Nerve conduction studies in adrenomyeloneuropathy

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Abstract

Objective—Adrenomyeloneuropathy (AMN) is an X linked metabolic disorder presenting with progressive spastic paraparesis in the third to fifth decade of life. Although peripheral neuropathy is also present in most patients, prominent pyramidal signs may make its clinical recognition difficult. The objective was to characterise the peripheral neuropathy in patients with AMN by nerve conduction studies.

Methods—Nerve conduction studies were performed in 99 men known to have AMN and in 38 heterozygous women, all of whom had neurological disabilities.

Results—Of the 13 variables obtained, at least one was abnormal in 82% of patients. The abnormalities were more common in men than in women (87% *v* 67%); in legs than in arms (77% *v* 38%); in motor than in sensory conduction (80% *v* 39%); and in latency (distal and F wave) and velocity compared with amplitude (80% *v* 29%). Twenty six patients had at least one nerve variable value in the demyelinating range. Four variables (sural velocity, peroneal amplitude, peroneal velocity, and peroneal F wave) were correlated with the expanded disability status scale; five variables (peroneal velocity, tibial H reflex, median distal latency, median conduction velocity, and median F wave latency) were correlated with serum very long chain fatty acids (VLCFAs); and two variables (sural amplitude and peroneal distal latency) were more likely to be abnormal in patients with normal adrenal function than in patients with Addison's disease.

Conclusions—Nerve conduction studies in patients with AMN are often abnormal and suggest a mixture of axonal loss and multifocal demyelination. Their correlation with disability status and serum VLCFAs suggests that measures from nerve conduction studies may be useful in evaluating future treatments.

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an X linked recessive peroxisomal disease characterised by accumulation of abnormally high concentrations of saturated very long chain fatty acids (VLCFAs) in tissues and body fluids.¹⁻⁷ Unlike ALD, which is a rapidly progressive fatal disorder of early childhood, AMN is a slowly progressive disorder of adulthood that causes dysfunction of the adrenal gland, spinal cord (myelopathy), and peripheral nerves (neuropathy). The typical clinical presentation of AMN is a man in his third or fourth decade of life, developing slowly progressive spastic paraparesis and sphincter disturbance. About 70% of patients with AMN develop adrenal insufficiency which may manifest as generalised weakness, weight loss, pigmentation, or attacks of nausea and vomiting, and which usually precedes the neurological symptoms. Careful examination shows the presence of peripheral neuropathy in most patients. At least 20% of heterozygous women develop neurological disability similar to that seen in men with AMN but milder and of later onset, in the fourth to fifth decade of life.⁶

Although peripheral neuropathy is present in most patients with AMN, prominent pyramidal signs often make its clinical detection difficult. Failure to recognise the associated neuropathy may lead to the misdiagnoses of multiple sclerosis or "idiopathic paraparesis".^{1,7,8} Nerve conduction studies are helpful in identifying neuropathy. The presence of peripheral neuropathy and myelopathy with positive family histories in these relatively young patients may lead the clinician to measure serum VLCFA concentrations and establish the correct diagnosis of AMN.

Only limited details of nerve conduction studies in patients with AMN are, however, available.^{1,9-18} From the few pathological descriptions of ALD that show multifocal demyelination and from the available case reports of patients with AMN, it is assumed that nerve conduction studies will show a demyelinating physiology. If a demyelinating neuropathy is not detected, the diagnosis of AMN is often wrongly excluded. The aims of this paper are (a) to present details of nerve conduction abnormalities in patients with AMN, (b) to analyse the proportion of patients with demyelinating physiology, (c) to compare nerve conduction study abnormalities in men with heterozygote women, and (d) to measure correlations of abnormalities noted on nerve conduction studies with the expanded disability status score (EDSS), the pyramidal score, plasma concentrations of VLCFA, and adrenal function.

