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The Progress of Adrenoleukodystrophy as Revealed by Auditory Brainstem Evoked Responses and Brainstem Histology

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Das Fortschreiten einer Adrenoleucodystrophie aufgezeigt mittels akustischer Hirnstammpotentiale und Hirnstammhistologie

Zusammenfassung. Ein sechs Jahre altes Kind erkrankte im 5. Lebensjahr an Adrenoleucodystrophie (progressive metabolische Erkrankung des ZNS mit rapider Degeneration). Die Krankheit begann mit Dysarthrie, Schwerhörigkeit und Gangunsicherheit. Später kam es zur spastischen Paralyse, zu hochgradiger Schwerhörigkeit und Erblindung. Tod durch Atemlähmung.

Während des Verlaufs wurden regelmäßig die Hirnstammpotentiale sowie die langsamen Rindenpotentiale abgeleitet. Dabei war mit fortschreitender Erkrankung eine deutliche Verminderung der Potentiale zu beobachten. Histologisch zeigten sich eine Entmyelinisierung des Hörnervs sowie Neuronenverluste im Verlauf der Hörbahn. Die Degeneration im Hirnstamm verlief dabei von rostral nach kaudal.

Schlüsselwörter: Adrenoleucodystrophie – akustische Hirnstammpotentiale – Entmyelinisierung des Hörnervs – Neuronenverlust der Hörbahn

Summary. Serial studies of auditory brainstem evoked responses (ABR) and slow vertex responses (SVR) were obtained during the progress of adrenoleukodystrophy in a 6-year-old boy. This child was normal until 5 years of age. His illness began with a gait disturbance, dysarthria, and hearing difficulty. Later, spastic paralysis, serious deafness, and blindness appeared. He died of respiratory failure 2 years after the onset.

The ABR was normal at onset but changed to an abnormal pattern. Initially, there was lengthening of the wave V-I interpeak interval. This was followed by the disappearance of the later components as his general condition deteriorated. At the terminal stage, only a prolonged wave I was recordable. The postmortem pa-

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thology revealed demyelination of auditory nerves and remarkable neuronal loss in the auditory pathways of the brainstem; in addition, there was a variety of extensive degeneration throughout the cerebrum, in particular the complete degeneration of the white matter with secondarily occurring ganglionic cell changes. These data suggest that degeneration of the brainstem from rostral to caudal levels occurred.

Key words: Adrenoleukodystrophy – Auditory brainstem evoked responses – Demyelination of auditory nerve – Neuronal loss in the auditory pathway of the brainstem

Adrenoleukodystrophy (ALD) is a progressive metabolic disease which results in the rapid degeneration of the central nervous system (CNS) (Allen et al. 1975). Both demyelination of white matter and hypermyelination of gray matter in the cerebrum have been associated with ALD (Schaumberg 1975). Initially, losses of hearing and/or vision are usually observed. The disease progresses rapidly until a decerebrate state appears in its terminal stage.

Because ALD progresses rapidly resulting in profound neurological dificits, it is difficult to locate lesions as they develop. The auditory evoked response offers a non-invasive method for assessing localized brain function. Moreover, the test procedure is simple and fast. For these reasons, the auditory evoked response is ideally suited to evaluate the course of ALD (Ochs et al. 1979).

The auditory evoked response has been divided into the early auditory brainstem response (ABR) and the late slow vertex response (SVR). The former typically consists of a series of seven vertex-positive peaks appearing within 10 ms after stimulation. It is believed to be generated primarily from major brainstem nuclei and fiber tracts along the classical auditory pathway (Jewett et al. 1970; Sohmer et al. 1972; Buchwald et al. 1975; Starr et al. 1976). The SVR is a positive-negative-positive complex appearing later (typical peak latencies are 65 ms, 100 ms, 150 ms, respectively) and is probably of cortical origin (Picton et al. 1974).

The purpose of this study was to follow the course of ALD using both the ABR and the SVR in a young patient who was referred to us. A combination of the two could provide some clues to the location of the primary site and the extent of the lesions.

Methods

The patient was tested in a supine position in an electrically shielded and sound attenuating room. Data were recorded with silver disc electrodes from the forehead referenced to the test ear mastoid. The opposite mastoid was grounded.

