Opsoclonus as a presenting symptom in thymic carcinoma

Opsoclonus is a rare paraneoplastic syndrome accompanying some malignant tumours (carcinoma of the lung, uterus, breast, and neuroblastoma in children). We report a patient with opsoclonus combined with ataxia preceding the diagnosis of thymic carcinoma.

A 65 year old man complained of dizziness and difficulties with walking before admission to hospital. This was followed by episodes of nocturnal sweating and diffuse abdominal pain. Medical, neurological and family history were normal. On admission examination showed the patient to be in a good general condition. The neurological examination revealed normal consciousness; speech and orientation for time and place were also normal. The most relevant finding was the patient's eye movements; there were rapid, chaotic and conjugate saccades of the eyes in all directions, considerably exacerbated by attempts to fix the gaze. The pupils were normal in size, reactive to light and accommodation and the funduscopy showed normal optic discs. The examination of the rest of the cranial nerves was normal. Myoclonic seizures were not seen. Superficial and deep reflex testing did not reveal any abnormalities.

Motor and sensory examinations were normal except for his gait which showed mild trunk ataxia. Finger-nose test, heel-to-knee and rapid alternating manoeuvres were within normal limits. The values of the laboratory tests including blood glucose, electrolytes, urea, uric acid, bilirubin, creatinine, serum albumin and globulin, calcium, phosphate, SGOT, alkaline phosphatase, ESR, haemoglobin and leukocytes count were within normal limits. Beta-human chorionic gonadotropin in the blood, alpha-feto-protein and 5-hydroxy-indol acetic acid in the urine were also within normal limits. The level of blood immunoglobulins was normal. Serological tests for syphilis were negative. The chest radiograph on admission revealed two mediastinal masses. Computerised tomography (CT) of the chest showed two masses in the right anterior mediastinal space, one of them attached to the pleura. Electroencephalogram, ECG, skull radiograph, thyroid and liver scans and two CT scans of the brain were within normal limits. Lumbar puncture showed normal CSF pressure. A CSF analysis for total protein, glucose, chloride and cell count was normal. The auditory brain stem evoked potentials. Bone biopsy and bone marrow did not reveal any malignant cells. The Tensilon test was negative.

One month after admission the patient had a right anterior mediastinostomy for biopsy of the masses. The histology revealed mixed thymic carcinoma (lymphoepithelioma type, poorly differentiated squamous cell carcinoma) with pleural metastases. The patient was treated with a combination chemotherapy regime which is used in the treatment of malignant thymoma. Three weeks later there was a further deterioration in the patient's general condition. Chest radiograph showed no change and CT scan of the brain was within normal limits. Chemotherapy treatment was continued with no subjective or objective change.

Following the failure of chemotherapy, the patient was treated with radiotherapy but with no improvement. The patient was discharged, but readmitted again after two months

for marked general and neurological deterioration, with severe ataxia, bilateral dysmetria, opsoclonus and chest pains. A trial treatment with clonazepam 2 mg/day orally for one week had no effect on the opsoclonus or ataxia, and this treatment was discontinued. His general condition deteriorated further and he died nine months after the onset of the symptoms of the disease. Permission for necropsy was refused.

Opsoclonus may occur in encephalitis and as a remote effect of systemic malignancy, such as neuroblastoma in children, carcinoma of the lung, breast, uterus and thyroid.¹ This phenomenon has also been found in cases of demyelinating disease, brain glioblastoma, thalamic haemorrhage, hydrocephalus, Friedreich's ataxia, intoxication with lithium and chlordecone and in non-ketotic hyperglycaemic states.² In our patient, the opsoclonus was accompanied by truncal and limb ataxia. These symptoms were the first manifestation of carcinoma of the thymus. The association of opsoclonus and ataxia with thymic carcinoma has not been previously reported. The site of the lesion that causes opsoclonus remains unclear. The association of myoclonus and a cerebellar syndrome in a few cases, implies a lesion in the dentate nuclei area or in the connection between the inferior olive, red nuclei and the dentate nuclei.³ However, there is no evidence that either a lesion in the dentate nuclei or in the red nuclei produces opsoclonus by itself.

In a few cases of opsoclonus and systemic carcinoma, the necropsy studies reported only inconsistent pathological findings of poor localising value, such as a mild loss of Purkinje cells, a peridentatal gliosis or slight loss of myelin in the cerebellum.² In other patients, perivascular infiltrates and gliosis in the pons, midbrain and hypothalamus were described. In a few patients necropsy studies had no demonstrable pathology in the brain or cerebellum.

