Abnormalities in sensory and mixed evoked potentials in ataxia-telangiectasia

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SUMMARY Electromyography, motor, sensory and mixed nerve conduction velocity, and H reflex were studied in four patients with ataxia-telangiectasia. The earliest and most striking electrophysiological finding was the reduced amplitude of evoked nerve potentials. In the oldest patient, findings suggestive of spinal atrophy and mild reduction of the motor and sensory nerve conduction velocities were found. Reduced amplitude in the evoked nerve potentials can be observed without clinical evidence of peripheral neuropathy. Electrophysiological abnormalities are more severe in older than in young patients. Sural nerve biopsy in one patient showed mild changes: loss of the largest myelinated fibres and demyelination of some fibres. The ratio between maximum conduction velocity of the sural nerve and the diameter of the largest fibres was in the lower limits of the normal range. The resemblance between electrophysiological abnormalities in Friedreich's ataxia and ataxia-telangiectasia is discussed.

Ataxia-telangiectasia is a hereditary syndrome, transmitted by an autosomal recessive gene (Tadjoedin and Fraser, 1965), and described first by Syllaba and Henner (1926) and Louis-Bar (1941). Later this syndrome was separated from other ataxias and considered as a new entity (Boder and Sedgwick, 1957, 1958).

The disease begins in infancy, and the main clinical features are progressive cerebellar ataxia, oculocutaneous telangiectasia, and frequent sinopulmonary infections. Other symptoms which may be observed are choreoathetosis, dysarthria, apraxia of eye movements, characteristic facies, and growth retardation. An immunological defect is constant: dysgammaglobulinaemia with decreased or absent serum IgA (Fireman *et al.*, 1964), atrophic thymus, and impairment of delayed hypersensitivity responses (Peterson *et al.*, 1963).

Necropsy reveals cerebellar degeneration (Boder and Sedgwick, 1957), loss of myelinated nerve fibres in the posterior columns of the spinal cord (Boder and Sedgwick, 1958; Strich, 1966), degenerative changes in the anterior horns, more striking in advanced cases (Aguilar *et al.*, 1968; Goodman *et al.*, 1969), and reduced size of the nerve cells with reduced number of the satellite cells in the dorsal root ganglia (Strich, 1966).

Muscle biopsy has shown signs of denervation atrophy in advanced cases (Engel *et al.*, 1966; Goodman *et al.*, 1969), especially in distal muscles (Strich, 1966). Only moderate changes in Schwann cells have been described in sural nerve biopsies and necropsies (Strich, 1966; Goodman *et al.*, 1969; Gardner and Goodman, 1969).

Electrophysiological studies have not been published extensively. The EMG is described as neurogenic (Goodman *et al.*, 1969), and nerve conduction velocity is reported in the low limits of normality (Dunn *et al.*, 1964) or in normal limits (Karpati *et al.*, 1965).

This paper presents an electrophysiological study in four patients with ataxia-telangiectasia, with special regard to pathological features of nerve action potentials which have been rarely described before.

Methods

Four patients (three males and one female) with ataxia-telangiectasia were studied. Their ages were 8, 7, 12, and 18 years. Cases 3 and 4 were siblings. Case 2 had been studied previously two years before.

The muscles were examined with coaxial needle electrodes. The motor conduction velocity (MCV) was determined in upper and lower limbs. Evoked potentials of muscle were recorded with coaxial

needle, and the nerves were stimulated percutaneously with supramaximal stimuli at two points.

Sensory nerve conduction velocity (SCV) was determined in the median nerve (digits 1 and 2 to wrist) and sural nerve (lateral malleolus of fibula to lower third of posterior part of leg, slightly lateral to midline). The evoked sensory nerve potential (SEP) was recorded with surface electrodes and bipolar technique (20 mm separation between electrodes). Mixed nerve conduction velocity (MxCV) was determined for the wrist-elbow segment, stimulating the median nerve at the wrist. An average of 100 ordinates was used to study the SEP and mixed evoked potential (MxEP). The H reflex was explored in cases 1 and 3. The MCV, SCV, and MxCV and the peak to peak amplitude of the nerve potentials were compared with normal values of healthy subjects of the same age.