Stimuli

Auditory stimuli were clicks (one cycle of a 3-kHz sine wave) produced by a signal generator (Dana Japan DA-502A) delivered through TDH-39 earphones. Clicks were given monaurally at intensities up to 85 dB

HL. For ABR recording, 2,000 clicks were given to the patient at the rate of 10 clicks · s^{-1} at each intensity level tested. For SVR recording, 50 clicks were given to the patient at the rate of 30 clicks · min^{-1}.

Procedure

Recordings were made at each intensity level beginning with the high intensity and successively reducing the level. This procedure was followed first for the ABR and then for the SVR. Both ears were tested. Records were replicated to assess reliability.

During the recording sessions, the patient was usually asleep. However, the EEG was continuously monitored for movement artifacts. When they occurred, recording was interrupted. Each recording session lasted 60 min. The sessions were spaced at least 2 months apart.

Recording

ABR data were differentially amplified (Nihon-Kohden RB-5; time constant 0.003 s; high-cut filter 1 kHz). For SVR recordings, the time constant was 0.3 s, and the high-cut filter was set to 100 Hz.

The amplified data were averaged and displayed by an on-line computer (Nihon-Kohden ATAC-201) and graphically recorded on an X-Y recorder.

Control Groups

ABR of six normal children of 5 years of age and ten normal adults were recorded for comparison with that of the patient. Mean latencies of the seven waves and the interval between the peaks of waves I and V are shown in Table 1A.

Case History

The patient developed normally until 5 years old when external strabismus of the right eye was noticed (August 1975). Then, hearing and visual disorders began. He first visited us for an examination of hearing acuity in June 1976. The results showed a moderate sensory-neural hearing loss (Fig. 1a), a normal ABR with a threshold of 15 dB (Fig. 2-*1*, Table 1B), and a normal SVR also with threshold of 15 dB (Fig. 3-*1*). During July 1976, hearing difficulty and visual disturbance worsened (Fig. 1b). A gait disturbance, dysarthria, and apraxia appeared. Soon afterward he was admitted.

On admission, neurological examination revealed hyperreflexia of extremities, decrease in superficial reflexes, and normal sensation of pain and touch. Six months after his admission, neurological abnormalities developed with mental impairment, losses of vision and hearing, and spastic paralysis. Finally, he became vegetative; a decorticate posture developed. Swallowing difficulty and respiratory distress ensued 1 year after his admission. He died of apnea on April of 1978.

ALD was diagnosed on the basis of abnormal endocrinological, immunological, and neuroradiological findings. The serum cortisol level was within normal limits in spite of the mild elevation of serum adrenocorticotropic hormone level (172 pg/ml). De-

Table 1

A. *Control group*

		Wave I	II	III	V	VI	VII	I–V	Wave V threshold
Children of 5 years of age n = 6	$\bar{X}$	1.39	2.28	3.61	5.49	6.90	8.77	4.12	9 dB
	SD	0.09	0.21	0.14	0.25	0.34	0.39	0.20	6 dB
Adults n = 10	$\bar{X}$	1.39	2.37	3.60	5.42	6.89	8.48	4.03	5 dB
	SD	0.07	0.14	0.13	0.25	0.34	0.40	0.31	3 dB

B. *The patient*

		Wave I	II	III	V	VI	VII	I–V	Threshold
L	1	1.43	2.18	3.82	5.80	6.64	8.91	4.37	15 dB
	2	1.55	2.45	4.05	6.36	—	—	4.81	25 dB
	3	1.55	2.64	4.55	6.82	—	—	5.27	45 dB
	4	1.67	2.91	—	—	—	—	—	55 dB
	5	2.00	—	—	—	—	—	—	65 dB
R	1	1.43	2.36	4.00	5.71	6.64	8.00	4.28	15 dB
	2	1.55	2.45	4.18	6.27	—	—	4.72	25 dB
	3	1.56	2.45	4.45	6.33	—	—	4.83	45 dB
	4	1.67	2.64	—	—	—	—	—	55 dB
	5	1.72	—	—	—	—	—	—	65 dB

ABR peak latencies and thresholds from five successive recording sessions
1: June 28, 1976
2: April 21, 1977
3: September 29, 1977
4: December 22, 1977
5: February 24, 1978

