An electrophysiological follow up of patients with n-hexane polyneuropathy

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Abstract

Electroneurographic (ENeG) and evoked potential (EP) studies were regularly performed on 11 printing workers with n-hexane polyneuropathy after cessation of exposure. At the initial examination, the ENeG studies simulated a demyelinative process. Further slowing of nerve conduction velocity, or further decreasing of action potential amplitude, or both in the follow up ENeG study were found in about half the patients. The motor distal latency did not worsen. Nerve conduction returned to normal earlier in the sensory than in the motor nerves. After the patients had regained full motor capability, conduction velocities in motor nerves were still significantly slowed. These ENeG characteristics correlate with the pathological and pathophysiological changes in experimental hexacarbon neuropathies. The initial findings from the EP studies indicated a conduction abnormality in the central nervous system (CNS). Delayed worsening occurred in the amplitude of visual EPs in three patients. On serial follow up, the interpeak latency and interpeak amplitude of visual EPs improved little. Residual abnormalities were also found in the interpeak latency of auditory EPs in the brainstem and in the absolute latency of scalp somatosensory EPs from the peroneal nerve. Astroglial proliferation in the CNS probably impedes recovery of the abnormalities in EP.

Electroneurophysiological assessment is important in clinical neurotoxicology. Electroneurographic (ENeG) studies provide valuable information to allow a distinction between a demyelinating and an axonopathic process in a toxic polyneuropathy, and further investigation of the causative agent may become easy. Evoked potential (EP) studies can objectively evaluate the toxic effect of a specific agent

on the central nervous system (CNS). In patients with n-hexane polyneuropathy, a noticeable fall in nerve conduction velocities (NCV), profound amplitude reduction of compound muscle action potentials (CMAPs) and sensory action potentials (SAPs), and obvious prolongation of distal latencies (DLs) were characteristic ENeG findings.¹⁻⁴ Prolongation of conduction times in the visual, auditory, and somatosensory pathways in the CNS has been shown by EP studies.⁵⁻⁷ Evolution of these electrophysiological abnormalities on recovery from n-hexane polyneuropathy, however, has never been systematically reported.

From December 1983 to February 1985, 28 printing workers in the Taipei area developed clinically overt n-hexane neuropathy as a result of occupational exposure. Epidemiological, ENeG, and EP findings in that outbreak have been reported.^{4,7,8} Eleven among these patients were regularly followed for a four year period at the Department of Neurology, National Taiwan University Hospital. Evolution of clinical manifestations after exposure had ceased has been published elsewhere.⁹ In the present paper ENeG and EP findings on recovery from n-hexane neuropathy are reported. Special attention is given to delayed worsening of the electrophysiological features.

Materials and methods

PATIENTS

Seventeen of the 28 patients in the Taipei outbreak of n-hexane neuropathy returned to south Taiwan and were lost to contact. The remaining 11 male patients were followed up monthly for the first two years, once every two months in the third year, and once every three months in the fourth year. They were not in contact with any organic solvents at work during this time. Their age ranged from 18 to 30 at the first examination.

Polyneuropathy was classified into grade 5, unable to stand without support or confined to a wheelchair; grade 4, able to stand without support but unable to walk; grade 3, able to walk with support; grade 2, able to walk without support but unable to walk on heels for 10 steps; grade 1, able to walk freely on heels but

unable to run; and grade 0, able to run. At the first visit, grade 5 polyneuropathy was found in one, grade 4 in two, grade 3 in one, and grade 2 in the remaining seven patients. All of the patients returned to normal daily activities, including running, within one to four years. The sensory disturbance disappeared much earlier than the motor problem.

ELECTRONEUROGRAPHIC STUDIES

An ENeG study was carried out with an MS6 or a Mystro 20 electromyograph (MEDELEC) at the first visit and repeated when the polyneuropathic manifestations improved to a better clinical grade. After the patients recovered to grade 0 of neuropathy, it was necessary to repeatedly persuade them to receive a further neurophysiological examination. The final ENeG study was therefore conducted six to nine months after apparently complete recovery. With conventional techniques, motor nerve conduction studies were performed in the median (elbow-wrist), the ulnar (elbow-wrist), the peroneal (knee-ankle), and the tibial (knee-ankle) nerves. Sensory conduction velocities were also measured in the median (wrist-finger), the ulnar (wrist-finger), and the sural (midcalf-ankle) nerves. To obtain reliable distal latencies, the distance between recording site and distal stimulation point was kept as constant as possible. Electroneurographic findings from the right limbs were statistically compared with those from the normal controls used in a previous report.⁵

