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Brainstem pathology of infantile Gaucher's disease with only wave I and II of auditory brainstem response

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Abstract

We studied the auditory brainstem response (ABR) and neuropathology in a female infant who died at six months of age because of typical infantile Gaucher's disease. The patient was hospitalized for hepatosplenomegaly and failure to thrive. Her ABR showed only waves I and II.

The neuropathological study disclosed that: (1) Gaucher's cells were found in the perivascular region of the cerebrum and anterior ventral nucleus of the thalamus. (2) Gliosis was found in the dorsal part of the brainstem rather than the ventral part. (3) Neuronal cells in the superior olivary nucleus were lost, and marked gliosis was found in the cochlear nucleus. The disappearance of wave III and later waves of ABR could be supported by these pathological findings.

Key words: Evoked responses, auditory; Gaucher's disease

Introduction

The auditory brainstem response (ABR) typically consists of a series of seven positive peaks appearing within 10 ms after click stimulation. It is considered to be generated primarily from the major brainstem nuclei and fibre tracts along the classic auditory pathway (Buchwald and Huang, 1975; Achor and Starr, 1980; Melcher *et al.*, 1996; Kaga *et al.*, 1997). An analysis of the ABR can provide indications of peripheral deafness, brainstem immaturity or brainstem lesions. For these reasons, the ABR is useful in diagnosing hearing disorders and brainstem diseases, especially in neonates, infants, and children.

Abnormal ABRs with partial disappearance of later waves have been reported in patients with infantile Gaucher's disease, but the correlation between ABR and brainstem pathology remains unclear (Kaga *et al.*, 1982; Lacey and Terplan, 1984). We report an infant with infantile Gaucher's disease who demonstrated the absence of all components of the ABR after waves I and II, correlating with brainstem pathology.

Case report

This female infant was born at 41 weeks of gestational age. Her birth weight was 3.380 g and appropriate for her age. The Apgar score was 10. There was neither consanguineous marriage nor contributory familial history. Congenital itchiosis was noted but this was treated by steroid ointment. Because of her poor responses to visual and auditory stimuli in her home, disturbances in vision and hearing were suspected. TORCH was screened and excluded. Since remarkable splenomegaly was found, she was referred to the paediatric division of Tokyo Teishin General Hospital. On admission her liver was palpable 3 cm below the right costal margin. Her spleen was firmly palpable and measured 5 × 5 cm. This hepatosplenomegaly was investigated and metabolic or haematological diseases were excluded.

Laboratory examination disclosed increased acid-phosphatase of 47.4 KU/L and increased immunoglobulin M of 535 mg/dl. Bone marrow aspiration demonstrated Gaucher's cells. Activity of β-glucosidase of cultured fibroblasts of skin was one twentieth of the normal activity level. Brain computed tomography (CT) scanning showed atrophy of bilateral temporal lobes. Behavioural observation audiometry showed poor responses to sound stimuli at four months of age. The behavioural thresholds for 0.5–,

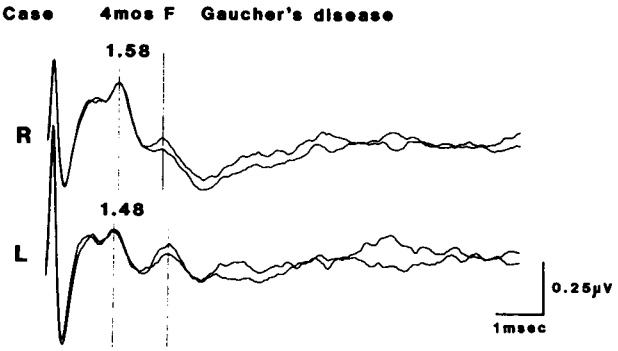

FIG. 1

Auditory brainstem response at four months of age. Only waves I and II were elicited in both ears.