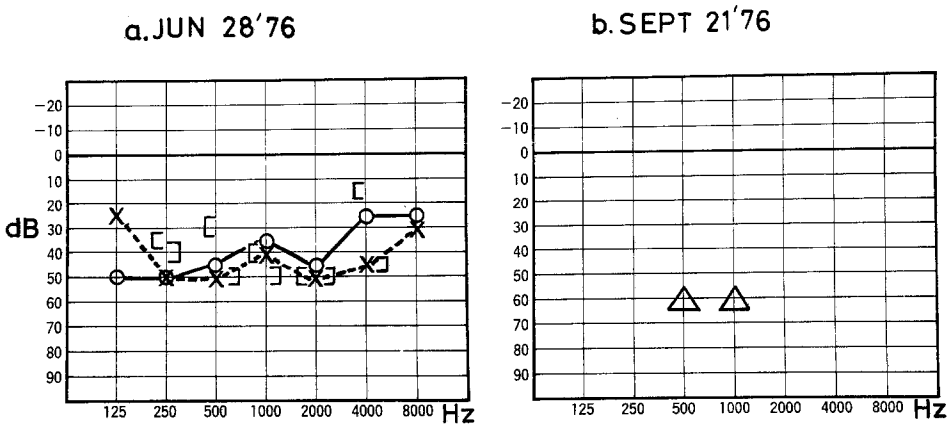

Fig. 1. *Left:* Audiogram by play audiometry at the first visit. *Right:* 3 months later; thresholds determined by behavioral observation audiometry

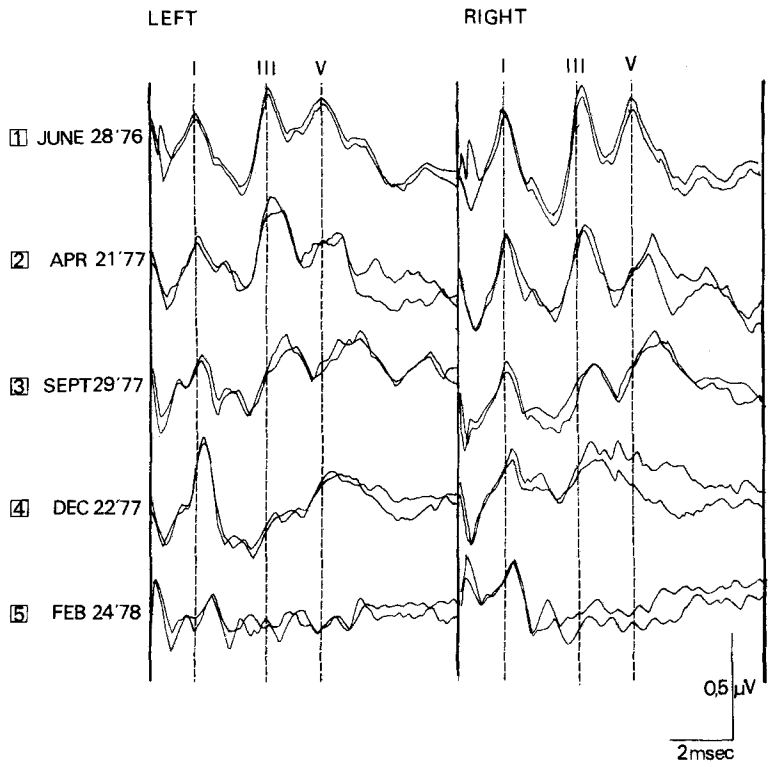

Fig. 2. Auditory brain stem evoked responses (ABR) from early stage (*1*) until terminal stage (*5*)

myelinating antibody test was positive and Mantoux test changed from a positive to a negative reaction after admission.

EEG recordings in light sleep showed high voltage slow waves in the early stage but almost flat patterns in the terminal stage.

CT scan was normal on admission, but another CT scan 6 months later showed bilateral high density areas in parieto-occipital subcortex, enlarged ventricles, and widened sulci. Subsequent CT scan showed widespread high density areas in the cerebrum but no visible change in the brain stem or the cerebellum.

ABR and SVR Findings

Successive ABR examinations revealed progressive configurational changes of the responses as his general condition deteriorated (Fig. 2). The first ABR on June 28, 1976, was normal but the response changed to an abnormal pattern on April 21, 1977. Initially, there was lengthening of the wave V-I interpeak interval (Fig. 2-*2*, 2-*3*). This was followed by the disappearance of the later components as the disease progressed.