EVOKED POTENTIAL STUDIES

Multimodality evoked potentials were recorded with a Pathfinder II machine (Nicolet) when the patient received an ENeG follow up. Visual evoked potentials (pVEPs) to checkerboard pattern reversals were recorded at Oz-Cz (10–20 system) with check size subtending 1°, 30', 15', and 7·5' of the visual angle at a reversal rate of 1·88/s. The number of trials was 256 and the analysis time was 250 ms. The N1 (N75), P1 (P100), and N2 (N135) latencies of the pVEP from a visual angle of 30' were measured. The amplitude measurements were referred to the N1–P1 and P1–N2 interpeak amplitudes.

Brainstem auditory evoked potentials (BAEPs) to 0·1 ms clicks were recorded at A2–Cz or A1–Cz (ipsilateral to the side of click stimulation). The auditory stimulus in both condensation and rarefaction polarities was set at an intensity of 60 dB above threshold for each subject and at a rate of 11·1 Hz. The analysis time was 10 ms and 2048 trials were averaged. Out of the seven positive peaks, the absolute latencies of waves I, III, and V were measured.

Somatosensory evoked potentials (SEPs) to median nerve stimulation were recorded at the contralateral central region of the scalp (C3' or C4'), at the 7th cervical spinous process, and at the

ipsilateral Erb's point. Square wave pulse electric stimulation of 0·1 ms duration at a rate of 2·7 Hz was applied to the median nerve at the wrist and adjusted to the minimal current for eliciting visible thumb twitching. The analysis time was 50 ms. The absolute latencies of the N1 (N20) component of scalp SEP, of the N13 peak of neck SEP, and of the negative peak of brachial nerve action potential (NAP) at the Erb's point were measured. Central somatosensory conduction time (CCT) was taken as the latency difference between scalp SEP latency (N1) and neck SEP latency (N13). Scalp SEPs at Cz' to stimulation of the peroneal nerve at the ankle were also recorded with an analysis time of 200 ms and at a stimulation rate of 2·1 Hz. The absolute latency of P1 (P40) was selected for analysis.

Visual evoked potentials from the right eye, BAEP findings from the right ear, and SEP findings from the right limbs were used for statistical comparison with those from the normal controls used in a previous report.⁴

EVOLUTION OF ELECTRODIAGNOSTIC ABNORMALITIES

Evolution curves of Z value of some important electrodiagnostic parameters were plotted on X–Y diagrams with mean Z value against different clinical grade on recovery. The Z value of an electrodiagnostic parameter was calculated as:

$$Z \text{ value} = \frac{\text{An obtained value} - \text{mean of controls}}{\text{Standard deviation (SD) of controls}}$$

Results

INITIAL AND FINAL ENeG FINDINGS (TABLES 1 AND 2)

Table 1 shows the motor and table 2 the sensory ENeG findings of the 11 patients at the initial and final examinations. The characteristic features at the first study, similar to those in the previous reports, were the noticeable fall of NCV, profound amplitude reduction of CMAP and SAP, and obvious prolongation of DL. Electroneurographic abnormalities were more severe in motor than in sensory conduction. The greatest abnormal findings were seen in the motor conduction of the peroneal nerve; the peroneal motor NCV ranged from 27·2 to 37·9 m per s, CMAP amplitude from 0·3 to 3·3 mV, and DL from 6·48 to 9·12 ms. In comparison with the normal controls, the motor NCVs at the final study were still significantly slower, whereas there was a tendency for higher MAP amplitudes from the median, the ulnar, and the tibial nerves. For sensory conduction in the final study, the patients had a faster mean sensory NCV and a lower mean SAP amplitude than the normal controls, but these differences did not reach statistical significance.