The pathophysiological mechanisms of the lesions that cause opsoclonus remain unknown. There are theories that viral infection of the CNS (as in cases of opsoclonus in patients with encephalitis) or immunological dysfunction (as in demyelinating disease or in malignant disease) may be involved in the process. In support of the immunological theory are the elevated levels of CSF-IgG in some cases,⁴ the effective response to corticosteroid therapy in others⁵ and the presence of specific antibodies to the Purkinje cells that have been found in two patients with systemic malignancy.^{6,7} In opsoclonus caused by a paraneoplastic syndrome, neurological signs fail to improve after treatment. In certain cases, clonazepam and thiamine were effective.² In our case, treatment with corticosteroids and clonazepam did not change or improve the evolution of the neurological signs.

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Standard neurodiagnostic tests in Sydenham's chorea

The recent resurgence of acute rheumatic fever in the United States¹ has served to focus attention on the procedures for diagnosing Sydenham's chorea (SC). No single test is available for this purpose and it is widely recognised that a rheumatic aetiology often cannot be established with certainty at the time of presentation of chorea.² In the era when acute rheumatic fever in the developed world was sufficiently common for large series of patients with SC to be collected, the standard neurodiagnostic tests were limited to electroencephalography (EEG) and analysis of cerebrospinal fluid (CSF) for total protein and white cell count.^{2,3} Furthermore, few alternative causes of chorea were sought. We report here the results of a series of contemporary neurodiagnostic tests in a prospective study of SC.

The subject group comprised five consecutive cases seen by one of the authors at Kalafong Hospital over a period of three years (January 1985 to December 1987). Kalafong is a general hospital on the outskirts of Pretoria serving the black community. All the patients were females, their ages ranging from seven to 16 years. Serologic evidence of recent streptococcal infection (antistreptolysin-O titre > 200 Todd units, or antistreptokinase titre > 1:1280, or both) was present in one patient. Four patients had clinical or echocardiographic signs of valvular heart disease.

Each patient fulfilled the following criteria, anamnestic details being provided, or corroborated, by a parent or close relative. 1) Involuntary movements typical of chorea developing insidiously in the setting of previously good health. 2) Alert mental state. 3) Absence within the family of a similar, but progressively disabling disorder. 4) Negative history for drug ingestion preceding, or concurrent with, the onset of chorea. 5) Normal test values for thyroid, renal and hepatic function. 6) Normal full blood count and red cell morphology. 7) Normal plasma glucose and serum sodium, calcium and phosphate. 8) Absence of Kayser-Fleischer rings, normal serum copper and caeruloplasmin. 9) Negative tests for rheumatoid factor, antinuclear antibodies, neurosyphilis (specific and non-specific). 10) Negative pregnancy test (where indicated).

Cerebrospinal fluid analysis, contrast enhanced computed tomography (CT) brain scan and upper (median nerve) and lower limb (tibial nerve) cortical somatosensory evoked potentials (SEPs) were normal in all

five patients. The EEG showed excess slow wave activity, of varied degree, in every case (table).

An abnormal EEG occurs frequently in SC. Diffuse slowing of spontaneous rhythms is the commonest reported change, with an incidence of between 55 and 87 per cent.³ Its occurrence in all five of the patients in this series may reflect the fact that each exhibited disturbed behaviour at the time of study. Behavioural disorders occur frequently in SC² and furnish an important diagnostic clue. They may be subtle and overlooked and distractibility or dysphoria attributed to chorea per se.

The absence of pathological change on CT brain scan has been a constant finding to date and is consistent with the poverty of lesions seen at autopsy.

