Cortical and Non-cortical Myoclonus of Creutzfeldt-Jakob disease

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Abstract

Aim of the study: Creutzfeldt-Jakob disease (CJD) is a prion protein disorders, characterized by rapid cognitive decline, myoclonus and periodic synchronous discharges (PSDs) on electroencephalograms (EEGs). We reported the case of a 75 -year -old patient with the typical clinical manifestations of CJD. After identifying and characterizing the distinct types of myoclonic jerks recorded in the patient, the jerk-locked EEG back-averaging technique was employed to determine whether there is a causal link between the myoclonus and PSDs.

Results: Four different waveforms of cortical potentials were obtained by averaging the EEG epochs. Two types of cortical potentials were locked to myoclonic jerks. One type of cortical potentials was not associated with any detectable muscle jerk, and 1 type of muscle jerk was not related to any cortical potentials.

Conclusion: The findings suggest that the myoclonus in CJD has a variable pathogenesis and is not always related to PSDs. Both cortical and subcortical mechanisms may be involved in this CJD patient.

Background

The characteristic symptoms of CJD include rapidly progressive cognitive decline and myoclonus [1]. Myoclonus in CJD patients is supposed to be associated with the appearance of periodic synchronous discharges (PSDs) on routine electroencephalograms (EEGs) [2]. However, a casual relationship between myoclonus and the PSDs has not been established. Here, we report the case of a CJD patient with positive myoclonus and analyze the cortical potentials locked to the myoclonic jerks.

Case Report

A 75-year -old man developed difficulty in targeting and catching objects with his left hand 3 weeks before visiting our neurological clinic. One month after the onset of initial symptoms, he started experiencing semi-rhythmic jerks in the left hand that were sensitive to pinprick stimuli. In the following 2 months, the patient showed significant memory and cognitive impairment, whereas muscle tone, muscle strength, and deep-tendon reflexes were intact. On examination, alien hand phenomenon without intermanual conflict was noted. The left hand tended to wander independently and grope nearby objects. Cerebrospinal fluid samples were negative for protein 14-3-3. The possibility of disorders such as thyroid function disorder, vitamin B12 and folate deficiencies, hepatitis B, vasculitis, and syphilis was excluded by the results of biochemical screening tests. EEG showed PSDs with the largest amplitude over the central parietal area of the right hemisphere (i.e., C4 and P4; Fig. 1a). Magnetic resonance imaging (MRI) study showed restricted diffusion over the right frontal, parietal, and occipital lobes in diffusion-weighted imaging (DWI) (Fig. 1b). ^{99m}Tc-TRODAT-1 revealed a bilateral decrease in striatal uptake values (Fig. 1c).

The patient's symptoms continously deteriorated. The patient became bedridden, and showed akinetic mutism and loss of swallowing capabilities at around 2.5 months after

the disease. According to WHO criteria (1998), probable CJD was diagnosed. The WHO criteria had a diagnostic accuracy of 96.5% in a follow-up study performed in 313 patients [1]. Protein 14-3-3 was absent in 9.9% of the patients diagnosed with probable CJD on the basis of the criteria [1].

Electrophysiological recordings

The myoclonic jerks were recorded by multi-channel surface electromyography (EMG). Jerk-locked back-averaged EEG recording was performed with 3 gold-plated electrodes (C3, Cz, and C4) affixed to the scalp. We adopted EMG onset of spontaneous myoclonic jerks from left hand triceps as the trigger for the EEG back-averaged sampling (sampling rate: 2 kHz, filtered band pass: 0.05-70 Hz). Artifact-free EEG epochs from 200 ms before to 300 ms after EMG onset were used for averaging. Somatosensory evoked potential (SEP) was also recorded.

Results

Surface EMG recording revealed semi-rhythmic bursts for the recorded muscles at a duration of around 60 ms (Fig. 1d). On the basis of the relationship between the left hand triceps jerks and the EEG signals, 4 distinct types (Type-A to -D) of conditions were characterized (Fig. 1e). Type-A jerks had a mean duration of 60.35 ± 10.11 ms and mean amplitude of 179.13 ± 64.12 μV. The mean latency of the jerk onset to the maximal EEG

negativity was 24.22 ± 11.07 ms. In comparison to type-A jerks, type-B jerks had a smaller amplitude (60.86 ± 40.43μV) and similar duration (56.85 ± 9.01 ms). No significant EEG potentials were detected by locking the onset of type-C jerks (mean duration: 32.45 ± 3.69 ms, mean amplitude: 24.3 ± 3.40 μV). Some PSD were not jerk-locked (Type-D). No giant SEP was found.

