immunocompromise may confer susceptibility to varicella-zoster infection.[10]

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Discordant HLA haplotype segregation in a family with progressive extrinsic ophthalmoplegia and ragged red fibres.

Sir: "Ophthalmoplegia plus" or "Oculocraniosomatic neuromuscular disease" is a complex syndrome that includes a great variety of clinical and pathological manifestations, with characteristic mitochondrial abnormality in muscular tissue.[1,2] Familial cases are very few and a wide spectrum of clinical patterns has been observed in a single family, suggesting that various clinical manifestations must be considered as a different expression of a single genetic defect, but no unequivocal transmission pattern has been found.[3–7]

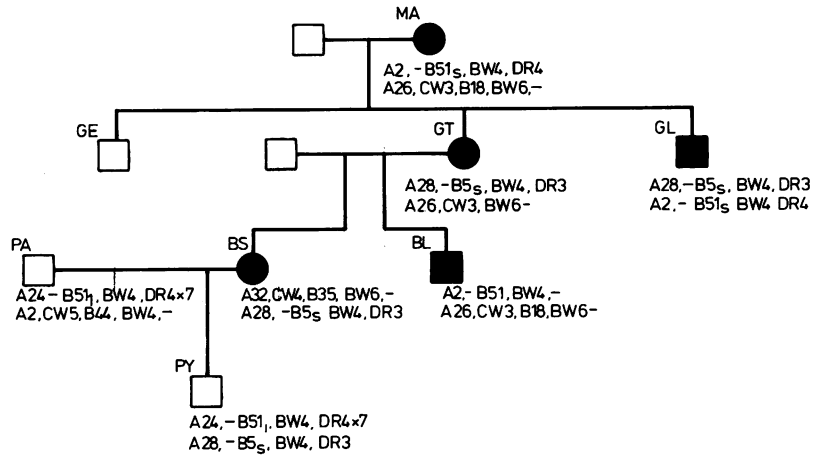

Fig 1 The family pedigree

We have seen a family with five members affected by "ophthalmoplegia plus". The pedigree of this family is shown in fig 1. Patients MA, GT, GL and BS developed the disease in their 3rd decade of life, with similar symptoms: bilateral progressive ptosis and short stature. Muscular strength was normal as well as serum muscular enzymes and EMG. Muscle biopsy performed in patient BS showed the presence of numerous ragged red fibres. Patient BL developed at age of 26 years a severe bilateral ptosis, ophthalmoplegia and signs of severe, generalised muscular weakness. Laboratory and clinical investigations revealed: (a) increased levels of serum lactic and pyruvic acid (both at rest and after ischaemic exercise test); (b) diabetes mellitus; (c) sensory neural hypo-acusia; (d) partial conduction heart block; (e) slight truncal ataxia and cerebellar atrophy on CT scan. Muscle biopsy showed the presence of numerous ragged red fibres. No information was obtained about subject GE. All the other members listed in fig. 1 apparently were healthy.

In this pedegree, "ophthalmoplegia plus" appears to be an autosomal dominant trait: no generation was skipped, no member of the family was affected without having a parent affected, males and females were equally affected. Indeed, the high frequency of disease in children of affected parents (50%) is a criterion for dominant inheritance as opposed to a chance finding.