In Table 1, latencies of each component are presented with accompanying ABR thresholds. These data suggest that degeneration progressed from rostral to caudal lev-

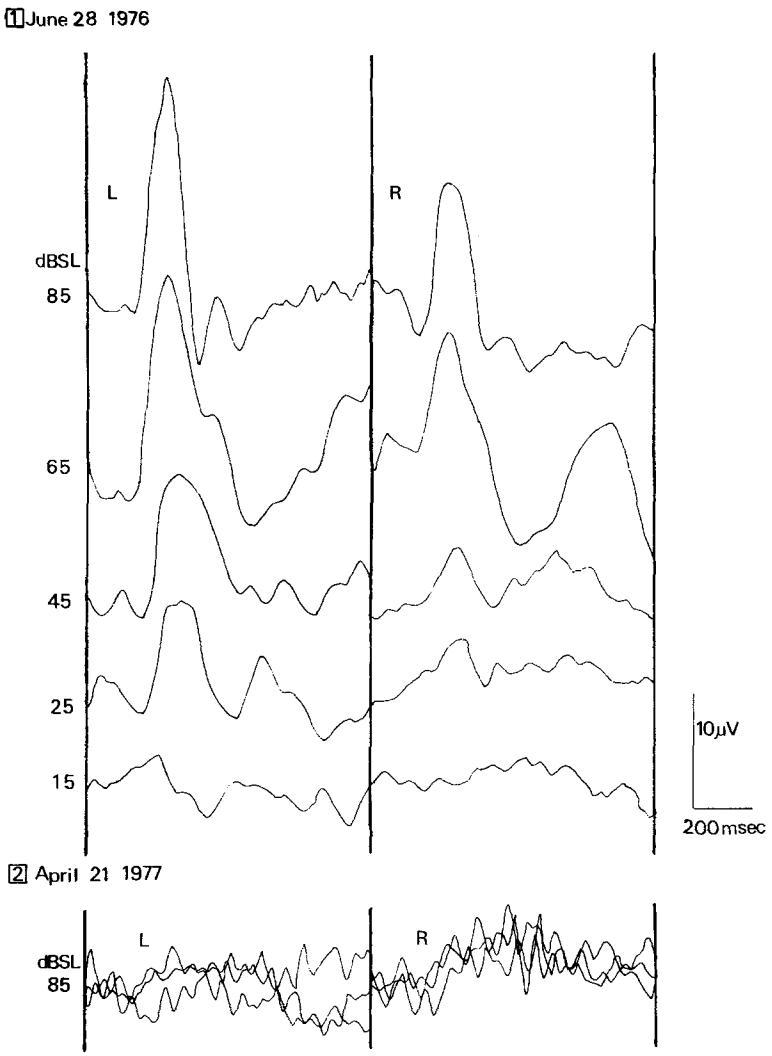

Fig. 3. Slow vertex potentials (SVR), at early stage (*1*), and 10 months later (*2*)

els because the prolongation of brain stem conduction time, as indicated by the increased V-I interpeak interval, was followed by the disappearance of later components until only wave I remained on February 24, 1978 (Fig. 2-*5*).

SVRs were recordable only at the early stage of the disease on June 28, 1976 (Fig. 3). Again this finding suggests a rostral-to-caudal progress of ALD.

Histological Findings of Cerebrum, Brain Stem, and Auditory Nerves

Histologically, the autopsy disclosed as the main alteration, extremely wide-spread demyelination of the white matter throughout the cerebrum, and as unusual findings,

