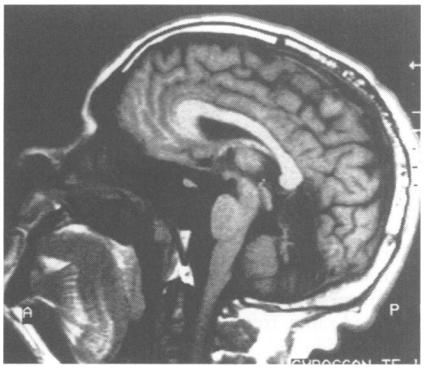

T1 weighted midsagittal MR image of the oldest patient (1) in which a severe cerebellar vermis hypoplasia is evident.

nystagmus, dislocation of the left lens in the vitreous humour, and multiple retinal atrophic lesions were also found.

An IQ of 49 was found on the Wechsler adult intelligence scale.[4] The neurological clinical examination showed cerebellar ataxia with limb and truncal ataxia and ataxic gait; also in this patient, mild hypertonia of the lower limbs, brisk tendon reflexes, and Babinski's sign on the left side were present. Speech was syllabic, poor, and echolalic.

Brain MRI showed a pronounced reduction in size of the vermis and of the cerebellar hemispheres and a mild cerebral cortical atrophy. An EEG was characterised by a slow background activity (6 Hz). No signs of muscular or peripheral nervous system involvement were found on EMG.

Routine blood and urine analysis, lysosomal enzymes, and blood and urinary neurometabolic screening were normal. Karyotype was 46, XY and the molecular analysis for the FMR-1 gene was normal.

These two patients represent a difficult diagnostic problem. They show some common features such as congenital ataxia, nystagmus, mental retardation, and ocular abnormalities (retinal atrophic changes) which make it difficult to include them in one of the groups already proposed.[2] In particular, the Gillespie syndrome is defined by the association of partial aniridia, congenital cerebellar ataxia, and mental retardation.[1] Our patients were both affected by different ocular abnormalities such as retinal atrophic lesions and nystagmus. Additionally, one of them also had keratoconus, for which surgical treatment was needed and the dystrophic changes of the iris reported above only occurred after the surgical manipulation of the eyes.

For these reasons, we think that our patients are a new example of the considerable clinical and genetic heterogeneity which characterise congenital cerebellar ataxia. Also, the family tree of our patients does not allow us to reach a conclusion on the mode of inheritance of the disorder, even if the strict consanguinity of the parents strongly suggests the possibility of an autosomal recessive inheritance.

It seems important to underline that the patients with congenital ataxia described in the previous literature are usually of a much younger age than our two brothers and that the memory loss reported in the brothers could represent the first symptom of a true dementia process, for which monitoring will be necessary in the future. In fact, even if no assessment of the cognitive status was performed before, our patients had presented a stable psychomotor picture before the development of memory loss. Thus memory loss and dementia may represent a long term complication of cerebellar ataxia syndromes.

In conclusion, we suggest that our patients may represent a new combination of congenital cerebellar ataxia, mental retardation, and atrophic retinal lesions. This might constitute a new clinical entity if similar patients are found in the future.

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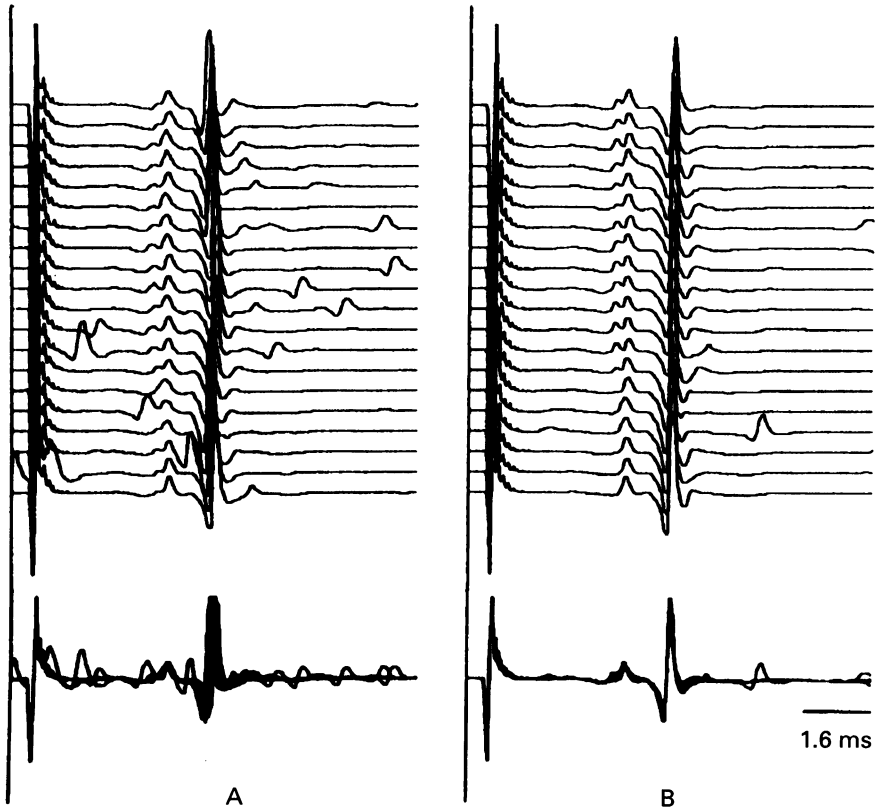
Stimulation single fibre EMG study in a patient with Schwartz-Jampel syndrome

