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### Bilateral ptosis, ataxia and areflexia—a variant of Fisher's Syndrome

Since the original description of the benign neurological syndrome of ophthalmoplegia, ataxia and areflexia (SOAA) by Fisher in 1956,<sup>1</sup> there has been a continuing debate as to whether the syndrome represents a variant of Guillain-Barré syndrome<sup>2</sup> or a form of brainstem encephalitis.<sup>3</sup> Some authors now prefer the hypothesis that SOAA is a unique syndrome combining central and peripheral involvement.<sup>4</sup>

A 56 year old male was admitted to University Hospital with a history of distal numbness in all four limbs, unsteadiness for four days, and severe bilateral ptosis for one day. He experienced a "flu-like" illness one week before admission. On examination, he was alert and orientated. Nasal tone in his speech was noted. Palpebral fissures were symmetrical and measured 3 mm on resting and 5 mm on maximal opening by using frontal muscles to compensate for the weakness (fig a, b). No limitation of extraocular movement in any direction could be detected. The pupils were 5 mm in diameter on both sides and reacted normally to light. There was no facial weakness or difficulty in swallowing. Normal convergence and Bell's phenomenon were easily demonstrated. Muscle power to all four limbs was normal. There was marked ataxia on walking and Romberg's sign was positive. Heel-to-shin test was poorly performed. Fin-

ger-to-nose and pronation-supination tests were mildly impaired. There was a generalised areflexia of the limbs. Sensory examination revealed a decrease in vibration and joint position senses in the lower limbs.

Laboratory investigations: CSF examination on the sixth day after onset showed a protein level of 90 mg/dl without pleocytosis. Nerve conduction studies (NCS) on the same day revealed absence of sensory action potential (SAP) in median and ulnar nerves. Somatosensory evoked potentials (SSEP) on the ninth day by stimulation of the median and peroneal nerves revealed prolonged brachial plexus potentials and scalp SSEP from the upper to the lower limbs. Brain stem auditory evoked potentials and patterned visual evoked potentials were all within normal limits. Cranial CT and EEG were normal. No improvement of ptosis occurred with a standard Tensilon test.

Only supportive treatment was given during admission to hospital. The ptosis started to improve four days after admission and completely resolved on the tenth day. Ataxic gait gradually improved during the same period of time. Only areflexia was recorded at four weeks. Follow up examination revealed no residual symptoms or deficit 11 months after discharge. Repeat NCS and SSEP studies showed marked improvement.

Among the three cardinal features, ophthalmological signs are so varied that they have received a lot of attention in the literature.<sup>5</sup> There have been a variety of clinical presentations documented which raise the possibility that the ocular problems may be supranuclear in origin, notably, a discrepancy between mild ptosis and marked external ophthalmoplegia.<sup>1,5</sup> This patient, however, presented with isolated and symmetrical ptosis of the upper eyelid of a severe degree without limitation of extraocular movements. Eyelid ptosis is usually explained by weakness of the levator palpebrae superioris muscle due to an oculomotor nerve lesion, or by weakness of Muller's muscle secondary to involvement of sympathetic innervation, or by intrinsic disorders of the lids and their musculature. Two other possible, but less well-known causes might be "cerebral"<sup>6</sup> and "midbrain"<sup>7</sup> ptosis. The former may be due to failure of some control of elevation of the eyelids exerted cortically.<sup>6</sup>

The latter form of ptosis may be due to the anatomical arrangement of neurons in the caudal midline of the third nerve nucleus which supply the levators of the eyelids. Clinical observation in this patient could not be explained by the involvement of infranuclear mechanism of oculomotor nerves. Transient, symmetrical ptosis in this patient was either due to a self-limiting and inflammatory response in the peri-aqueductal area as proposed by Meienberg<sup>5</sup> or to a failure of a corticobulbar influence.

Prolongation of neck or scalp SSEP latencies in this patient with abnormal NCS were in agreement with a sensory neuropathy involving large myelinated fibres as suggested by Guiloff.<sup>8</sup> It is likely that sensory polyradiculopathy plays an important role in the ataxia and areflexia of this syndrome.<sup>2</sup> Based on neuro-ophthalmological observations and electrophysiological results in this patient, combined central and peripheral involvement is probable. The clinical manifestations, laboratory findings and clinical course closely resemble those reported cases of SOAA except for the ophthalmological features. Such combinations may be regarded as one of the variations of SOAA.