In case 1 muscular and nerve biopsies were performed.

Results

Ataxia-telangiectasia was diagnosed with the above-mentioned criteria. The main features are shown in Table 1.

The EMG was normal in cases 1 and 2, not performed in case 3, and abnormal in case 4. Fibrillation, positive sharp waves, and fasciculation were detected in the tibialis anterior muscle, and a neurogenic pattern (high-voltage, long duration, and discrete motor unit activity during full effort) in tibialis anterior and rectus femoris muscles. Case 4 was the most severely affected patient (Table 1), and she is confined to a wheel chair (Fig. 1). This patient presented muscular atrophy and muscular weakness in the lower limbs, equinovarus (Fig. 1), loss of deep sensation in the legs, and kyphoscoliosis.

The MCV was in the lower limits of the normal range in the knee-ankle segment of the peroneal nerve in case 1, and in the elbow-wrist segment of the median nerve in case 4. Terminal motor latency was mildly prolonged in the peroneal and posterior tibial nerves in case 1.

The most interesting data were obtained from study of the SCV and MxCV. Low amplitude of nerve action potentials was the most striking feature. Conduction velocity of the sural nerve was slow in cases 1, 2, and 3; it was not estimated in case 4. Amplitude of the SEP in the sural nerve was severely reduced in two patients. SCV (digit 1-wrist) was normal in two cases, in the low normal range in one, and also slow in one (case 4). SCV (digit 2-wrist) was normal in three cases, and SEP was not evoked in case 4. The amplitude of the SEP (finger-to-wrist segment) was severely reduced in three patients

Table 1 Main features in four cases of ataxia-telangiectasia

Case	1	2	3	4
Age (yr)	8	7	12	18
Family history	—	—	+	+
Consanguinity of parents	—	+	+	+
Age of onset of neurological features (mo)	16	12	12	8
Progressive cerebellar ataxia	+	+	+	+
Diminished or absent deep reflexes	—	—	+	+
Babinski sign	—	—	—	—
Romberg's sign	—	—	—	Not explored. Confined to wheel chair
Loss of deep and/or superficial sensation	—	—	—	+
Muscular atrophy	±	—	—	+
Choreoathetosis	+	+	+	+
Characteristic facies	+	+	+	+
Apraxia of eye movements	+	+	+	+
Fixation nystagmus	+	+	+	+
Dysarthria	+	+	+	+
Mental deficiency	—	—	—	—
Oculocutaneous telangiectasia	+	+	+	+
Frequent sinopulmonary infection	+	+	+	+
Kyphoscoliosis	—	—	—	+
Pes cavus	—	—	—	—
Cardiopathy	—	—	—	—
Delayed hypersensitivity responses	+	+	+	+
Low or absent serum Ig A	+	—	+	+

+ Present.

— Absent.

± Doubtful.

and was in the low-normal range in one (Table 2). MxCV (wrist-to-elbow) was performed only in cases 3 and 4; in both patients it was slow, and the amplitude of the mixed nerve evoked potentials was reduced considerably (Table 2). Patient 2 had been investigated two years before when results of electrophysiological study were normal.

The H reflex was checked and found to be absent in cases 1 and 3.

A biopsy study of the sural nerve in patient 1 showed, essentially, loss of the largest myelinated fibres, and demyelination of some fibres (Fig. 2). The ratio between maximum conduction velocity and diameter of the largest fibres was 3.6 (Fig. 2). Muscle biopsy of the same patient was normal.

Discussion

The most striking feature in our cases of ataxia-telangiectasia is the reduced amplitude of the evoked nerve potentials in upper and lower limbs. Only in the youngest patient (case 2: 7 years of age) was the amplitude of the SEP in the low normal range. However the SCV was normal or, in the oldest patients, moderately reduced. Only slight changes were observed in MCV. Neurogenic patterns were

Fig. 1 Case 4, 18 years of age, confined to a wheel chair. Muscular atrophy and equinovarus.