Schwartz-Jampel syndrome is a rare congenital disorder characterised by short stature, oculofacial abnormalities, bone and joint deformities, clinical myotonia, and persistent spontaneous activity. Lehmann-Horn and colleagues[1] showed two muscle membrane abnormalities in Schwartz-Jampel syndrome by voltage clamp and patch clamp techniques. The abnormalities included reduced Cl^- conductance and synchronised late opening of Na^+ channels. These findings indicate that the origin of the spontaneous activity in Schwartz-Jampel syndrome is located in the muscle membrane itself. However, some reports suggested that the origin of the spontaneous activity may be found in the nerve or end plate because curare seems to decrease or abolish these activities. Single fibre EMG (SFEMG) has been widely employed to study the involvement of nerve or neuromuscular transmission. However, difficulty is anticipated during jitter measurement in Schwartz-Jampel syndrome because the spontaneous involuntary activities may be elicited during voluntary muscle contraction. We employed stimulation SFEMG in a patient with Schwartz-Jampel syndrome in an attempt to obtain a more precise assessment of the neuromuscular transmission. We are unaware of any previous application of this technique in Schwartz-Jampel syndrome.

The patient was a 27 year old woman diagnosed as having Schwartz-Jampel syndrome. She presented clinically with short stature, oculofacial abnormalities, joint and skeletal deformities, percussion and action myotonia, and hypoactive deep tendon reflexes. Concentric needle EMG (CNEMG) performed when the patient was 13 years old disclosed spontaneous activity evoked by needle movements and muscular contraction that persisted at rest. Neither curare nor lidocaine suppressed the spontaneous activity, but it was suppressed by local ischaemic exercise. The following electrophysiological studies were done: (1) routine nerve conduction studies, including 3 Hz repetitive ulnar nerve stimulation; (2) routine CNEMG; (3) voluntary SFEMG; (4) stimulation SFEMG. Routine nerve conduction studies, repetitive nerve stimulation, and EMG (Counterpoint, Dantec Corp, Denmark) were performed with concentric needle electrodes (Medelec CN-35, UK) and single fibre electrodes (Medelec SF-25, UK). Stimulation SFEMG was performed at the extensor digitorum communis muscle, which showed spontaneous activities without any weakness according to standard methods. Stimulation frequency was set at 5 Hz.

Routine nerve conduction studies that included measurement of distal latencies, conduction velocities, and amplitudes of compound muscle action potentials (CMAPs) and sensory action potentials in upper and lower limbs were normal. Repetitive ulnar nerve stimulation at 3 Hz showed no significant decrement of amplitude and area of CMAPs. CNEMG showed that needle insertion, mechanical stimulation, and mild muscular contraction induced two types of spontaneous activity which persisted even at rest. One type of spontaneous activity was typical myotonic discharges that showed increment and decrement of firing rates and amplitudes. The maximal firing rate was 100 Hz and the duration of the myotonic run was about 10 seconds. Another type of spontaneous activity was high frequency biphasic simple discharges that did not show variations of frequency and amplitudes, and that had a firing rate of about 50 Hz and a duration of 10–30 seconds. Fibrillations were rarely seen. Precise analysis of motor unit potentials (MUPs) were difficult because of interference from spontaneous activities. Among those MUPs measured, the durations were either normal or slightly increased. Findings by SFEMG during voluntary contraction showed that most of the spontaneous activity consisted of single muscle fibre action potentials, different from complex repetitive discharges (CRDs), and frequent occurrence of extradischarges. Although jitter and fibre density measurements by voluntary SFEMG were difficult to perform due to the influence of spontaneous activities, a few jitter values found measurable without interference by spontaneous activity were normal. On stimulation SFEMG, we were able to perform jitter measurement of 21 units, although spontaneous activity induced by electrical stimulation sometimes interfered. On occasions of interference by spontaneous activity, the jitter seemed to be increased. We therefore measured only the periods without spontaneous activity (figure). The mean jitter values (19·0 μs: normal value at 5 Hz 14·2 (6·6) μs) and individual jitter values were normal except in one end plate.

The electrophysiological studies in the present case of Schwartz-Jampel syndrome are summarised as follows: (*a*) normal nerve conduction studies; (*b*) no abnormal decrement by repetitive nerve stimulation; (*c*) spontaneous activity of typical myotonic discharge and atypical myotonic-like discharge but not CRD, and (*d*) normal neuromuscular transmission. Based on these electro-



Stimulation SFEMG findings with (A) and without (B) interference of spontaneous activities in the same recordings with the same stimulation strength. Jitter was increased with interference of spontaneous activity because of myogenic jitter. The propagation velocity along the muscle fibre changes with activity, particularly when it is irregular such as during spontaneous discharges.

physiological studies, the nerve does not seem to be the origin of spontaneous activities in our patient. Pharmacological studies support this hypothesis. Stimulation SFEMG confirmed a normal neuromuscular transmission in Schwartz-Jampel syndrome, whereas voluntary SFEMG was not helpful due to technical difficulties.