Table 1 Motor neurographic findings in 11 patients with *n*-hexane polyneuropathy

	Initial study (mean (SD)) (n = 11)	Final study (mean (SD))* (n = 11)	Normal controls (mean (SD)) (n = 72)	p Value (final study v controls)
Median nerve:				
CMAP amplitude (mV)†	4.1 (2.1)	10.0 (2.1)	8.9 (3.0)	NS§
Distal latency (ms)	6.08 (0.74)	3.87 (0.39)	3.71 (0.44)	NS
NCV (m/s)‡	42.9 (7.1)	57.3 (2.5)	61.9 (4.6)	<0.005
Ulnar nerve:				
CMAP amplitude (mV)	4.2 (1.7)	8.5 (1.1)	7.8 (2.2)	NS
Distal latency (ms)	5.04 (0.78)	3.05 (0.24)	3.03 (0.40)	NS
NCV (m/s)	40.8 (4.6)	52.8 (4.1)	55.4 (4.0)	<0.05
Peroneal nerve:				
CMAP amplitude (mV)	1.8 (1.0)	5.6 (2.5)	5.9 (1.9)	NS
Distal latency (ms)	8.18 (1.09)	4.82 (0.89)	4.71 (1.03)	NS
NCV (m/s)	31.9 (3.3)	46.1 (4.9)	53.1 (4.4)	<0.0005
Tibial nerve:				
CMAP amplitude (mV)	4.0 (2.4)	10.7 (5.7)	10.2 (3.7)	NS
Distal latency (ms)	7.59 (1.28)	4.51 (0.24)	4.53 (0.81)	NS
NCV (m/s)	34.5 (4.3)	46.3 (4.8)	49.6 (3.9)	<0.05

*The final study was conducted six to nine months after apparently complete recovery.

†CMAP = Compound muscle action potential.

‡NCV = Nerve conduction velocity.

§NS = Non-significant (p > 0.05).

DELAYED WORSENING OF ENeG ABNORMALITIES

In the second ENeG study, which was performed when the neuropathic manifestations improved to the next clinical grade (five to 10 months after the initial evaluation), a further reduction of MAP in one or more nerves occurred in six patients, mainly in the peroneal nerve. The peroneal nerve became unexcitable in one patient. Five patients had a further fall in motor NCV. No delayed worsening of motor DL occurred. At sensory ENeG follow up, a further decrease of SAP amplitude was seen in five patients, mainly in the sural nerve. Further falls in sensory NCV occurred in five patients. Electrodiagnostic worsening did not correlate with the clinical "coasting phenomenon" and also occurred even in those patients with a continuous improvement of neuropathic manifestations.

EVOLUTION OF ENeG ABNORMALITIES

Recovery of ENeG abnormalities was slow regardless of clinical severity or delayed electrodiagnostic worsening. Figure 1 shows evolution curves of the mean Z value in the NCV, the DL, and the amplitude of CMAP or SAP. When the clinical recovery reached grade 2, there was a more rapid improvement of these electrodiagnostic abnormalities. Residual abnormal findings were still seen, however, even after the patients regained their full motor capability.

INITIAL AND FINAL EP ABNORMALITIES (TABLES 3-5)

Tables 3, 4, and 5 list the pVEP, SEP, and BAEP findings at the initial and final studies. Patterns of EP abnormalities at the first examination were the same as those previously reported—that is, decreased pVEP amplitude, delayed absolute

Table 2 Sensory neurographic findings in 11 patients with *n*-hexane polyneuropathy

	Initial study (mean (SD))* (n = 11)	Final study (mean (SD)) (n = 11)	Normal controls (mean (SD)) (n = 72)	p Value (final study v controls)
Median nerve:				
SAP amplitude (μV)	16 (8)	35 (6)	41 (18)	NS
Distal latency (ms)	3.08 (0.33)	2.36 (0.17)	2.49 (0.25)	NS
NCV (m/s)	46.0 (4.7)	59.6 (4.2)	57.1 (5.9)	NS
Ulnar nerve:				
SAP amplitude (μV)	14 (5)	27 (5)	34 (15)	NS
Distal latency (ms)	2.79 (0.25)	2.32 (0.31)	2.27 (0.25)	NS
NCV (m/s)	43.4 (3.9)	54.6 (3.7)	53.4 (5.1)	NS
Sural nerve:				
SAP amplitude (μV)	11 (4)	18 (3)	20 (9)	NS
Distal latency (ms)	3.62 (0.28)	2.94 (0.22)	3.06 (0.50)	NS
NCV (m/s)	42.5 (3.7)	51.3 (3.8)	50.4 (4.2)	NS

*At the initial study, sensory action potential (SAP) could not be elicited at the median nerve in one, the ulnar nerve in one, and the sural nerve in five patients.

See table 1 footnotes for other explanations.

