KAWASAKI MED. J. VOL. 9 : NO. 2, 73-80 (1983)

Development of Changes in VEP and Associate Neuropathology on Creutzfeldt-Jakob Disease

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Accepted for Publication on April 9, 1983

ABSTRACT. A case, 74-year-old female, of Creutzfeldt-Jakob disease (CJD) was reported with a chronological changes of visual evoked potentials (VEPs) and neuropathological findings. The disease started with a disturbance of visual integration and developed to blindness, myoclonus, mental deterioration and akinetic mutism. A clinical diagnosis was made by a periodic synchronous discharge of EEG and other neurological specificity. Autopsy findings showed a peculiar spongy degeneration of the cerebral cortex.

The flash VEP showed a loss of w-shaped wave and a marked delay of the peak latencies in the early stage. Subsequently, the once delayed latency was shortened with the advance of the illness in the middle stage and the N_{70}-P_{100} amplitude became a huge triphasic wave like inversed ERG. Topographic distribution of the focus of huge component appeared on the left parieto-occipital region. At the terminal stage, the amplitude of huge component reduced. The mechanism of specific VEP changes in this case was interpreted to be due to the loss of generator due to spongy degeneration and the existence of cell fusion in the occipital cortex.

Key words : Creutzfeldt-Jakob Disease — VEP — Neuropathology

A neuroophthalmological interests in Creutzfeldt-Jakob disease (CJD) is the disease involves cortical blindness with a huge early potential of VEP and the disease is transmissible by keratoplasty.

Our previous paper by Tsutsui, Kawashima, Terao and Shirabe[1] reported the peculiar VEP and related pathology as our first case. In this second case, some advanced study had been conducted on the chronological change of VEP and the influence of diazepam on VEP.

CASE RECORD

The patients was a 74-year-old female and she had no remarkable past

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and family history. The illness started with visual disturbance and reduction of calculating ability from July 10, 1981. From the end of July, irritability and emotional instability were observed and amnesia and loss of memory were increased. From early August, there appeared a mutism, delirium and hallucination, and athetotic movement. From the middle of August, myoclonus and akinetic mutism started. On August 31, she was hospitalized in our hospital and was diagnosed as CJD.

Neurological signs were mental deterioration, akinetic mutism, decorticated rigidity and myoclonus seizure. Computerized tomography showed a slight cortial atrophy (Fig. 1). EEG showed a theta and delta wave and periodic synchronous discharge of more than 200 msec duration with a cycle of 0.6–0.8 sec.

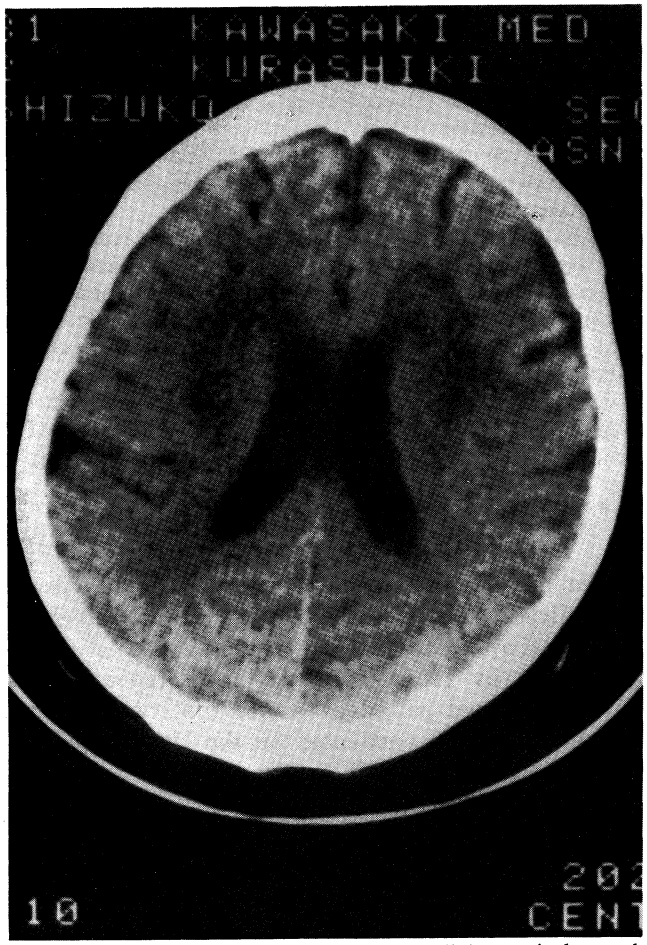

Fig. 1. Computerized tomography showed a slight cortical atrophy.