We are not aware of a published account documenting a series of cases of SC, SEP recordings or analysis of CSF for oligoclonal immunoglobulin (Ig) G bands. It is generally accepted that value for CSF total protein and white cell count in SC are normal,⁴ although the evidence for this is not well documented. Our findings substantiate this traditional doctrine. The absence of oligoclonal bands is somewhat at variance with the result of an apparent selective increase in CSF IgG reported previously.⁵ In this case, however, the evidence for local CSF IgG synthesis was based on an elevated IgG/total protein ratio where spuriously high values may be found when, as happened in that patient, there exists an abnormally high serum IgG. The detection of oligoclonal bands is an accurate method for demonstrating intrathecal synthesis of IgG. The negative result in all of our patients tested argues against a primarily antibody mediated pathologic immune reaction within the central nervous system being responsible for SC.^{6,7}

What role cortical SEP results may have in the differential diagnosis of chorea has yet to be determined. Our findings differ from those in a recent report of a single case of SC in which central sensory conduction time was prolonged.⁸ However, this patient exhibited psychomotor retardation, tonic gaze deviation, facial weakness, hyperactive deep tendon reflexes and the plantar response was extensor, all of which are atypical signs for SC.² Normal results in SC stand in contrast to the situation in Huntington's disease, where the early cortical components are either reduced in size or absent.⁹ This disparity may be explained by differences in the pathologic anatomy of the two diseases. Cortical SEPs also have been reported to reveal abnormalities in patients with Wilson's disease,¹⁰ whereas results in benign hereditary chorea⁹

and chorea gravidarum (personal observations) have been normal.

The results of this study emphasise that EEG abnormalities and associated behavioural disturbances are frequent concomitants to chorea in patients with SC. While clinical features remain the cornerstone in diagnosing SC, our experience suggests that the stereotyped pattern of results may allow standard neurodiagnostic tests to be of some discriminatory value.

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MATTERS ARISING

Outpatient referrals

I was astonished to read that among 7836 successive new outpatient referrals analysed by G D Perkin,¹ that "conversion hysteria" with 297 examples in ten years was number six in the top twenty of his diagnoses and constituted 3.8% of the total. Moreover, conversion hysteria was twice as common as either Parkinson's or post traumatic syndrome and almost three times as common as depression. In my experience, depression is a very common symptom and presents in many guises often with somatic symptoms. Conversion hysteria is, by contrast, a very rare disorder and I do not think that I make this diagnosis more than once or twice a year in the whole of my clinical practice. Does Dr Perkin have special criteria for the diagnosis of conversion hysteria or is his outpatient practice biased heavily by referrals from psychiatric colleagues?

I was also surprised that no diagnosis was made in 26.5% of patients—surely an unusually high percentage. I should have thought that 5% would be nearer the mark. I recognise that in an outpatient clinic one may make an inaccurate diagnosis but I do not think that one should make no diagnosis at all in more than a quarter of the patients.

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- 1 Perkin GD. An analysis of 7836 successive new outpatient referrals. *J Neurol Neurosurg Psychiatry* 1989;52:447-8.

Dr Perkin replies:

The criteria that I use for the diagnosis of conversion hysteria are the presence of physical signs which by their nature can only be explained on the basis of an elaborated disability on the part of the patient. I would disagree that the condition is rare. The cases that I discussed were seldom, if ever, referred by the psychiatrists. They appear to share Dr Niemann's view about the scarcity of the problem. I have analysed some of this data in greater detail elsewhere,¹ where, I found that approximately half the patients with features of conversion hysteria had the additional characteristics of Briquet's syndrome. That particular syndrome with or without evidence of conversion hysteria has been found remarkably frequently in those patients who are frequent attenders of medical outpatient clinics.

I find Dr Niemann's use of the word "should" in the last but one line of his comment, a curious one. It almost suggests a compulsive need on the part of the neurologist to make a diagnosis in his patients. Indeed that compulsive need, I suspect, often produces spurious diagnoses which may possibly help the doctor but do little to assist the patient. It maybe that all patients who develop giddiness on turning their head have vertebro-basilar insufficiency. I rather doubt it and because of this doubt, this would be one category of patients that I would leave undiagnosed in many circumstances. If, on

Table Results of neurodiagnostic tests

Case	Age (y)	Duration of chorea (mo)	EEG	CSF		
				White cells ($\times 10^6/L$)	Total # protein (g/L)	Oligoclonal μ IgG bands
1	7	1/4	Diffuse excess theta	1*	0.10	Neg
2	12	1/4	Excess theta with posterior dominance	0	0.19	Neg
3	11	3	Excess theta with right dominance	3*	0.22	Neg
4	16	9	Diffuse excess theta	0	0.23	Neg
5	13	12	Diffuse delta and excess theta	0	0.13	Neg

95 per cent reference range (black adults) 0.10 to 0.50 g/L.

μ Two or more bands, not present in serum, identification by agar gel electrophoresis with silver stain.

* Lymphocytes.

Neg = Negative.