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Figure Facial appearance of the patient at the time of admission (A and B). A) Bilateral ptosis on resting state. B) Compensatory frontalis muscles contraction on maximal opening.

### Progressive supranuclear palsy as the sole manifestation of systemic Whipple's disease treated with pefloxacin

Oculomasticatory myorhythmia (OMM) with progressive supranuclear oculomotor palsy has been reported only as a cerebral complication of systemic Whipple's disease<sup>1,2</sup> and is thus possibly a unique and pathognomonic movement disorder in this condition. Whipple's disease may be confined to the CNS so that when OMM occurs without symptoms, positive evidence for Whipple's disease may be difficult to find especially when perendoscopic and peroral jejunal biopsy specimens are normal. CSF examination and brain imaging may also be normal. In these circumstances, some authors suggest that cortical brain biopsies have a low sen-

sitivity.<sup>1</sup> We present a case of OMM without symptoms of Whipple's disease and with negative peroral jejunoileal biopsies, which indicates the usefulness of laparotomy for jejunoileal biopsies as an alternative to brain biopsy to confirm Whipple's disease.

A 47 year old woman was admitted in May 1988 in a depressed state. In June 1987 she had noted progressive visual disturbance. Rhythmic elevations of her right upper lip appeared, and later, paroxysmal hypersomnia and considerable weight gain (10 kg). A nine month course of treatment for depression was ineffective and her symptoms and signs progressively deteriorated. Examination on admission showed complete vertical and horizontal ophthalmoplegia with sparing of oculocephalic reflexes (which appeared spontaneously, giving the doll's eyes phenomenon with all movements of the head). Her eyes, face, and proximal part of her limbs were affected by myorhythmia, which consisted of masticatory movements with synchronous adduction of her eyes (convergence) and limbs at about 1 cps. Her soft palate was not involved. Movements also occurred during sleep. Gait disturbance and a slight facial akinesia was noted but no neck rigidity. Her mental state was normal. There was a pseudobulbar type dysarthria but no difficulty in swallowing. No other systemic sign or symptom was recorded; there was no diarrhoea. Her CSF was normal with no PAS positive cells present. EEG, CT, and T1-weighted (DTPA-Gadolinium enhanced) and T2-weighted MRI scans yielded normal results, as did endoscopy and 30 peroral distal and proximal jejunal and ileal biopsies. Erythrocyte sedimentation rate was 35 mm per hour. Schilling's test was 5% (normal range 12-30%), suggesting distal ileal involvement.

A laparotomy was performed and surgical biopsy specimens of the jejunum and mesenteric lymph nodes were taken. Pathological examination showed no jejunal abnormality but PAS positive cells with positive Gram stain in the mesenteric lymph nodes were found, confirming Whipple's disease. Treatment with rifampicin and tetracycline for two months stabilised the disease. Trimethoprim-sulfamethoxazole and chloamphenicol were then given for a further two months. The results of Schilling's test returned to normal but signs and symptoms did not improve. Chloramphenicol had to be withdrawn and was replaced by pefloxacin.

Two and a half years after the onset of treatment there was mild improvement of signs. Masticatory movements remained the same, but the adduction of the eyes had disappeared; the eyes could be displaced to the left and right to 50% and slightly downward but not upward. Unsteadiness of gait, probably due to the supranuclear oculomotor palsy, persisted. Her mental state was largely unaffected (minimal status was 30/30). Her full scale intellectual quotient on the WAIS fell slightly from 92 to 86 then increased to 96 in 1990. An uncontrolled new synchronous movement of flexion extension of the right thigh appeared when she relaxed in bed. Worsening of hypersomnia and appearance of cataplexy required high doses of imipramine which gave partial relief.