Table 2 Sensory and mixed nerve conduction velocities in four cases of ataxia-telangiectasia

	Electrophysiological measurements					
	Case 1 (8 yr) male	Case 2 (7 yr) male	Case 3 (12 yr) male	Normal mean (6–12 yr) $\pm$ SD	Case 4 (18 yr) female	Normal mean (17–29 yr) $\pm$ SD
Median nerve (sensory)						
Digit 1–wrist						
SCV	39.6	44.6	34.7	42.4 $\pm$ 4.43	36.0	44.2 $\pm$ 3.28
Amplitude SEP	9.0	24.0	5.0	33.6 $\pm$ 4.92	1.0	40.3 $\pm$ 9.37
Duration SEP	1.3	1.2	1.3	1.06 $\pm$ 0.11	1.5	0.94 $\pm$ 0.10
Digit 2–wrist						
SCV	47.7	47.5	42.6	48.6 $\pm$ 4.72	No	54.6 $\pm$ 4.10
Amplitude SEP	5.0	11.0	2.0	15.6 $\pm$ 3.25	potential	16.3 $\pm$ 4.47
Duration SEP	1.2	1.2	1.3	1.18 $\pm$ 0.16	present	1.06 $\pm$ 0.07
Median nerve (mixed)						
Wrist–elbow						
MxCV			53.7	64.7 $\pm$ 5.30	50.9	71.0 $\pm$ 3.35
Amplitude MxEP			5.0	41.4 $\pm$ 15.60	0.8	33.1 $\pm$ 12.39
Sural nerve						
SCV	39.4	46.6	36.6	54.1 $\pm$ 3.47		
Amplitude SEP	2.5	5.0	2.0	12.4 $\pm$ 4.25		

Conduction velocity is expressed in metres per second, amplitude (peak to peak) in microvolts, and duration of the nerve evoked potentials in milliseconds. Case 2 was explored two years before with normal findings.

MxCV = Mixed nerve conduction velocity (m/s).

MxEP = Evoked action potential of mixed nerve (μ V).

SCV = Sensory nerve conduction velocity (m/s).

SEP = Evoked action potential of sensory nerve (μ V).

only seen in the EMG of the oldest patient (case 4: 18 years of age). These results indicate loss of the large myelinated sensory nerve fibres in all the cases and spinal atrophy in one case.

We think that the electrophysiological abnormalities in our cases of ataxia-telangiectasia are essentially like those described in the apparently 'pure' cases of Friedreich's ataxia. In Friedreich's ataxia the sensory and mixed evoked potentials are very reduced

in amplitude or absent, with normal or moderately reduced SCV, whereas the MCV is normal or slightly slow, and neurogenic EMG patterns are detected only in some of the oldest cases (Preswick, 1968; Downie, 1969; McLeod, 1971; Joong and Halsey, 1973).

The electrophysiological abnormalities detected in ataxia-telangiectasia were less severe than those observed in our cases of Friedreich's ataxia (Cruz Martínez, 1974). In ataxia-telangiectasia, the changes

Fig. 2 Case 1, 8 years of age. Ratio between electrophysiological and histopathological findings. Sural nerve. A: distribution of diameter and number of myelinated fibres. B: sural nerve action potential recorded at the lower third of the leg, posteriorly. The nerve was stimulated at the lateral malleolus. C: focal loss of largest myelinated fibres. The normal ratio between conduction velocity and the diameter of the largest fibres (4.4 ± 0.37) has been published by Behse *et al.* (1975).

were more severe in older than in younger patients, and were detected without clinical evidence of peripheral neuropathy in cases 1, 2, and 3.