Figure 1 Evolution curves of mean Z value in electroneurography in 11 patients with *n*-hexane polyneuropathy (NCV = nerve conduction velocity; DL = distal latency; MAP = muscle action potential; SAP = sensory action potential; number of cases for each point = one for grade 5, three for grade 4, four for grade 3, and 11 for grades 2, 1, and 0).

latencies of pVEP and SEP, and prolonged auditory and somatosensory central conduction times. In comparison with normal controls, there were still significant prolongations of interpeak latency and reduction of interpeak amplitudes of pVEP at the final study. In the BAEP study, prolongation in the absolute latencies of wave III and V leading to prolongation of interpeak latencies was also statistically significant at the final examination. For the SEP findings, the only significant difference found was in the scalp SEP latency from the peroneal nerve.

DELAYED WORSENING OF EP ABNORMALITIES

Transient delayed worsening of EP findings only occurred in the interpeak amplitudes of pVEP. It was seen in three patients with grade 2 neuropathy. There was no concomitant complaint of visual worsening.

EVOLUTION OF EP ABNORMALITIES

Figure 2 shows evolution curves of the mean Z value for some important EP parameters. For pVEPs, both the interpeak latency and interpeak amplitude improved little throughout the whole course. For SEPs from the median nerve, the central conduction time recovered earlier than the neck SEP latency. The interpeak latencies of BAEP improved rather slowly.

Discussion

A careful nerve conduction study offers clinicians useful clues to distinguish between a demyelinating and an axonal polyneuropathy. Obvious slowing of NCV and prolongation of DL are characteristic of demyelination, whereas axonal damage generally results in obvious amplitude loss of CMAP and SAP. Although the axon is the primary target in hexa-

Table 3 Findings of patterned visual evoked potential study in 11 patients with *n*-hexane polyneuropathy

	Initial study (mean (SD)) (n = 11)	Final study (mean (SD)) (n = 11)	Normal controls (mean (SD)) (n = 44)	p Value (final study v controls)
N1 latency (ms)	75 (5)	73 (4)	72 (4)	NS
P1 latency (ms)	102 (9)	96 (6)	96 (3)	NS
N2 latency (ms)	141 (14)	133 (8)	127 (7)	<0.05
N1-N2 interpeak latency (ms)	66 (13)	61 (10)	55 (5)	<0.01
N1-P1 interpeak amplitude (μV)	4.99 (2.48)	5.13 (2.01)	8.00 (3.49)	<0.05
P1-N2 interpeak amplitude (μV)	6.68 (4.43)	7.44 (3.10)	9.36 (2.85)	=0.05

See table 1 footnotes for explanations.

Table 4 Findings of somatosensory evoked potential study in 11 patients with n-hexane polyneuropathy

	Initial study (mean (SD)) (n = 11)	Final study (mean (SD)) (n = 11)	Normal controls (mean (SD)) (n = 84)	p Value (final study v controls)
Scalp SEP* latency from median nerve (ms)	20.68 (0.97)	18.78 (0.77)	18.44 (0.80)	NS
Neck SEP latency from median nerve (ms)	14.57 (0.77)	13.01 (0.54)	12.73 (0.72)	NS
Central conduction time from median nerve (ms)	6.14 (0.61)	5.77 (0.41)	5.70 (0.45)	NS
Brachial NAP† latency from median nerve (ms)	10.60 (0.68)	9.32 (0.48)	9.14 (0.53)	NS
Scalp SEP latency from peroneal nerve (ms)	44.88 (3.00)	41.24 (1.74)	39.13 (2.45)	<0.01

*SEP = Somatosensory evoked potential.

†NAP = Nerve action potential.

See table 1 footnotes for other explanations.

carbon intoxication, pronounced slowing of NCVs simulating a demyelinating process has been reported in patients with hexacarbon neuropathy.¹⁻⁴ The initial ENeG findings for the present patients with n-hexane neuropathy (tables 1 and 2) also showed these features. Such an electrodiagnostic paradox is regarded as a result of secondary paranodal demyelination due to giant axonal swelling in hexacarbon neuropathy.¹⁻³

The ENeG abnormalities in the present patients were more obvious in motor than in sensory conduction. This discrepancy was consistent with the fact that the motor deficit was more prominent than the sensory impairment.⁷ It also correlates well with findings in experimental rats exposed to 2,5-hexanedione (2,5-HD) in which axonal transport was more vulnerable in motor than in sensory fibres.¹⁰