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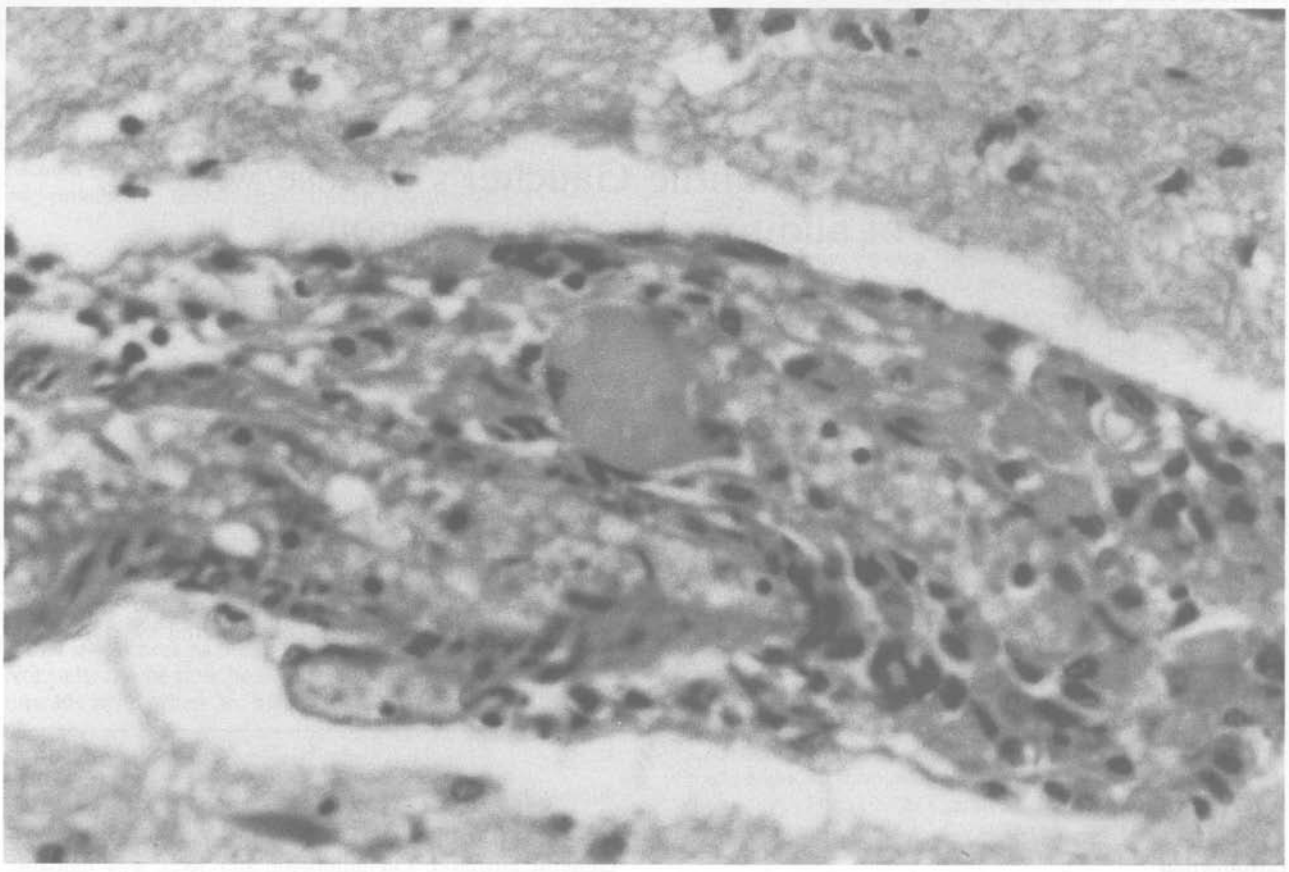

FIG. 2
A large Gaucher's cell in the anterior ventral nucleus of thalamus. (H & E; × 100)

1–, 2– and 4–kHz tones were determined by taking the lowest of the thresholds for eliciting auropalpebral, startle, or the Moro reflex for each frequency of sound stimuli in the open field settings. Auditory brainstem responses were recorded at four months of age and all recordings disclosed only waves I and II with normal latencies. However, subsequent waves were absent in both ears (Figure 1).