Jitter studies have been performed in three previous reports of Schwartz-Jampel syndrome.[2-4] However, adequate numbers of single fibre action potential pairs for quantitative measurement were not obtained in these studies. Their data showed abnormal jitter with rare blocking. In one case,[4] electrophysiological and morphological studies, including a quantitative end plate measurement, suggested no abnormalities in the nerve and end plate despite the presence of an abnormal jitter. The jitter with voluntary SFEMG can be derived not only from the involvement of nerve and end plate but also from the muscle itself. The so called "myogenic jitter" is usually due to interdischarge interval (IDI) dependent jitter which results from the velocity recovery function (VRF). The main causes of irregularity of IDI is the irregularity of MUP firing and is enhanced by large differences of propagation velocity induced by differences of muscle fibre diameters (for example, hypertrophy of muscle fibres in Schwartz-Jampel syndrome[5]). In instances when spontaneous activity and extradischarges occur, irregularity of IDI may be even more pronounced. Stimulation SFEMG, on the other hand, does not produce IDI dependent jitter because of a steady stimulus frequency. An exercise of caution is needed during jitter measurement should there be spontaneous activity, interference of MUP, or extra discharges as these may change IDI due to supernormal VRF.

The present stimulation SFEMG study, with a careful analysis, showed normal end plate function and strongly supports the hypothesis that the origin of spontaneous activities in our patient with Schwartz-Jampel syndrome is in the muscle itself.

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Apolipoprotein E polymorphism and late onset Alzheimer's disease in Argentina

Several genes and, possibly, environmental factors are involved in the initiation, progression, and severity of Alzheimer's disease (AD). The inheritance of the three common Apolipoprotein E gene (APOE) alleles ($\varepsilon 2$, $\varepsilon 3$, and $\varepsilon 4$) can induce a differential individual susceptibility to Alzheimer's disease. There is a large body of evidence showing that the $\varepsilon 4$ allele of APOE is a genetic risk factor for late onset of Alzheimer's disease in an allele dose dependent manner.[1]

The $\varepsilon 4$ allele frequency varies with the ethnic background as inferred from Japanese and Spanish studies, in which values for the general population are lower than those from the United States, Canada, and northern European countries. The $\varepsilon 4$ frequencies reported range from 0·24 to 0·52 in patients with Alzheimer's disease, 0·06 to 0·18 in controls, and 0·1 to 0·2 in the general population, regardless of the prevalence of Alzheimer's disease in each country (for review see Adroer *et al*[2]).

As little is known about the $\varepsilon 4$ allele frequency and Alzheimer's disease in Hispanic people from South America, we conducted a case-control study in Argentina. The aim of our work was to evaluate the association between the APOE allele genotype and late onset Alzheimer's disease in a population with a heterogeneous genetic background due to the fusion of South American Indian natives with northern and southern European immigrants.

We studied 45 patients (mean age 74·72 (SD 5·5) years, mean age of onset 69·61 (SD 4·7) years) with a diagnosis of probable Alzheimer's disease according to NINCDS-ADRA criteria. Sporadic patients were defined as those with no first or second degree relatives with dementia in at least two generations back.[3] The 45 age matched controls (mean age 71·89 (SD 7·2) years) had a normal neuropsychological evaluation and no history of psychiatric and vascular diseases or alcoholism. In addition, we studied 101 healthy blood donors younger than 50 years (mean age 33·81 (SD 8·5) years) to determine the $\varepsilon 4$ allele frequency in the general population. All the subjects included in the study were Hispanic and at least the second generation of native Argentinians. The study protocol and informed consent from all subjects or their relatives was approved by the institution's ethics committee.

Genomic DNA was obtained from peripheral blood by standard procedures and APOE genotyping was performed using the polymerase chain reaction and HhaI digestion.[4] The $\varepsilon 4$ frequency was calculated by allele counting and the differences between groups tested with Fisher's exact statistics. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated with GraphPad InSat (1994) V2·05a software.

The table shows the genotypes and allele frequencies of each group. The $\varepsilon 4$ allele frequencies for late onset Alzheimer's disease patients and controls were 0·22 and 0·077 respectively. Homozygosity for the $\varepsilon 4$ allele was found in three patients in the Alzheimer's disease group and was absent among controls. Our young population had an $\varepsilon 4$ allele frequency of 0·153 which agrees with the reported frequencies for white populations. We found a statistically significant difference between patients with late onset Alzheimer's disease and controls ($P = 0·015$) but not between the Alzheimer's disease group and the young general population ($P = 0·26$). The OR for our case control study, in the presence of one or two $\varepsilon 4$ alleles, was 3·33 (95% CI 1·204–9·020). Although our results are in general agreement with most reports, we found a rela-