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Adrenomyeloneuropathy (AMN) is one of the phenotypes of adrenoleukodystrophy (ALD),

Subjects and methods

Baseline nerve conduction studies were performed in 137 patients with an AMN phenotype, all of whom were participating in an ongoing clinical trial of dietary treatment with "Lorenzo oil" at the Kennedy Krieger Institute. The diagnosis was based on established clinical criteria and raised concentrations of plasma VLCFAs.⁶ All patients were symptomatic adults with primarily spinal cord involvement and included 99 men and 38 heterozygous women. Table 1 gives the data, including age, sex, VLCFA concentrations, mean EDSS, pyramidal scores, and percentage with adrenal dysfunction. More detailed clinical data on this population are available elsewhere.^{4,6,19}

In each patient nerve conduction of the right sural and median sensory nerves, right peroneal and median motor nerves including F wave latencies, and right tibial H reflex latency were recorded with techniques standard in our laboratory. All studies were performed with an infrared temperature control system to maintain surface limb temperature (lateral border of the right foot and tip of digit 3) at 34°C. Thirteen variables of nerve conduction were measured in each patient as follows: sural and median sensory nerve action potential (SNAP) amplitudes and velocities; common peroneal and median distal latencies, conduction velocities, compound muscle action potential (CMAP) amplitudes, F wave latencies, and H reflex latency. For sensory nerves, SNAP amplitude was measured from peak to peak and velocity calculated by dividing the distance by onset latency; for motor nerves, CMAP amplitude was measured baseline to peak, distal latency and conduction velocity were calculated in the standard fashion, and F wave latency was obtained as the shortest of 10 trials; the onset latency was measured for the H reflex.

Table 1 Characteristics of the patients with AMN

	Men	Women
No	99	38
Mean age (range) (y)	33 (17–74)	48 (29–73)
% With adrenal dysfunction	78	0
Mean VLCFA concentration (μg/ml) (SD)		
(Control C26:0 μg/ml)	0.96 (0.44)	0.63 (0.25)
Mean EDSS (SD)	3.8 (1.5)	3.7 (1.4)
Mean pyramidal score (SD)	2.3 (1.1)	2.4 (0.9)

Table 2 Patients with AMN: mean (SD) of 13 variables

	Men Mean (SD)	Women Mean (SD)	Normal values
Sur amp* (μV)	20 (11)	25 (12)	≥ 10
Sur CV (m/s)	45 (8)	48 (7)	≥ 40
Per DL* (ms)	5.2 (1)	4.5 (0.9)	≤ 5.2
Per Amp (mV)	4.0 (2.2)	4.0 (2.0)	≥ 2
Per CV* (m/s)	37 (7)	42 (5)	≥ 40
Per F wave* (ms)	58.4 (9.6)	51 (5.7)	≤ 55
H ref (ms)	27 (15.1)	28 (12)	≤ 35
MS amp (μV)	29 (14)	29 (14)	≥ 10
MS CV (m/s)	56 (8)	56 (11)	≥ 50
M DL* (ms)	3.7 (0.7)	3.2 (0.8)	≤ 4.2
MM amp (mV)	10.5 (3.3)	10.5 (2.5)	≥ 4
MM CV (m/s)	54 (6)	56 (5)	≥ 50
Med F wave* (ms)	29.6 (3.6)	27.1 (3.6)	≤ 31

*P < 0.05 men v women.

For explanation of abbreviations see footnotes of fig 2.

Abnormal values for each variable were based on the standardised upper and lower limits of normal for our laboratory (table 2). Based on modifications of previously published criteria,²⁰ individual values of latency and conduction velocity were considered demyelinating if they met the following criteria: conduction velocity < 70% of the lower limit of normal, and distal motor or F wave latencies > 125% of the upper limit of normal. Values that were abnormal and not in the demyelinating range, an absent response, and abnormal amplitude values were all considered axonal affects for the purpose of this study.

