patients treated with intravenous Ig and in one patient after corticosteroids. In contrast, 9 of 10 patients with paraneoplastic OMS consistently improved after tumour removal whereas immunotherapy with intravenous Ig and corticosteroids alone or in combination as well as plasmapheresis had no effect. Altogether, the available evidence suggests that intravenous Ig is an effective treatment in parainfectious and idiopathic OMS and superior to corticosteroids. Intravenous Ig therefore may prove useful as first line treatment. Moreover, a favourable response to intravenous Ig or other immunotherapies may help to differentiate parainfectious or idiopathic OMS from paraneoplastic forms of the syndrome. The effectiveness of intravenous Ig as an immunomodulatory agent supports the assumption that autoimmune pathomechanisms are involved in the emergence of parainfectious and idiopathic OMS. Treatment with intravenous Ig is safe, very rarely hyperviscosity, and consecutive thromboembolic events may complicate its use.³

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Central and peripheral fusiform aneurysms six years after left atrial myxoma resection

Central nervous system embolisation of left atrial myxoma is well documented.¹ The most common neurological sequel is acute cerebral ischaemia secondary to vessel occlusion by tumour.² Delayed neurological complications are much less common and may result from tumour recurrence with embolisation, progressive vascular stenosis, aneurysm formation with subsequent rupture, or parenchymal metastasis.² We report the occurrence of multiple myxomatous aneurysms in a patient six years after resection of a left atrial myxoma who was experiencing transient ischaemic attacks in the same distribution as the largest aneurysms. These lesions included bilateral fusiform aneurysms of the superior cerebellar and posterior cerebral arteries.

Case report

A 60 year old woman had a two week history of progressive occipital headache, intermittent visual changes, right facial pain, and imbalance. On examination, she had mild left upper and lower extremity weakness and mild cerebellar asymmetry. The patient reported a history of left atrial myxoma resection six years before presentation. Atherosclerotic risk factors included remote tobacco use and raised serum cholesterol. Pertinent drug treatment included fluvastatin and clopidogrel.

Magnetic resonance imaging (MRI) of the brain suggested aneurysms of the superior cerebellar arteries or posterior cerebral arteries. The MRI also revealed areas of previous infarction in multiple vascular distributions including the left superior cerebellar artery and both posterior cerebral arteries. Digital subtraction angiography showed large irregular fusiform aneurysms of the proximal superior cerebellar arteries (fig 1A). Fusiform dilatation of the P1 segment of the right posterior cerebral artery and the P2 segment of the left posterior cerebral artery were also noted. Small peripheral fusiform aneurysms were identified in multiple vascular territories including the right anterior cerebral artery territory and both middle cerebral artery distributions (fig 1B). The angiographic appearance of the aneurysms was not specific and the differential diagnosis included an infectious (bacterial or fungal) or neoplastic aetiology (myxoma, choriocarcinoma), connective tissue disorders (Ehlers–Danlos syndrome, Marfan's syndrome), and neurocutaneous syndromes (for example, neurofibromatosis type 1). There were no branch vessel occlusions. There was no evidence of atherosclerotic disease in the head or neck and no radiographic evidence of myxoma recurrence in the heart.

A right pterional craniotomy was undertaken and showed grossly abnormal superior cerebellar arteries. The right superior cerebellar artery was more involved than the left and had a markedly thickened, whitish, partially calcified wall. No component of the aneurysm was suitable for clipping. The superior cerebellar arteries were reinforced with a cotton wrap before closure. The risk of obtaining a pathological specimen without significant bleeding complications was felt to be too high. Given the patient's history of myxoma resection and lack of clinical or objective evidence for an alternate aetiology, the aneurysms were felt to be secondary to remote myxoma embolisation.

Discussion

Cardiac myxomas account for more than 50% of primary cardiac neoplasms, with over 70%

occurring in the left atrium.³ Up to 45% of left atrial myxomas embolise systemically, and as many as half involve the cerebral vasculature.¹ Neurological symptoms attributable to cardiac myxoma can be categorised as acute or delayed. In the acute setting, tumour embolisation with branch vessel stenosis or occlusion resulting in cerebral ischaemia is the proposed mechanism. It is more common for neurological symptoms related to cardiac myxoma to precede the diagnosis.² In a Mayo Clinic series of 40 patients with atrial myxoma, 10 (25%) experienced neurological symptoms at the time of diagnosis. Thirty five of these patients were followed for 12 to 235 months: one patient (3%) had a probable delayed neurological complication.

There are several case reports of delayed neurological symptoms related to cerebral myxomatous embolisation, ranging between one and eight years from initial diagnosis and reflecting a unique underlying neuropathology.⁴ Delayed imaging findings include fusiform and saccular aneurysms, vessel irregularity with stenosis, and intraxial metastasis.^{4,5,6,7} Myxomatous aneurysms can rupture, but the risk of this has not been quantified.⁵ Intracranial myxomatous aneurysms occur with the highest frequency in the peripheral arterial branches of the anterior and middle cerebral artery distribution, although central fusiform aneurysms have been reported.³ Saccular aneurysms are a less common feature of myxomatous emboli.