After admission, hepatosplenomegaly increased very rapidly. Although a nasonutritional tube was used to provide milk, typical neurological signs of external strabism, trismus, opistotonus and dyspnoea appeared. She died at the age of six month because of central respiratory failure.

Autopsy findings

Her height was 61 cm and her weight was 7.0 Kg at death.

(1) General findings

(a) Lungs were mildly oedematous and congested with blood presenting Gaucher's cells in the alveolar cavities.
(b) The liver weighed 500 gm and the spleen weighed 185 g. Remarkable proliferation of Gaucher's cells was found in both visceral organs.
(c) Remarkable proliferation of Gaucher's cells was found in the lymph nodes, thymus, bone marrow and adrenal glands.

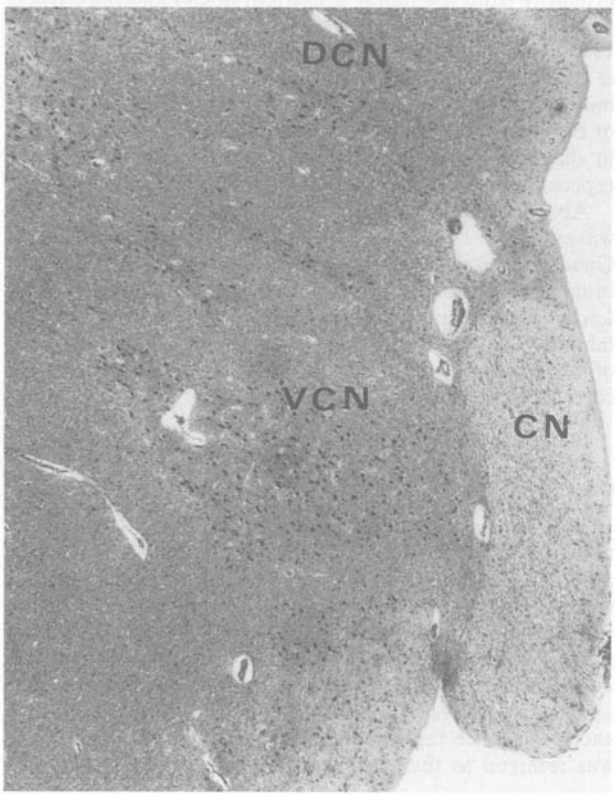

FIG. 3
Gliosis in the cochlear nerve (CN) and the cochlear nucleus (H & E; × 40) VCN: Ventral cochlear nucleus. DCN: Dorsal cochlear nucleus.