STATISTICAL ANALYSES

Mean (SD) values were obtained for each of the 13 variables. Values for men were compared with those for women. Correlation of each of the variables with adrenal dysfunction, EDSS,²¹ pyramidal dysfunction,²¹ and concentrations of VLCFAs were assessed. Numbers of patients with normal values, abnormal values in the axonal range, and abnormal values in the demyelination range were noted for each of these variables. P values were calculated when appropriate.

Results

Table 2 gives the mean (SD) of the 13 variables for the men and women. Significant differences between men and women were found in the sural amplitude, peroneal motor distal latency, conduction velocity, and median motor distal latency. At least one of the 13 variables obtained was abnormal in 82% of patients. Eighty one per cent of the patients had an abnormality noted in at least one nerve; 47% had two or more nerves that were abnormal; 31% had abnormalities in three nerves; and 7% showed abnormality in all four tested nerves. Based on the abnormalities in at least one nerve, the abnormalities were more often seen in men than women (87% v 67%); in lower limb nerves than in upper limb nerves (77% v 38%); and in motor nerves than in sensory nerves (80% v 39%) (fig 1). In both men and women, common peroneal F wave latency was most often abnormal (64% of patients), followed by peroneal conduction velocity (53% of patients) and the H reflex latency (44% of patients). Variables related to latencies (distal and F wave) and conduction velocity were more often abnormal than the amplitudes (80% v 29%) (figs 2 and 3).

At least one value in the demyelinating range was found in 26% of patients; 9% had two or more; 3% had three or more, and 1% had four or more. Demyelinating values were detected more often in men (31%) than in women (12%) and in the nerves of the lower limbs (19%) than in the nerves of the upper limbs (9%), where noted changes could be easily attributable to focal nerve entrapment (figs 2 and 3).

Demyelinating changes did not appear uniformly distributed over the length of a motor fibre. For example, prolongations of distal

Figure 1 Nerve conduction studies: findings in patients with AMN. The percentages for normal, axonal, and demyelinating are calculated based on abnormal findings in at least one variable.

Figure 2 Nerve conduction studies: findings in the 13 tested variables in men with AMN. Sur = Sural; Per = peroneal; MS = median sensory; MM = median motor; Amp = amplitude; DL = distal latency; CV = conduction velocity; F = F wave latency; and H ref = H reflex latency.

Figure 3 Nerve conduction studies: findings in the 13 tested variables in women with AMN. Abbreviations as in fig 2.

Table 3 Comparison of peroneal distal latency (DL) and conduction velocity (CV) in men with AMN showing the non-uniformity along the length of the nerve

	DL Normal	DL ↑(ax)	DL ↑↑(dem)
CV Normal	28	9	1
CV ↓(ax)	23	18	6
CV ↓↓(dem)	9	2	3

Ax = axonal; dem = demyelinating; ↓ = reduced; ↑ = prolonged.

motor latencies were not always associated with proportional reductions in conduction velocity—among men with AMN, 32 had reduced peroneal conduction velocity but normal distal motor latency and 10 had prolonged peroneal distal motor latency but normal conduction velocity (table 3).

In men with AMN, the following correlations were significant: (1) men with AMN and Addison's disease showed higher sural SNAP amplitudes and lower peroneal distal motor latency values than did men with AMN and normal adrenal function ($P < 0.05$); (2) serum concentrations of very long chain fatty acids were significantly correlated with the peroneal amplitude, tibial H reflex, median distal motor latency, median conduction velocity, and median F waves; (3) sural conduction velocity, peroneal amplitude, peroneal conduction velocity, and peroneal F waves were significantly correlated with EDSS; and (4) peroneal amplitude and conduction velocity were significantly correlated with pyramidal scores. In women heterozygous for ALD, on the other hand, except for median motor conduction velocity and EDSS, no significant correlations were detected.