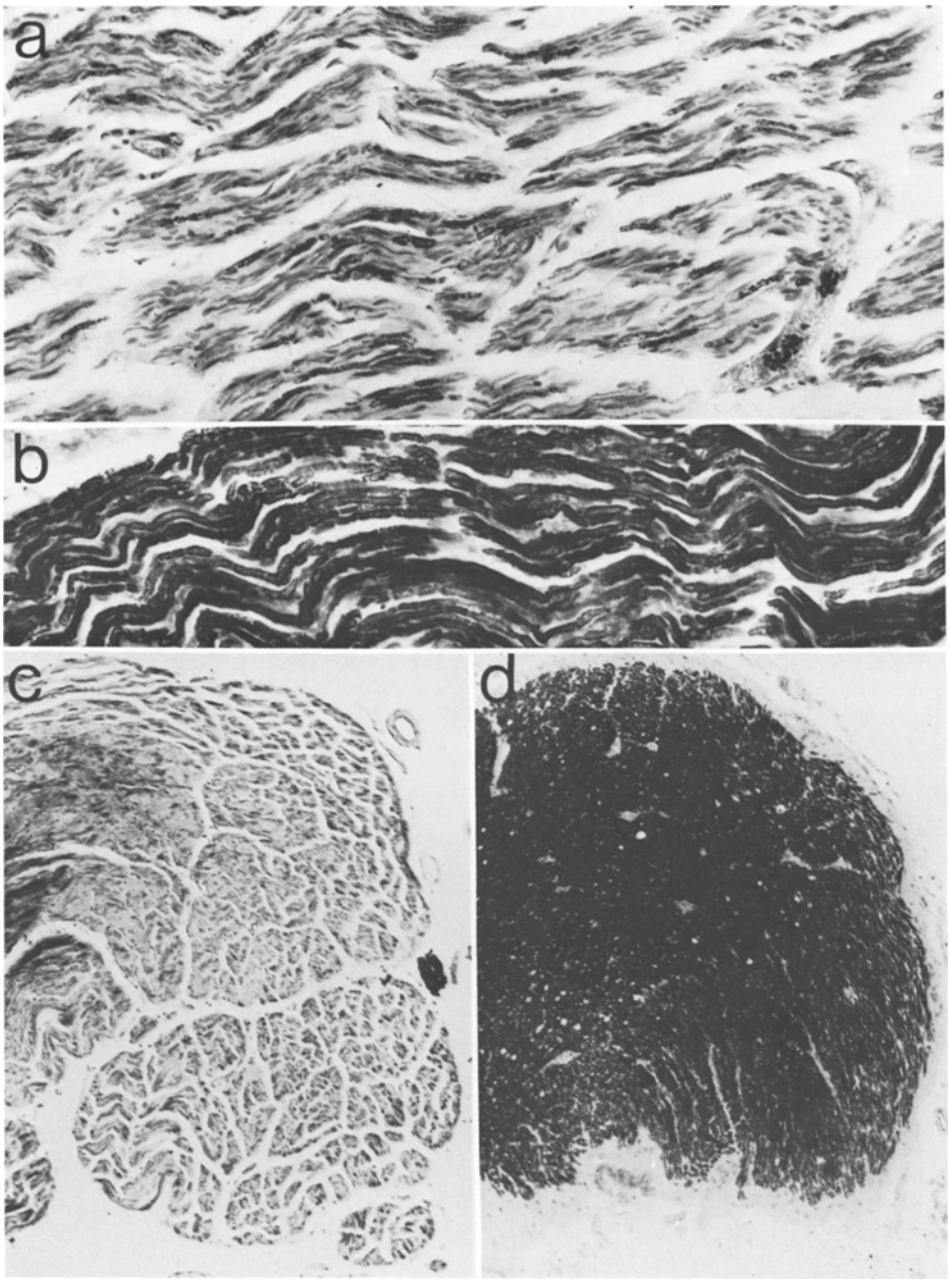

Fig. 4. Auditory Nerves: The VIII nerves (**a** longitudinal section; **c** transverse section) are demyelinated but facial nerves (**b** longitudinal section; **d** transverse section) are not damaged histologically. Luxol fast blue-cresyl violet stain. Longitudinal section × 40 and transverse section × 100