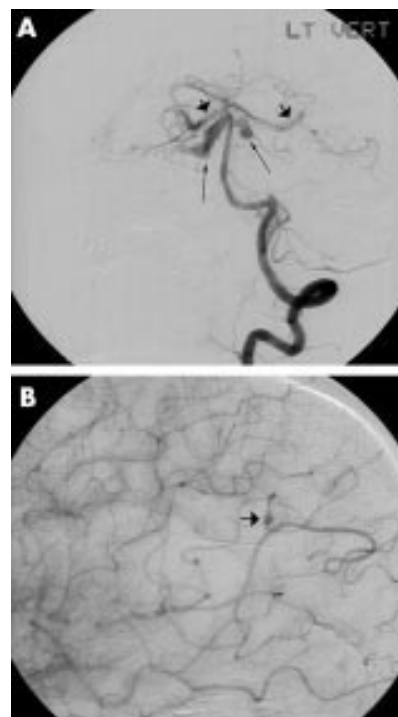


Figure 1 Digital subtraction angiography of the cerebral vessels in a 60 year old woman six years after left atrial myxoma resection. (A) Left vertebral artery arteriogram, transfacial view, shows large irregular fusiform aneurysms of the proximal superior cerebellar arteries bilaterally (long arrows). Involvement of the P1 segment of the right posterior cerebral artery and the more distal left posterior cerebral artery is noted (short arrows). (B) Right internal carotid arteriogram, magnified lateral view, shows a peripheral fusiform aneurysm of a distal posterior right middle cerebral artery branch (short arrow).

Thromboembolic events emanating from an aneurysm can result in transient ischaemic attacks, which are radiographically occult. Haemodynamically significant vessel stenosis can cause intermittent ischaemic symptoms. Parenchymal and intraventricular metastases, although uncommon, result in symptoms referable to the area of brain involved and the mass effect they create.

Two theories on the pathophysiology of myxomatous aneurysms have been widely accepted. The original theory suggested that postembolic vascular damage and subsequent scarring resulted in an alteration of flow dynamics that promoted aneurysm formation.³ In later studies, histopathological evidence showed active invasion of the vascular wall by viable tumour emboli.^{4,5,6} The ensuing inflammation and fibrosis weaken the elastic media, resulting in erosion of the arterial wall and subsequent aneurysm formation. This process can be slowly progressive and may help explain why patients with myxomatous aneurysms present several years after resection of the primary tumour.

The current case highlights the occurrence of neurological symptoms at a time remote from the initial diagnosis of cardiac myxoma. The development of delayed symptoms is unusual but is a well documented phenomenon and should be considered in patients with an appropriate history. Although we cannot prove the relation between the symptoms and the aneurysms, we felt it compelling that our patient's transient ischaemic attacks were concordant with the areas of brain supplied by the largest aneurysms. Moreover, the right superior cerebellar artery aneurysm was in close proximity to the right trigeminal nerve and could have played a role in her right facial pain. The patient has been stable on maximal medical management.

This case also illustrates the diagnostic value of conventional angiography in detecting vascular neuropathology related to myxomatous embolisation. Although the larger, posterior circulation aneurysms were suspected on MRI, and might have been detected on magnetic resonance or computed tomographic angiography (MRA, CTA), it is less likely that alternate vascular imaging studies would have detected multiple small peripheral aneurysms that are more typical of this disease. Several of the peripheral aneurysms were detectable only by delayed washout of contrast relative to the arterial phase, a finding that cannot be appreciated on MRA or CTA. Because small peripheral aneurysms are more frequent, the most sensitive vascular imaging study should be used for their detection.

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Anti-titin antibodies are not associated with a specific thymoma histology

After the first description of antibodies to titin in patients with thymoma associated myasthenia gravis in 1990, this finding was independently confirmed and the main immunogenic region of titin (mgt30) identified.¹ This 30 kDa part of titin is now also commercially available as antigen for detecting anti-titin antibodies. Furthermore, in a series of 276 patients, we could confirm the clinical usefulness of measuring anti-titin antibodies for predicting the presence of a thymic epithelial tumour in patients with myasthenia gravis that was significantly better than the conventional anti-striational antibody test.² This has been confirmed independently, at least for patients under the age of 60.³ As Marx *et al* had reported a high titin epitope expression in cortical thymoma and well differentiated thymic carcinoma,⁴ we were now interested whether there was a correlation between anti-titin antibodies and the histology of the thymic epithelial tumour according to the Müller-Hermelink classification,⁵ especially whether it might be possible to identify the presence of a carcinoma.

A total of 28 myasthenia gravis patients with pairs of thymoma histology and serum were analysed, 13 from the 1997 study,² an additional nine from the University of Barcelona (II), five from the Case Western University Cleveland (HK), and one additional patient from the University of Tübingen (NS). No thymoma patients without myasthenia gravis were analysed. As 10 of the first 14 patients were anti-mgt30 antibodies positive using ELISA² but 11 using western blot, we used western blot for defining the antibody status. Thymoma histology was classified according to the criteria of Müller-Hermelink⁵ into cortical, medullary or mixed thymoma, or a well differentiated thymic carcinoma. A statistical analysis of the correlation was performed using SAS software (Fisher's exact test).

There was no significant correlation nor a trend for an association between anti-titin antibodies and thymoma histology. Of the six well differentiated thymic carcinomas, three serum samples (50%) were anti-titin positive, as were 11 of the 16 cortical thymomas (69%). All four mixed thymomas were antibody positive.

The presence of anti-titin antibodies may point towards an underlying thymoma.^{1–3} If consistent with radiology, thymectomy is performed also to exclude the presence of an infiltrating thymic carcinoma. As our data now show, titin antibodies are not correlated with thymoma histology and therefore do not add to the presurgical information on the tumour. Why there is no correlation between antibodies and thymoma histology, whether this is attributable to expression of the immunogenic titin epitope in all thymomas or elsewhere independent of the thymoma type, must remain speculation.

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