Discussion

X Linked adrenoleukodystrophy (ALD) is a disorder of very long chain fatty acid metabolism characterised by diffuse abnormality of cerebral white matter and adrenal atrophy. In a recent review, Moser *et al*⁴ described several phenotypic variants of ALD (estimated frequency of occurrence: childhood cerebral (43%), adolescent cerebral (5%), adult cerebral (3%), AMN (26%), Addison only (11%), and asymptomatic (7%)). It is known that the peripheral nervous system is involved in AMN. Identification of additional peripheral neuropathy in a patient with myelopathy is helpful in narrowing the differential diagnosis of slowly progressive spastic paraparesis. Because upper motor neuron signs predominate in AMN, clinical signs of peripheral neuropathy may not be so clearly evident. Nerve conduction studies are extremely helpful in confirming the presence of peripheral nerve affection, thus distinguishing AMN from multiple sclerosis, familial spastic paraparesis, and structural cord lesions. Furthermore, nerve conduction studies are helpful in characterising its pathophysiology (axonal *v* demyelinating), identifying the different fibre types affected (sensory *v* motor), and defining the distribution and severity which may be useful for longitudinal follow up and for assessing effects of different therapeutic interventions.

Until now detailed descriptions of nerve conduction study findings in patients with AMN have not been available. Although it is known that most patients with AMN have peripheral neuropathy, one of the criteria for its diagnosis, its precise frequency in men and heterozygous women, characteristics, severity, pathophysiology, relation with adrenal function, VLCFA concentrations, pyramidal dysfunction, and EDSS are unavailable. The

Table 4 Nerve conducting studies in patients with AMN: review of publications

Reference	AMN Men	AMN Women	Motor nerves	Sensory nerves
Griffin <i>et al</i> 1977 ¹	5	—	CV ↓↓ in 3/4; LL > UL	ND
Davis <i>et al</i> 1979 ¹²	1	—	CV ↓ LL	CV ↓
Askanas <i>et al</i> 1979 ⁹	1	—	NL	NL
Martin <i>et al</i> 1982 ¹³	4	—	CV ↓ in 2/4 LL	NL 4/4
Vercruyssen 1982	5	—	CV ↓ 3/4; LL > UL	CV ↓ in 1/5
Berkovic <i>et al</i> 1983 ¹⁵	3	—	CV ↓ 3/3; LL > UL	ND
Tobimatsu <i>et al</i> 1985 ²⁴	1	—	CV ↓ in 1/1	ND
Noetzel <i>et al</i> 1987 ¹⁶	—	1	NL	—
Elrington <i>et al</i> 1989 ¹⁷	2	—	CV ↓ in LL	CV ↓ in 1
Aubourg <i>et al</i> 1992 ¹¹	17	—	CV ↓ 15/17 LL	CV ↓ 12/17
Moser <i>et al</i> 1992 ⁴	76	25	CV ↓ 52; LL and 7 UL	ND
van Geel <i>et al</i> 1996 ¹⁸	18	5	CV ↓ 16 LL; 5 in UL	CV ↓ 5 (UL); ↓ 11 (LL)
			Distal latency ↑ 13 LL; 8 UP	Amp ↓ 3 (UL); 5 (LL)
			Amp ↓ 10 LL; 0 UL	
			F wave ↑ 8 LL; 5 UL	
Chaudhry <i>et al</i> 1996 (this paper)	99	38	CV ↓ 110; LL > UL	CV ↓ 53; LL > UL

ND = not done; NL = normal; CV = conduction velocity; LL = lower limb; UL = upper limb; ↓ = reduced; ↑ = prolonged.

present study attempts to answer these questions.

FREQUENCY

Nerve conduction studies confirmed the presence of neuropathy in most of the patients with AMN. Men with AMN were more likely to show abnormal findings than heterozygous women; motor nerves to show more frequent abnormalities than sensory; and lower limb nerves to show more frequent changes than upper limb nerves.