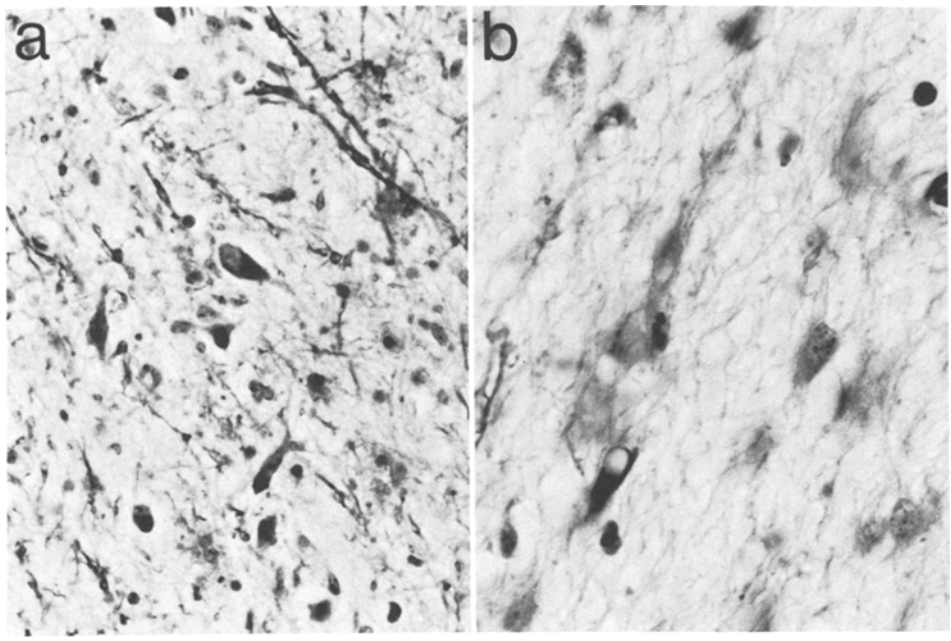

Fig. 5. Cochlear nucleus: **a** Most of ganglionic nerve cells in dorsal cochlear nucleus are lost and the nerve fibers are demyelinated × 100. **b** Most of ganglionic nerve cells in ventral cochlear nucleus are severely atrophic and some of them contain vacuoles × 200. Luxol fast blue-cresyl violet stain

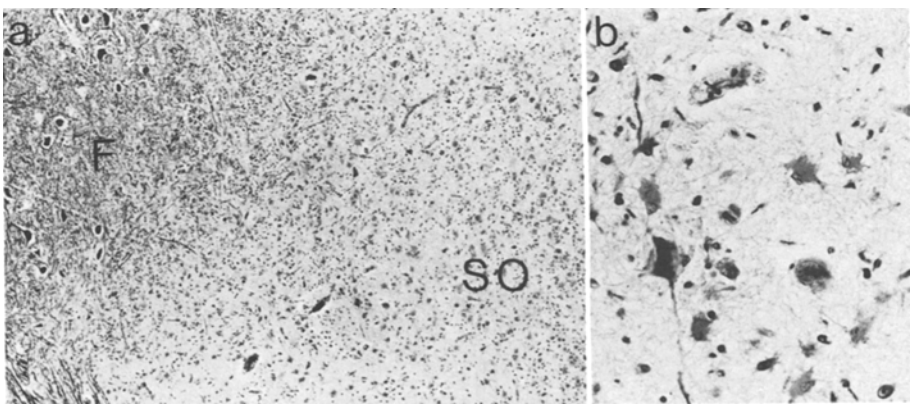

Fig. 6. Superior olivary complex and facial nucleus: **a** A great number of ganglionic nerve cells in superior olivary complex (*SO*) are pleomorphically degenerated and lost, but facial nucleus (*F*) which is adjacent to superior olivary complex is not damaged (**a**) × 25. **b** High power view of superior olivary complex. × 125. Luxol fast blue-cresyl violet stain