Although some neurological and symptomatic treatments were given, the patient died on October 2nd and the autopsy was carried out.

In the neuroophthalmological examination, the corneal blink reflex disappeared but pupillary light reaction was remained normal. Ocular movement showed a random purposeless movement. Fundi showed a slight angiosclerosis of retinal artery (KW II) but the optic disc was of normal appearance.

ELECTROPHYSIOLOGICAL EXAMINATION

Simultaneous recordings of ERG and VEP were performed 4 times during 21 days. Flash stimuli (1 joule, 1 Hz, distance 50 cm) were given under the eye closed condition. The ERG was normal throughout the clinical course. The chronological changes in VEP showed three major trends.

A change of the early stage was characterized by a marked delay in all components (Fig. 2). The component corresponding to N_{70} and P_{100} had a

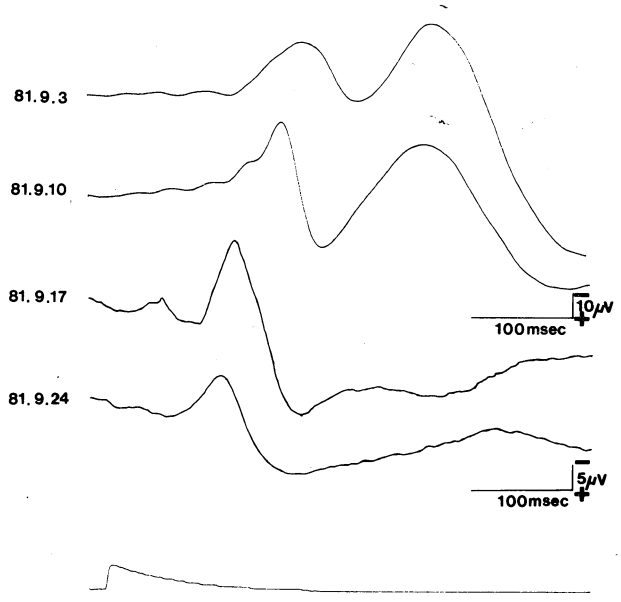

Fig. 2. Chronological changes in VEP. Upward negativity.

remarkable delay to N_{191} and P_{252}. The change of the middle stage featured an early huge negative wave. The once delayed first negative peak latency decreased gradually from 191 to 87 msec and the first negative and positive peak amplitude increased sharply from 20 μV to 66.6 μV to become early large negative peak or a triphasic wave like an inversed ERG wave. The late component became a longstanding positive change with a disappearance of

negative deflection. The topographical distribution of the early huge negative peak was the largest (-61.3μV) at the left parietooccipital region (Fig. 3).

In the terminal stage, the huge potential, however, decreased to 18.3 μV on the day before death.

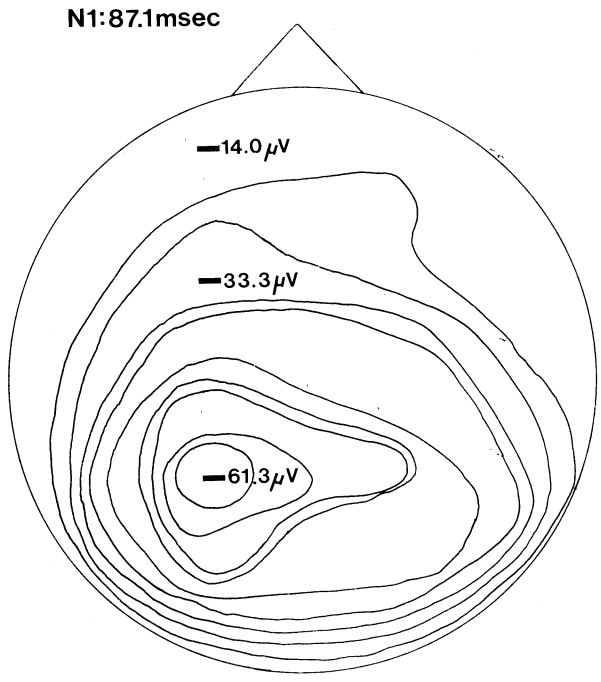

Fig. 3. Topographical distribution of the early huge negative peak.

The effect of diazepam on VEP was also investigated because this drug was sometimes used to reduce the myoclonus. The early component showed no influence but the late component disappeared and inversed polarity was noted. However, this phenomenon recovered to the original state after 60 minutes (Fig. 4).