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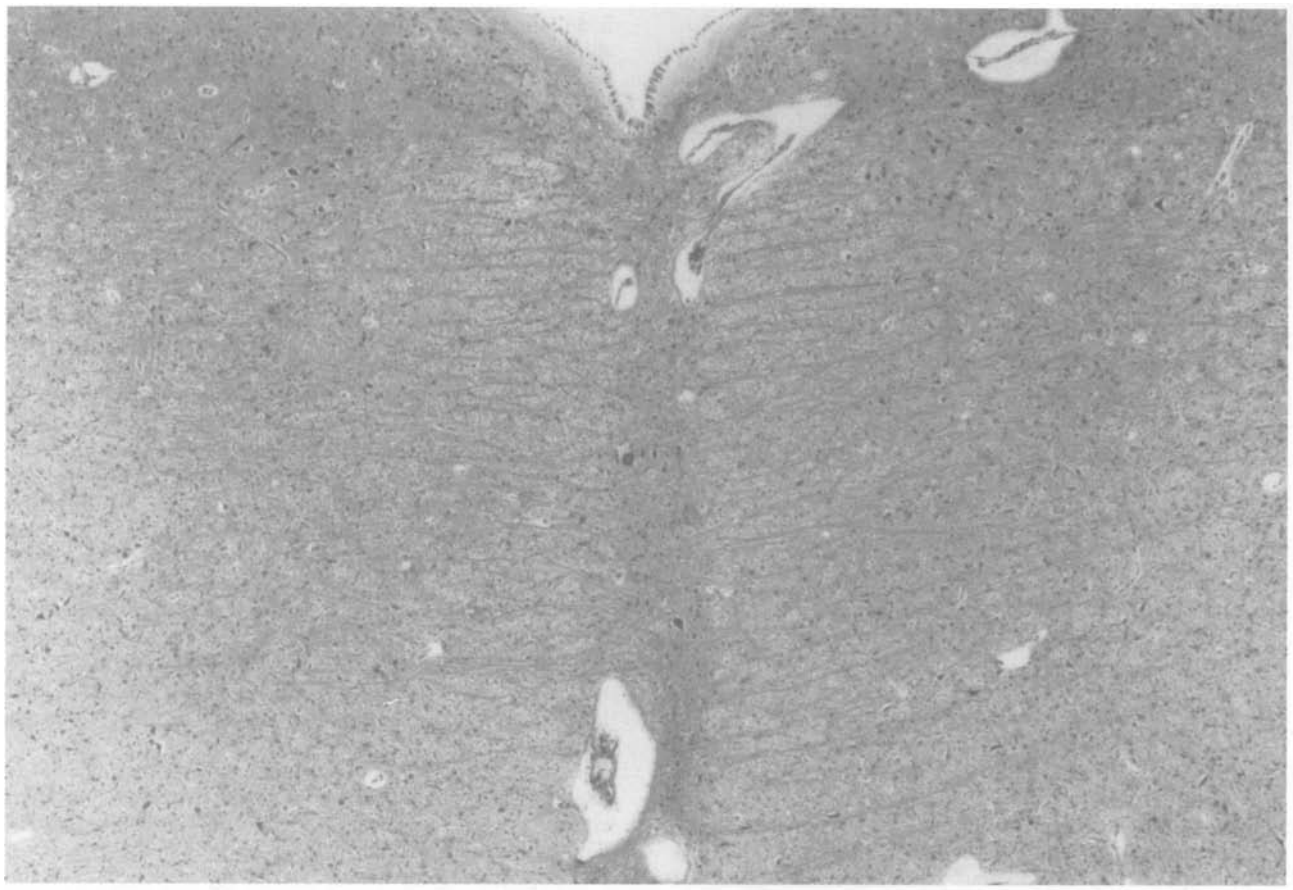
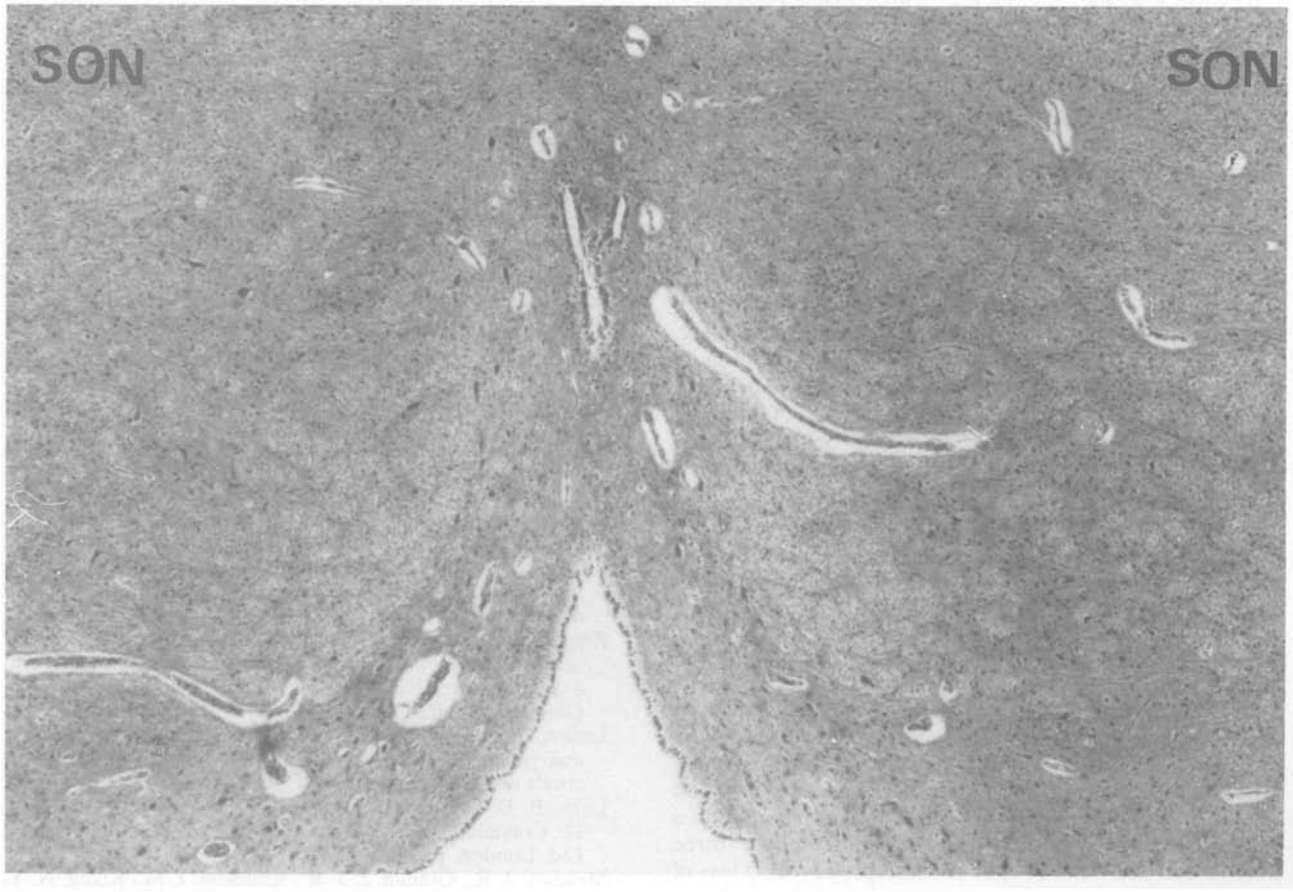