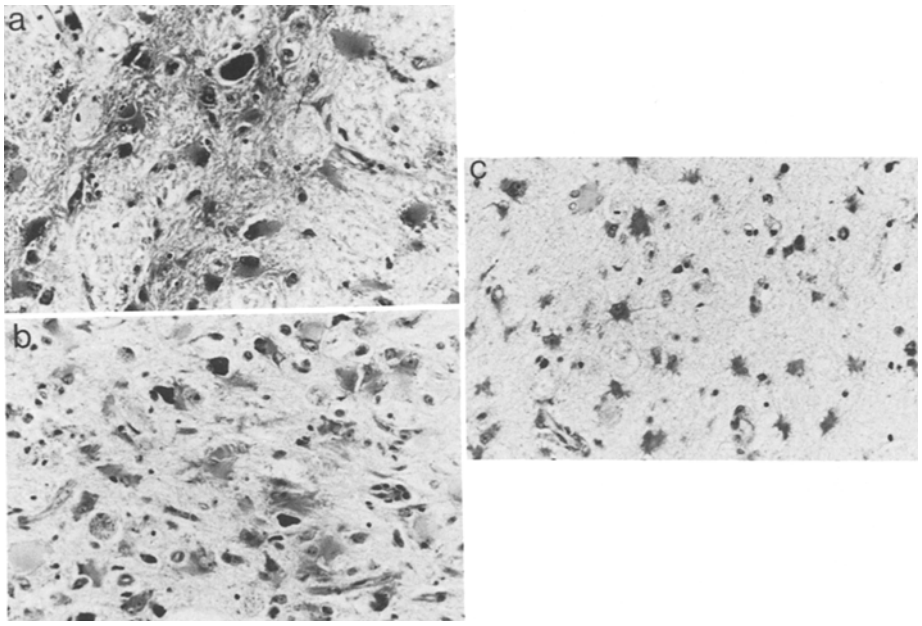

Fig. 7. Lateral lemniscus, Inferior colliculus and Medial geniculate body: **a** The ganglionic nerve cells in lateral lemniscus are degenerated and become ghost-like. **b** The ganglionic nerve cells in inferior colliculus are degenerated showing multiform in shape and size and scattered ghost-like cells. **c** The ganglionic nerve cells in medial geniculate body are ill shaped and degenerated. × 96. Luxol fast blue-cresyl violet stain

spotty hypermyelination of gray matter in localized areas. In addition, rather characteristic swelling of the cells in the adrenal cortex was observed. The histology of the brain stem revealed a remarkable neuronal disappearance and various kinds of degeneration of auditory nuclei and tracts including the cochlear nucleus, superior olivary complex, nuclei of lateral lemniscus, inferior colliculus, and medial geniculate body. The auditory nerves were observed to be demyelinated. On the other hand, vestibular nuclei, facial nuclei, and their nerves were not damaged (Fig. 4–7).

Biochemical analysis of the cerebrum revealed substantial proportions of long fatty acids (longer than 22 carbon atoms) and lipids both in the white and gray matter.

Discussion

ALD is now generally classified as a demyelinative disease primarily involving the white matter of the cerebral hemispheres, with onset in childhood or adolescence (Allen et al. 1975; Schaumburg et al. 1975). Our patient presented the typical picture of progressive blindness and also dementia. Hearing difficulty and spastic paralysis as were seen in our case are common signs of ALD.

Histologically, our case was generally consistent with those of Schaumberg et al. (1975). In this patient, cerebral lesions as a whole were distributed mainly in the

temporo-parietal and occipital areas; there was extensive demyelination of the cerebral white matter. Judging from the demyelinating process alone, the cerebral white matter was almost completely destroyed; furthermore, the corticospinal and corticobulbar tracts were also involved. Except for the ABR evidence that our patient's brainstem auditory pathway was affected, our patient was quite typical.

The evoked response findings were in close agreement with the clinical manifestations and behavioral observations. The SVR showed early abnormalities while the ABR was normal. This pattern is characteristic of cortical pathology as were the observations of hearing and vision losses. As the disease progressed, the ABR revealed abnormal delays of the later components suggesting increases in brainstem conduction time (Hecox et al. 1974; Robinson et al. 1975; Starr et al. 1975; Stockard et al. 1977). These findings were associated with motor signs which could be explained by the involvement of descending fiber tracts which run in close proximity to the auditory pathway in the brainstem. Finally, the absence of all ABR waves beyond wave I, which is of peripheral origin, suggested a severe impairment of brainstem function (Starr 1975; Stockard et al. 1976; Uziel et al. 1978). The clinical picture was again consistent at this stage. In addition, the histological findings confirmed extensive damage of central and peripheral auditory pathways in the brainstem from the cochlear nucleus to the medial geniculate body with demyelination in the auditory nerves. The decerebrate posture as well as respiratory impairment would follow from extensive brainstem involvement.

These findings indicate that the disease progressed in a caudal direction beginning in the cerebral hemispheres. Whether this caudal progression reflects a concentration gradient of the demyelinating agent, or a difference in myelin susceptibility, or differences in cell sensitivity to demyelination is a question which remains to be resolved.

This study also illustrates an important capability of auditory brainstem evoked responses. Not only can they help to identify the location of lesions (Ochs et al. 1979), but also they can be used to evaluate the progress of degenerative diseases such as ALD.

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