Progressive supranuclear palsy is a feature of Steele Richardson Olszewski disease, a degenerative disorder of unknown aetiology and with no known treatment. A supranuclear oculomotor palsy for downgaze is one of the main characteristics of this syndrome, together with axial rigidity and

pseudobulbar palsy. The association of supranuclear gaze paresis with oculomasticatory myorhythmia, however, seems to be pathognomonic of the effects of Whipple's disease on the CNS.<sup>1,2</sup> This led us to perform surgical jejunal and mesenteric lymph node biopsies rather than a brain biopsy despite negative endoscopic and numerous peroral distal jejunal and ileal biopsies. The normality of the CT and MRI scans also supported this decision.

The possibility of brain involvement without systemic manifestation in Whipple's disease should be kept in mind. This necessitates a search for the disease by endoscopic and peroral jejunoileal biopsies in all patients with unexplained supranuclear oculomotor palsy. Despite two single reports of reversible CNS involvement,<sup>4,5</sup> however, the treatment of CNS Whipple's disease has so far been disappointing.<sup>6</sup> The mild improvement in neurological states on pefloxacin was important in our patient but needs further confirmation. Pefloxacin is a quinolone which readily diffuses across the blood-brain barrier (BBB) and is effective against intracellular micro-organisms such as those supposed to be the cause of Whipple's disease. Nevertheless, taking into account the specificity of OMM in the diagnosis of Whipple's disease and the poor efficacy of treatment<sup>6</sup> were we justified in performing a laparotomy to confirm the diagnosis? We think that this condition needs to be formally recognised and confirmed before embarking on such a long and difficult treatment.

Riggs has suggested that incidental use of antibiotics may eradicate gastrointestinal involvement in presymptomatic Whipple's disease but not the meningeal involvement because of their poor BBB diffusion.<sup>7</sup> This may explain the apparently isolated and late CNS involvement. Such a hypothesis considers only the infectious mechanism and does not explain the poor effect of some antibiotics which are well able to cross the BBB. Unlike most infectious diseases, there are no established cases of direct transmission of Whipple's disease from one patient to another, no reproduction of the disease in laboratory animals, and no convincingly specific organisms isolated by culture in

vitro.<sup>8</sup> Whipple's disease is associated with immunodeficiency.<sup>8</sup> Thus intestinal wall macrophages are ineffective in phagocytosing intracellular gram positive bacilli, resulting in inability to eliminate chronic infection.<sup>9</sup> This suggests that Whipple's disease may be considered as a disease of macrophages.<sup>8</sup> The periventricular and periaqueductal distribution of the CNS involvement in Whipple's disease consists of macrophagic infiltration and subependymal nodules. Such a "tumoural" involvement may explain why antibiotics with good BBB diffusion are not effective in this CNS disease.

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### Binswanger's clinical and neuropathological criteria for "Binswanger's disease"

Bennett *et al*<sup>1</sup> have made a timely and critical attempt to standardise the diagnostic criteria for "Binswanger's disease". They have based

their suggestions on current English and French literature. It might be of interest to compare these modern criteria to Binswanger's original description,<sup>2</sup> which had only been available in English in a grossly truncated form.<sup>3</sup>

The table shows the clinical hallmarks

Table Binswanger's clinical and neuropathological criteria for the diagnosis of "Encephalitis subcorticalis chronica progressiva"<sup>2</sup>

#### Clinical criteria: (verbatim from reference 2, page 1184)

the disease begins at the onset of senility (early in the fifties) or in advanced old age (early in the sixties); slow impairment of intellectual capabilities manifesting primarily by the progressive impairment and ultimate loss of the association between cortical sensory and motor areas; most frequently observed are aphasic disturbances (as in the present case), hemianopia or hemianopsia, hemiparesis with loss of the sense of pressure, position or touch; these circumscribed deficits are of a stable character during the fully developed disease and they are combined with the slow and relentless deterioration of intellectual performance; (... until) the patients resemble decerebrate laboratory animals.

#### Neuropathological criteria: (from reference 2, page 1137)

we find a pronounced atrophy of the hemispheric white matter, either restricted to one or more gyri in one brain area or of several hemispheric regions affected with variable severity; these changes are most clearly found in the area of the occipital and temporal lobes, so that the temporal and occipital horn are widened into bag-like cavities, while the anterior portion of the lateral ventricle shows relatively little enlargement and the frontal white matter is almost unaffected by the disease process. The cortex does not show any remarkable macroscopic change apart from a slight narrowing. Invariably, these cases show severe atheroma of the cerebral arteries.