(a)



(b)

FIG. 4

Cross-section of lower brainstem gliosis was more marked in the dorsal part (a) than in the ventral part (b), and loss of neuronal cells in the superior olivary nucleus was seen (H & E; × 4) SON: Superior olivary nucleus, DCN: Dorsal cochlear nucleus.

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(2) Neuropathological findings

The brain weighed 644 g and showed mild swelling, but there were other abnormal microscopic findings.

(a) Remarkable gliosis was found in the optic nerve and CA_2 of the hippocampus. Gaucher's cells were found in the brainstem, the perivascular area of the cerebrum and anterior ventral nucleus of the thalamus (Figure 2).
(b) Gliosis was remarkable in the poximal division of the cochlear nerve and in the dorsal part of the brainstem but not in the ventral part (Figure 3).
(c) Loss of neuronal cells was prominent in the oculomotor, facial and trigeminal nuclei in order. No clinical signs were found in spite of the loss of neuronal cells in these nuclei. In brainstem auditory nuclei, loss of neuronal cells was prominent in the superior olivary complex and gliosis was observed in the cochlear nucleus (Figure 4).
(d) In the cerebellum, the external granular cell layer and nucleus of dentatus were lost and the Purkinje cells were swollen.

Discussion

Our patient showed only waves I and II on ABR at four months of age. The aetiology was determined as Gaucher's disease by lysomal deficiencies on bone marrow aspiration before death. Although lesions in the brain were wide spread, brainstem pathology revealed loss of neuronal cells in the superior olivary nucleus and remarkable gliosis of the cochlear nucleus and cochlea nerve. These neuropathological findings could be well correlated with the ABR abnormality.