Discussion

PSD is a common and characteristic EEG finding in CJD patients [3]. An abnormal subcortical pacemaker, which is probably synchronized with the cortical potentials, was supposed to play a pivotal role in the PSD generation [4]. Impairment of normal inhibitory function at the cortical level may further amplify the influence of this pathological pacemaker [4]. Myoclonus is another important symptom for the diagnosis of CJD. They are often diffuse, generalized and relatively rhythmic in CJD patients. In asymmetric cases, the jerks are usually accompanied by dystonia or alien hand syndrome [5]. Both positive and negative myoclonus have been reported in CJD. Some cases did not show a giant SSEP or enhanced C reflex [6]. To which extent the observed PSD in CJD patients is relevant to the myoclonus remains unclear. Shibasaki et al. employed a jerk-locked SEP technique and reported that cortical excitability was suppressed between periodic myoclonic jerks, and this suppression was associated with PSD in a CJD patient [7]. Our findings for the current CJD patient provide further insight into this phenomenon and illustrate that the cortical potentials may or may not lock to the myoclonic jerks and vice versa. One of the possible explanations for this finding is that the generators of the myoclonic jerks are located at different cortical and subcortical levels. The fact that some jerks were not associated with any detectable cortical potentials

may indicate that their generator was located very far away from the cortex, i.e. subcortically located, and such jerks were unable to be recorded during the current scalp EEG recording; alternatively, these jerks were randomly evoked and not locked to any specific cortical potentials in a fixed time period. In a typical subcortical myoclonus, i.e., reticular reflex or hyperekplexia, the jerks may involve all 4 limbs and the muscles innervated by the cranial nerve. The jerk duration may range from 50 to 100 ms [8], which is longer than the duration of the type-C jerks observed in the present study. In contrast, the appearance of robust cortical potentials or PSDs were not always restricted to any myoclonic jerks. These findings support the notion that the generalized PSD may have different influences on the motor neuron excitabilities at cortical and subcortical levels. The subcortical involvement in the current patient was also evidenced by the bilaterally decreased striatal uptake (Fig.1c), although this phenomenon may be irrelevant to the generation of jerks or PSDs.

The direct evidence that confirmed the cortical origin of type-A and-B of the jerks was the presence of a jerk-locked EEG event. The latency between the onset of jerks and the peak of the cortical potentials was ~24 ms, which is close to the physiological range of the SEP. In the cases of jerk-locked EEG events, we did not find giant SEPs in the scalp recordings. Giant SEPs was classically found in patients with cortical myoclonus [9,10]

and are caused by hyperexcitability of the primary sensorimotor cortex [11]. However, giant SEP was not seen in all patients with cortical myoclonus. This finding implied that either these patients have no abnormality in the cortical processing of sensory inputs, or the dysfunction is not sufficient to be detected by classical SEP studies [12]. For example, there was usually no giant SEPs in corticobasal degeneration patients with cortical myoclonus. This may result from cortical lesions with functional loss at the corresponding area [13,14] and this could also be the reason in the current CJD patient, who showed a lateralizing cortical involvement in DWI (Fig. 1b).

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Figure legends

Fig 1a. Routine EEG study shows periodic synchronous discharges with predominance over the C4 and P4 electrodes.

Fig 1b. Increased signal intensity in diffusion weighted image (DWI) at right frontal, parietal, and occipital cortical areas.

Fig 1c. ^{99m}Tc-TRODAT-1 SPECT analysis of the brain shows a specific uptake in right striatum (1.12) and left striatum (1.07). The specific uptake is obtained by subtracting the mean counts per pixel in the occipital cortex (OC) and the mean counts per pixel in the whole striatum (ST) and dividing the result by the mean counts per pixel in the background. (Equations: (ST-OC)/OC; referential normal values in striatum:1.69-2.15)

Fig 1d. Surface EMG recorded from left hand triceps muscle of the patient. The signals showed a semi-rhythmic pattern of the EMG bursts.

Fig 1e. Four types of the averaged EMG and EEG recorded from the patient. Type-A and type-B myoclonic jerks are locked to the cortical potentials, most obviously at C4, and

are shown in the first and the second row, respectively. The third row demonstrated the absence of time-locked cortical potentials for some of the myoclonic jerks. The fourth row shows the cortical potentials without time-locked myoclonic jerks. The number of the averaged EEG epochs was 193, 43, 129 and 114 for types A, B, C, and D respectively.