To investigate the mechanism of inheritance of the disease, we investigated the HLA haplotype segregation of this family. If a gene predisposing to disease, but distinct from the HLA genes, is located in close proximity to the Major Histocompatibility Complex (MHC) within a particular family pedigree, the susceptibility to the disease preferentially segregates with a particular HLA haplotype. This would be true even in the absence of an association between the disease susceptibility and a given HLA antigen. Subjects were typed for HLA-A, B, C, DR specificities by means of the standard cytotoxicity techniques.[8] HLA haplotypes within the family are reported in fig 1. These data do not support an HLA linkage for "ophthalmoplegia plus" in this family, since the segregation of HLA haplotypes is clearly discordant with the disease segregation. Indeed, HLA types in this pedigree showed an unexpected and puzzling concentration of HLA-B5 cross-reacting group antigens (that is $B51_s$, $B51_l$, $B5_s$).[9–11] This finding could suggest an interaction between environmental factors with a particular genome, and may explain the different clinical patterns observed in a same family with a common "disease susceptibility" load. From this, interest rises in HLA typing of both familial and sporadic cases of the disease. The suggestion to go further and to look for a population associated as well as to extend linkage analysis of affected families is only apparently contradictory with the present observation. Clear examples exist in which HLA-population association with a disease suggests tight linkage,[12] but the family studies are conflicting[13] and do not support any linkage.[14] Several explanations can be advanced which might partly account for population-family discrepancy: genetic heterogeneity between familial and non-familial cases of the disease, heterogeneity of aetiology, epistatic

interaction, the presence of important additional non-HLA genetic factors. All these possibilities need to be investigated. Thus, we think that HLA studies in "ophthalmoplegia plus" should be usefully extended to test, in families, the linkage with genes on chromosome 6 other than HLA ones (that is Bf, glyoxalase, phosphoglucomutase polymorphism).

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Post-traumatic tremor and myoclonic jerking

Sir: Andrew *et al*[1] described myoclonic jerking in most of their cases of severe post-traumatic tremor. Patients with severe essential tremor, multiple sclerosis, head trauma and, more rarely, cases of hereditary neuropathy may show what clinically appears to be a combination of tremor and myoclonus. However, we believe that careful analysis may indicate that, in many instances, the jerks are actually an exaggeration of a beat of the on-going tremor. Such occurrence is illustrated by the following patient: a 13-year-old girl who had a head injury two years ago. She was in coma for a few days, but recovered over the following weeks. One year after the accident, neurological examination showed mild mental impairment, truncal ataxia, signs of precocious puberty and gross incoordination of the right arm. A severe, regular tremor of the right upper limb was present upon maintaining the arms outstretched, but sudden and large displacement of the arm, resembling myoclonic jerking often interrupted the rhythm of the tremor. Voluntary movements were greatly hampered by this dyskinesia. Electromyographic recording from the affected muscles revealed that the jerks were due to sudden increments in the amplitude of the EMG bursts, producing the tremor (fig). The patient was treated with propanolol (50 mg per/day) added to valproic acid (800 mg per/day). A marked improvement of the tremor and of motor control of the right arm was observed two weeks after reaching the optimal dosage of propanolol (80 mg daily). Placebo controlled studies showed the real efficacy of the treatment. Interestingly, both drugs were required to maintain control of the tremor.

A certain degree of confusion exists when referring to coarse, severe tremor affecting the limbs, which worsens during action. While English speaking authors often employ the term "red nucleus tremor", Garcin[2] introduced in France the name "hyperkinesie volitionelle" for this movement disorder. However either term fails to portray any useful clue as to the aetiology, pathophysiology, pathology or treatment of this abnormal movement and probably should be discarded. Like Andrew *et al*,[1] one could refer to the type of dyskinesia, that is action tremor, action myoclonus and to the aetiology when this is known, until more precise information about the pathological basis of this tremor is obtained. Pharmacological treatment may obviate the need for stereotaxic surgery in some patients. The combination of drugs acting at different levels of the peripheral and central nervous system seems a promising approach for the treatment of severe postural and action tremor.

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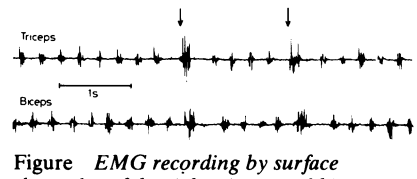

Figure *EMG recording by surface electrodes of the right triceps and biceps muscles while the patient was keeping both arms outstretched. Rhythmical alternating EMG activity at a frequency of 4·5–5 Hz was seen. The arrows point to the bigger EMG bursts which coincided with larger myoclonic jerks observed clinically.*

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