Gaucher's disease is classified into three types, affecting adults, infants and juveniles, respectively (Lake, 1984). Infantile Gaucher's disease is called type 2, acute neuronopathic Gaucher's disease, and usually presents within six months of birth, the neonatal period often being normal. The first signs of hepatosplenomegaly, failure to thrive or difficulty in feeding can occur singly or in combination. Motor delay is evident by six months and this progresses to cranial nerve and extrapyramidal tract involvement. Fits are not common. Death, usually from pulmonary infection, occurs before the second birthday. The gross appearance of the brain is not abnormal in type 2. However, Lake (1984) summarized abnormal microscopic findings of the brain in type 2 of infantile Gaucher's disease which is described below: 'In the cerebral cortex there is no evidence of neuronal storage and only a mild loss of neurons is seen in layers 3 and 5. Myelination appears normal for age. Free Gaucher's cells are found in the cortex and perivascularly. In the basal ganglia and brainstem, marked to moderate neuronophagia and gliosis is evident, while in other neurons there is mild cytoplasmic swellings suggesting storage'.

Kaga *et al.* (1982) recorded only waves I, II and a small wave III in a case of infantile Gaucher's disease at six months of age and only waves I and II by eight months of age, but the autopsy showed relative preservation of the nuclei and tracts of the auditory pathways in the brainstem. Lacey and Terplan (1984) recorded only waves I, II and III, then soon after only waves I and II were recorded in a case of infantile Gaucher's disease who died at three months and one week of age. The autopsy revealed loss of neuronal cells in the cochlear nucleus and superior olivary nucleus as well as the vestibular nucleus, fasciculus cuneatus, inferior olivary nucleus and dentate nucleus.

In our patient, the location of lesions clearly included the lower brainstem, as shown in the neuropathology and by the ABR which demonstrated only waves I and II without subsequent waves. Similar abnormal configurations of the ABRs have been reported in patients with lower brainstem neurological diseases (Starr and Hamilton, 1976). In lesion studies and field analysis in animal experiments, the origins of wave I and wave II were demonstrated as the ipsilateral auditory nerve and cochlear nucleus (Buchwald and Huang, 1975; Achor and Starr, 1980; Melcher *et al.*, 1996; Kaga *et al.* 1997). The origins of wave III were reported as the bilateral superior olivary complexes (Buchwald and Huang, 1975; Achor and Starr, 1980). These reports of the origins of the ABR in clinical and animal studies would predict involvement of the projections to the olivary complexes or the nuclei themselves in our case. The work of Møller *et al.* however, suggests the intracranial portion of the auditory nerve itself as the generator of wave II (Møller *et al.*, 1981; Møller and Janetta, 1983). If this interpretation is correct, then it would seem reasonable that the cochlear nucleus itself was damaged in our case but waves I and II were elicited. Lesions at other locations in the brain of our case cannot be ruled out by the ABR; since the auditory pathways were interrupted above the level corresponding to wave II, no information could be obtained about a higher level beyond the superior olivary nucleus by the abnormal ABR.

Brain CT scans and electroencephalography, which are useful tools for diagnosing lesions, showed nothing remarkable in this case with infantile Gaucher's disease. Thus, it is emphasized that the ABR was the only electrophysiological means of finding evidence of brainstem lesions in particular patients. At the time of this case report we did not have the facility of magnetic resonance (MR) scanning.

Finally, it is noted that ABR abnormality was well correlated with brainstem pathology in our case. We emphasize that the ABR is a very useful tool in evaluating brainstem function and pathology in infantile Gaucher's disease if the brainstem involvement exists in the brainstem auditory pathway. It is quite possible to have a normal ABR in some early cases. On the other hand, ABR latencies can be very useful in some cases to look at involvement of the auditory pathways and serial ABRs may be helpful to assess the progress.

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