PATHOLOGICAL FINDINGS

Because the neuropathological changes in whole brain of this case had reported by two of the authors, Shirabe and Terao,[2] only related findings with VEP is introduced here.

According to the macroscopic findings, the brain weighed 960g and narrowing of the gyrus and enlargement of the sulcus were observed. On the cut surface, at the frontal section located 4 cm from the posterior pole, atrophy of the cortex

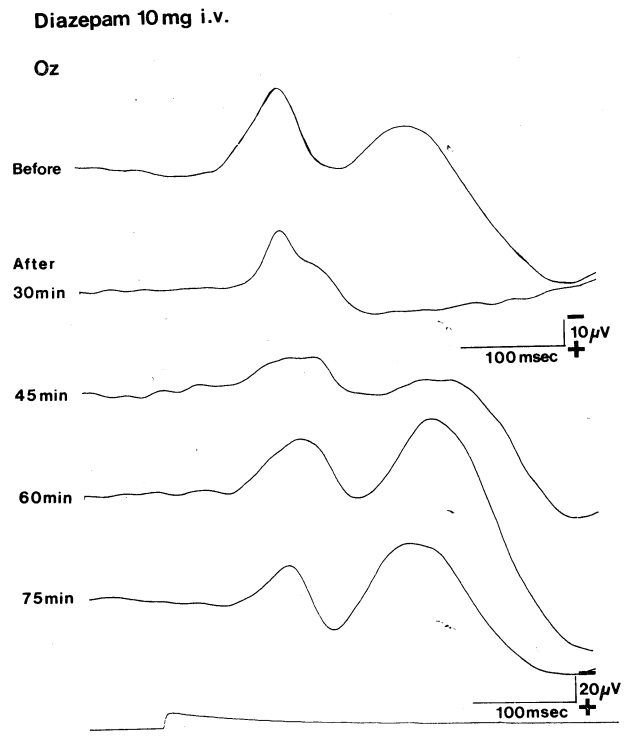

Fig. 4. Diazepam effect in VEP.

was most clearly seen in Area 17 and 18 (Fig. 5). In the light microscopic findings, the cerebral cortex lost the lamellar structure and thinning-out decrease of nerve cells mainly of the 2nd and 3rd layer were conspicuous to present spongy degeneration (Fig. 6). Besides marked astrocytic proliferation and reactive gliosis were observed. The midbrain, pons, medulla oblongata, optic nerve and lateral geniculate body were normal. Quantitative analysis of the residual nerve cell showed 66% in Area 17: 36% in Area 18: 52% in Area 19: 45% in temporal lobe, 67% in parietal lobe, 93% infrontal lobe, 62% to 90% in basal nucleus, 72% to 97% in thalamus, and 53% in the anterior nucleus.

According to electron microscopic findings, the vacuole formation was seen around the neuropil (Fig. 7). There was no findings of cell fusion nor gap junction. The pathological diagnosis of this case was established as diffuse cerebral type of CJD.

DISCUSSION

In this case study, the influence of a progressive cortical degeneration on the chronological change of VEP was investigated. Since this case is our second

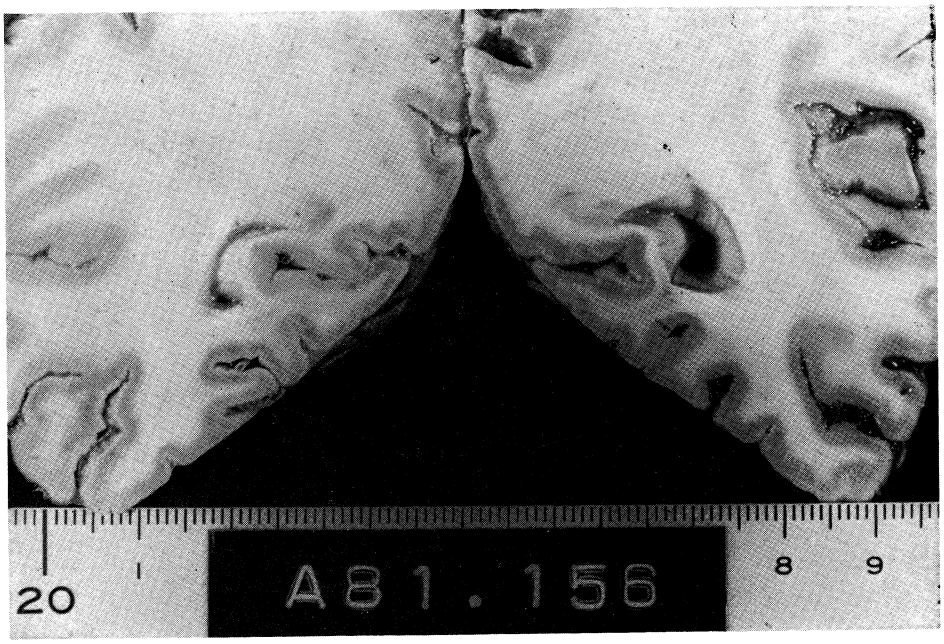

Fig. 5. The cut surface, at the frontal section located 4 cm from the posterior pole.