Since the electrophysiological abnormalities are similar, a comparison of the pathology in peripheral nerves between both diseases could be interesting. The information in the literature about the pathology of the peripheral nerve in Friedreich's ataxia is well-documented. Sural nerve biopsy shows a selective decrease in large myelinated fibres (Dyck *et al.*, 1968), and the compound action potentials in sural nerve removed at biopsy show a selective reduction in amplitude of the alpha potential (Lambert and Dyck, 1968), with normal or moderately reduced conduction velocity. These results are consistent with degeneration of the large neurones of the dorsal root ganglia. Dyck and Lais (1973) later found segmental demyelination and remyelination in cutaneous nerves in Friedreich's ataxia, probably secondary to axonal atrophy. These findings would explain the electrophysiological abnormalities.

Unfortunately, information about the pathology of the peripheral nerve in ataxia-telangiectasia is not extensive. Loss of myelinated nerve fibres in the posterior columns of the spinal cord, degenerative changes in the anterior horns, and neuromelanosis, reduction of the number of satellite cells and nerve cells smaller than normal in spinal root ganglia, have been described in necropsy studies by Boder and Sedgwick (1958), Strich (1966) and Aguilar *et al.* (1968). In biopsy studies of sural nerve, small

changes are described: absence of demyelination, few enlarged hyperchromatic Schwann cell nuclei, and presence of lipid cytosomes in Schwann cells (Gardner and Goodman, 1969; Goodman *et al.*, 1959). Muscle biopsy is described usually as normal or, in older patients, with findings suggestive of a denervation atrophy (Engel *et al.*, 1966; Gardner and Goodman, 1969).

In the sural nerve biopsy of our case 1, a reduced number of large myelinated fibres and demyelination of some fibres were found. These results would account for the reduction in amplitude of the nerve evoked potentials and the absence of the H reflex which we observed. The ratio between maximum conduction velocity and diameter of the largest fibres was 3.6 (Fig. 2); this value is in the lower part of the normal range (4.4 ± 0.37) published by Behse *et al.* (1975). Normal (or within low limits) ratios between maximum conduction velocity and diameter of the largest fibres have been observed in axonal degeneration (Behse *et al.*, 1975). Other electrophysiological abnormalities, such as normal or slight changes in conduction velocity, have been published previously (Dunn *et al.*, 1964; Goodman *et al.*, 1969), and are similar to our findings. Fasciculation, fibrillation, and reduction in the number of motor units found in case 4 have also been published in long-surviving patients (Goodman *et al.*, 1969).

Although the electrophysiological findings are similar, some clinical and biological features are different between ataxia-telangiectasia and Fried-

reich's ataxia. Cardiopathy, pes cavus, loss of deep sensation, Romberg and Babinski signs are habitual or frequent in Friedreich's ataxia, but not in ataxia-telangiectasia. Impairment of delayed hypersensitivity responses, low or absent serum IgA, and oculocutaneous telangiectasias are not described in Friedreich's ataxia (Young *et al.*, 1964). Ataxia-telangiectasia usually has an earlier onset than Friedreich's ataxia. However, the clinical manifestations of ataxia-telangiectasia are not definitively established, and new neurological, skin, and hair features can be observed in long-surviving patients. In the oldest patients, spinal muscular atrophy (Goodman *et al.*, 1969), features of peripheral neuropathy (Engel *et al.*, 1966; Gardner and Goodman, 1969), and progressive evolution to resemble Friedreich's ataxia are described (Martin, 1966).

The progression of the electrophysiological abnormalities is clear in our patients. Case 2 was explored at the age of 5 years with normal electrophysiological findings. Later, at age 7 years, the amplitude of the SEP was in the low limits of the normal range. In patients 1 and 3 (8 and 12 years of age), the electrophysiological abnormalities were more severe than in case 2. The oldest patient (case 4) had absent deep reflexes, loss of deep sensation, muscular atrophy, and deformities in lower limbs. Electrophysiologically, neurogenic atrophy, slight slowing of motor and sensory conduction velocities, and severe reduction in amplitude of evoked nerve potentials were found in this case.

Our conclusion is that reduction in amplitude of the nerve evoked potentials is the earliest and most striking electrophysiological feature in ataxia telangiectasia. This abnormality can be observed without clinical evidence of peripheral neuropathy. Later, in the older patients, mild reduction of the MCV and SCV, and suggestive findings of spinal atrophy can be found.

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