CHARACTERISATION

Even though the absolute value of changes in the nerve conduction study variables were in the axonal range, the pattern of physiological abnormalities noted was not typical of a distal axonopathy. For example, measures related to functioning myelin (distal latency, F wave latency, and conduction velocity) were more commonly affected than amplitude, a measure generally associated with the number of functional axons; motor nerve abnormalities were more frequent than sensory nerve abnormalities; and the findings appeared non-uniform over adjacent nerve segments (table 3). However, the distribution of affected nerves was length dependent, as typically seen in an axonopathy, and individual latency values were rarely in the range associated with primary demyelination. Overall, this mixed pattern suggesting multifocal demyelination and axonal loss is well described in “metabolic neuropathies” such as diabetes.²²

Other studies also support the notion that the peripheral neuropathy associated with AMN has both axonal and demyelinating features. Microscopically, sural nerves have been reported to show a mixture of axon and myelin loss. Some report frequent formation of small “onion bulbs” and thinly myelinated fibres suggestive of remyelination.^{1 13 23} Also, teased fibre studies have confirmed the existence of chronic demyelination-remyelination.¹³ Muscle biopsy from peroneal muscles shows changes of denervation and reinnervation secondary to axonal loss.¹³ Other evidence of peripheral nerve demyelination comes from the results of somatosensory evoked potentials, which have shown prolonged peripheral conduction time in both lower and upper limb nerves.^{10 24}

PATHOGENESIS

Although the association between AMN and VLCFA accumulation is in no doubt, it remains uncertain whether fatty acid abnormality is the direct cause of the neuropathology, whether secondary pathogenetic factors are required, or whether VLCFA excess is an epiphenomenon. There is evidence that accumulation of VLCFA has a deleterious effect on membrane structure and function,²⁵⁻²⁷ but the great variability of the ALD phenotypes even within families, and the lack of correlation of VLCFA concentrations with neurological disability, suggest that other factors beyond accumulation of VLCFA are involved in pathogenesis. One such factor may be immune mediated damage. The rapid neurological progression in the childhood cerebral form is associated with demyelination and an intense perivascular inflammatory response. Recent studies suggest that cytokines such as tumour necrosis factor- α are involved in this process.²⁸ It may be that the abnormal accumulation of lipids in AMN acts, in some patients, as an antigen initiating immunological damage.³ As this immune mediated process might be expected to be non-uniform, it offers a possible explanation for the multifocality of the changes seen here.

CORRELATIONS OF NERVE CONDUCTION STUDY FINDINGS WITH OTHER FEATURES OF AMN

Sural amplitude and peroneal distal motor latency values were more towards the normal range in patients with Addison’s disease than in patients with normal adrenal function. This may reflect earlier diagnosis in the patients with adrenal insufficiency. Although no other consistent correlations of nerve conduction study findings were present with Addison’s disease, EDSS, pyramidal score, serum VLCFA concentrations, and different variables of the common peroneal nerve seem to show correlations most consistently. However, as this nerve also has the most frequent abnormality some correlation of this with different aspects of AMN is not surprising. Serum VLCFA concentrations have not been shown to correlate with EDSS or pyramidal scores themselves even though they seem to play a crucial part in pathogenesis.⁴

A review of previous nerve conduction studies in AMN showed that they were consistent

with our findings (table 4), although detailed descriptions were limited and patient numbers were small. A recent publication¹⁸ is interesting in this regard. Similar to our study, the abnormal findings were more prominent in lower limb nerves than in upper limbs and in latency and conduction velocity values than in amplitude values. And even though 26% of patients had demyelinating findings in one or more nerves, the conclusion of the paper was that neuropathy in patients with AMN is due to primary axonal demyelination. We think that this supports the concept that the neuropathy has mixed features of axonal degeneration and multifocal demyelination.

In conclusion, we report that results of nerve conduction studies are often abnormal in men and heterozygous women with AMN, are helpful in diagnosis and prognosis, and may be useful in future therapeutic trials. The findings have features of both a multifocal demyelinating process and an axonopathy. Common peroneal motor nerve conduction studies are the most useful for screening, for longitudinal follow up, and to assess the results of a therapeutic intervention.

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