case of CJD, more detailed and advanced data than the first case could be obtained. Moreover, the influence of diazepam which is frequently used in the treatment of this disease could be avoided. Complete neuropathological data including electronmicroscopic findings gave a significant value to make an interpretation of the electrophysiological change.

Since the visual pathway and the lateral geniculate body had been quite normal up to the terminal stage, the delayed latency in the VEP in the early stage indicate a disturbance of the interneuronal connection in the visual cortex. Landis et al.[3] reported that the histopathological change of CJD in early stage is a disruption of the interneuronal dendrite in the cortex or cortico-cortical projection. In this case, the less intensive cortical damage was seen in the frontal lobe and the interneuronal damage was the main finding. Reduced activity of the cortical nerve cells may bring a delayed generation of VEP but the main component of VEP still existed, though the patient was already blind in this stage.

In the second stage of this disease, the necrosis of cortical nerve cells increased. The reduction of responsible nerve cells in the cortex showed a second stage of VEP change which was characterized by the huge negative deflection. Judging from a topographical findings, a focus of the huge negative wave was located in the occipito-parietal area especially in the left hemisphere. As the cause of huge potential, we consider the following two reasons. The

Fig. 6. Microscopic findings of the left occipital lobe. Hematoxylin Eosin staining. ×62.

disturbance of cortical suppression to the lateral geniculate body may be accountable for a large amplitude. As the second explanation, the electrogenesis of this huge potential was explained by the findings of cell fusion. Kindson[4] and Moreau–Debois[5] have recently been reported that nerve cells themselves produce cell–fusion in CJD. According to Traub,[6] this fused nerve cell would be in a state of electrotonic coupling and elicit the huge potentials. However in this case, we failed to prove the cell fusion morphologically because the autopsy was done in the stage of reduced huge negative wave. This fact suggested a considerable advance of degeneration of the nerve cells. As another change, in our first and the second case also, the triphasic wave of VEP was characteristic. We confirmed that it appeared in the middle to the late stage. The once delayed N_{70} in the second stage is shortened with the progress of stage of illness. Such a paradoxical phenomenon has not been reported in CJD. Since the spongy degeneration of the visual cortex advanced in this stage, the generation of VEP might be subcortical level. The long tailed positive deflection after the huge negative wave also suggests a subcortical condensation of impulses

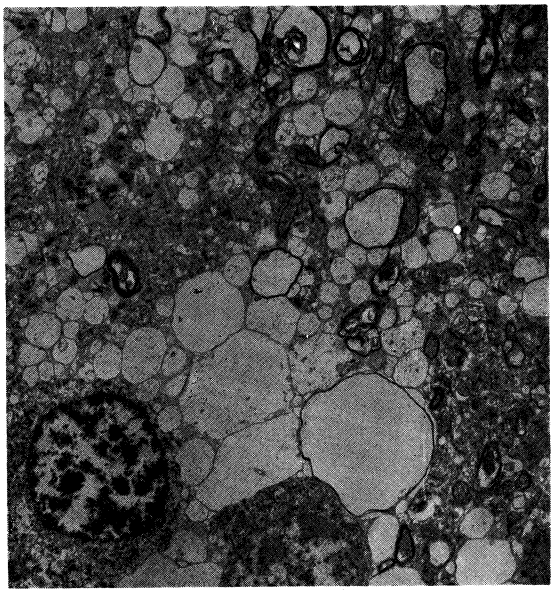

Fig. 7. Electron microscopic findings of the right occipital lobe. ×6000.

which might be the result of loss of cortical treatment of the visual input. The huge negative and tailed positive components became very small amplitudes at the terminal stage. This evidence corresponded the extensive loss of nerve cells seen in the histopathological findings.

Published in the Fourth Meeting of the International Society of Neuro-ophthalmology, June 15, 1982, Hamilton, Bermuda.

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