Delayed worsening of ENeG abnormalities after exposure to hexacarbon had ceased was first mentioned by Allen *et al*¹¹ for workers in the outbreak of methyl n-butyl ketone (MnBK) polyneuropathy which occurred in Ohio, although they did not point out the ENeG parameters with delayed worsening. Cianchetti *et al*¹² noted a progressive fall in motor NCV and reduction in MAP among shoe industry workers with n-hexane neuropathy even after removal from the work environment. Takahashi *et al*¹³ reported that a Japanese girl with n-hexane polyneuropathy had a further fall of median motor NCV despite obvious improvement of DL, when her walking improved six months later. In the present group, ENeG parameters with delayed worsening included motor NCV, sensory NCV, CMAP

amplitude, and SAP amplitude. Motor DL was not affected.

Recovery of ENeG abnormalities in our patients (tables 1 and 2 and fig 1) was earlier and more complete in sensory than in motor conduction and slowing of motor NCVs was still evident at the last follow up. Motor DL was no longer prolonged at the final examination. Exemption from delayed worsening and normalisation early in recovery in the motor DL probably have the same mechanism. Spencer and Schaumburg¹⁴ and Saida *et al*¹⁵ found that changes in experimental MnBK or 2,5-HD neuropathy appeared first in tibial nerve branches or the main sciatic trunk, and not in more distally placed nerves or in motor nerve terminals. If the most distal segments of motor nerve fibres are also less affected in n-hexane neuropathy in man, the motor DL, which reflects ENeG behaviour of distal motor fibres, would be spared from delayed worsening and would return to normal earlier.

At the final ENeG examination, higher CMAP amplitudes and faster sensory NCVs than those in normal controls were probably related to a younger age in the patient group than in the controls (24.5 v 27.0 years). Mean SAP amplitude at the final examination seemed lower than the normal controls, but the difference did not reach statistical significance.

Main EP abnormalities in both the hexacarbon exposed subjects⁵⁻⁷ and hexacarbon treated animals¹⁶ were prolongation of central conduction times and reduction of amplitudes. The findings in man, indicating neurotoxic effects on the CNS, fit well

Table 5 Findings of brainstem auditory evoked potential study in 11 patients with n-hexane polyneuropathy

	Initial study (mean (SD)) (n = 11)	Final study (mean (SD)) (n = 11)	Normal controls (mean (SD)) (n = 50)	p Value (final study v controls)
Wave I latency (ms)	1.66 (0.15)	1.62 (0.08)	1.62 (0.13)	NS
Wave III latency (ms)	3.97 (0.58)	3.89 (0.31)	3.70 (0.15)	<0.005
Wave V latency (ms)	5.99 (0.19)	5.72 (0.18)	5.55 (0.15)	<0.005
I-III interpeak latency (ms)	2.31 (0.14)	2.18 (0.12)	2.08 (0.12)	<0.05
III-V interpeak latency (ms)	2.02 (0.16)	1.91 (0.12)	1.85 (0.14)	NS
I-V interpeak latency (ms)	4.33 (0.14)	4.09 (0.17)	3.94 (0.16)	<0.01

See table 1 footnotes for explanations.

Figure 2 Evolution curves of mean Z value in evoked potentials in 11 patients with n-hexane polyneuropathy (IPL = interpeak latency; IPA = interpeak amplitude; CCT = central conduction time from median nerve; number of cases for each point = one for grade 5, three for grade 4, four for grade 3, and 11 for grades 2, 1, and 0).

with a pathological pattern of central peripheral distal axonopathy found in experimental animals. Recovery of EP abnormalities was much more unsatisfactory, however, than that of ENeG abnormalities. As shown in tables 3, 4, and 5, many EP findings in the final study were still significantly different from the normal controls. Astroglial proliferation triggered by hexane induced axonal degeneration impedes regeneration in the CNS; therefore poorer recovery of EP abnormality is understandable. Moreover, n-hexane maculopathy¹⁷ is also probably responsible for poor recovery of pVEP abnormalities.

Reasons for delayed worsening of electrophysiological abnormalities and clinical manifestations are not clear. After discovering more vulnerability in retrograde than anterograde axonal transport in rats treated with 2,5-HD, Braendgaard and Sidenius¹⁰ suggested that such a discrepancy could lead to structural changes (for example, axonal swellings) due to intraaxonal accumulation of membranous materials and cellular organelles. If the axonal transport recovers in a reverse order, the process of axonal change may continue for a period and then delayed worsening would ensue. This hypothesis needs careful confirmation, however.

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