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 woman 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 examination showed the patient to be in a good general condition. The neurological examination revealed normal consciousness; speech and oromotor function were 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 exaggerated by atropine. The Vести-vestibular system was not involved. Superficial and deep reflex testing did not reveal any abnormalities.

Motor and sensory examinations were normal except for his gait which showed mild truncal 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 leucocytes 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. Tensilon test was positive. The chest X-rays revealed two mediastinal masses. Computerised tomography (CT) of the chest showed two masses in the right anterior mediastinal space which were attached to the pericardium. 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, 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 Tension test was negative.

One month after admission the patient had a right anterior mediastinotomy 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 six weeks 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 was observed in waxing and waning cases of demyelinating disease, brain glioblastoma, thalamic haemorrhage, hydrocephalus, Friedreich's ataxia, intoxication with lithium and chlordecone and in several 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 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 that the dentate and the 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 peridendal giosis or slight loss of myelin in the cerebellum.4 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. The role of antibodies that have affinity with 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,5 the effective response to corticosteroid therapy in others6 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.7 In our case, treatment with corticosteroids and clonazepam did not change or improve the evolution of the neurological signs.

M SCHWARTZ
B SHARP
Department of Neurology,
Bnai Zion Medical Center,
Faculty of Medicine, Technion, Haifa
and
ZIDAN
Department of Oncology,
Rambam University Hospital,
Haifa, Israel


Standard neurodiagnostic tests in Sydenham's chorea

The recent resurgence of acute rheumatic fever in the United States 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 agreed that a rheumatic aetiology often cannot be established with certainty before the time of presentation of chorea.1 In the era when acute rheumatic fever in the developed world was sufficiently common for large numbers 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 Futhermore, few definitive causative antibodies 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 Todt units, or antistreptokinase titre of 1:100) was sought 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 unit of a genetically progressive disabling disorder. 4) Negative history for drug ingestion preceding, or concurrent with, the onset of chorea. 5) Normal tests 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 ceruloplasmin. 9) Negative tests for rheumatoid factor, anti-nuclear antibodies, neureyphilis (specific and non-specific). 10) Negative pregnancy tests (where indicated).

Cerebrospinal fluid analysis, contrast enhanced computed tomography (CT) brain scan and upper (median nerve) and lower limb (tibial nerve) somatosensory evoked potentials (SEP)s 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 activity, in this respect, is the commonest reported change, with an incidence of between 55 and 87 per cent. 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 SC, 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 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, 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 results of an apparent selective increase in CSF IgG reported previously. 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.

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. 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. Normal results in SC stand in contrast to the situation in Huntington's disease, where the early cortical components are either reduced or absent. 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, whereas results in benign hereditary chorea and chorea gravidarum (personal observations) have been normal.

The results of this study emphasize 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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R F GLEDHILL
Division of Neurology,
Department of Internal Medicine,
University of Pretoria and Kalafong Hospital, 
South Africa
PD THOMPSON
University Department of Clinical Neurology, 
Institute of Neurology, 
Queen Square, London

Correspondence to: Dr RF Gledhill, Neurosciences Department, Rashid Hospital, PO Box 4545, Dubai, United Arab Emirates

| Table Results of neurodiagnostic tests
<table>
<thead>
<tr>
<th>Case</th>
<th>Age (y)</th>
<th>Duration of chorea (mo)</th>
<th>EEG</th>
<th>CSF</th>
<th>White cells (× 10^9/L)</th>
<th>Total # protein (g/L)</th>
<th>Oligoclonal IgG bands</th>
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<tr>
<td>1</td>
<td>7</td>
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<td>Diffuse excess theta</td>
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<td>2</td>
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</tr>
<tr>
<td>3</td>
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<td>3</td>
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<tr>
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<td>Diffuse delta and excess theta</td>
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<td>0</td>
<td>0.13</td>
<td>Neg</td>
</tr>
</tbody>
</table>

*95 per cent reference range (black adults) 0.10 to 0.90 g/L.
*Two or more bands, not present in serum, identification by agar gel electrophoresis with silver stain.
Neg = Negative.

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, 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 frequent 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 may be 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