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Case report

Primary progressive aphasia with focal periodic sharp wave complexes: An unusual manifestation of Creutzfeldt-Jakob disease

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ABSTRACT

Background: Creutzfeldt-Jakob disease (CJD) is a devastating degenerative brain disorder caused by an abnormal isoform of a cellular glycoprotein which is known as the prion protein. A diagnosis of CJD is usually based on specific clinical signs, EEG and MRI findings, as well as the presence of the 14–3-3 protein in the cerebrospinal fluid. Although end-stage CJD usually has a typical clinical presentation, early symptoms may be variable.

Case presentation: We present an uncommon case of CJD which manifested with primary progressive aphasia, leading to an incorrect diagnosis of frontotemporal dementia. EEG performed eight months after symptom onset revealed focal periodic sharp wave complexes that later evolved into diffuse EEG abnormalities characteristic of CJD. Brain MRI also suggested the diagnosis of CJD. Later, the patient developed rapidly progressive dementia, visual symptoms, ataxia, extrapyramidal symptoms, followed by dysphagia and mutism, and died 34 months after disease onset.

Discussion and conclusion: PPA is a relatively uncommon first manifestation of CJD, occurring only in about 1% of all CJD cases. Our case is also remarkable because we were able to capture focal periodic sharp wave complexes at the stage of the CJD when aphasia was the only clinical manifestation. We demonstrate that both brain MRI and wake and sleep EEG should be a mandatory part of the diagnostic workup for patients presenting with primary progressive aphasia.

1. Introduction

Primary progressive aphasia (PPA) is a highly heterogenous syndrome of neurodegenerative origin characterized by isolated gradually progressive speech impairment. Based on the clinical pattern of speech disturbance, several subtypes of PPA can be identified, including agrammatic, semantic, and logopenic variants (Gorno-Tempini et al., 2011). Frontotemporal lobar degeneration (FTLD) and Alzheimer disease (AD) are the most common causes of PPA, accounting for about 60 % and 40 % of all PPA cases, respectively (Mesulam et al., 2021). Nevertheless, speech disturbance suggestive of PPA may occur as an atypical variant of other neurodegenerative diseases with movement disorders, such as progressive supranuclear palsy (~4.8 %) and corticobasal degeneration (up to 19 %) (Armstrong et al., 2013; Respondek et al., 2017; Tan et al., 2019).

PPA as the first clinical manifestation has also been described in Creutzfeldt-Jakob disease (CJD), a fatal neurodegenerative disorder associated with an abnormal isoform of the prion protein (Johnson et al., 2013; Martory et al., 2012). Classic CJD presents with rapidly progressive encephalopathy with global cognitive impairment, as well as a variety of neurological manifestations such as cerebellar ataxia, vision impairment, myoclonus, and akinetic mutism. Depending on the etiology, all CJD cases can be classified into familial, sporadic, and acquired forms. Irrespective of the etiology of the disease, CJD is usually characterized by rapid disease progression to death. EEG plays an important role in diagnostic workup. The most distinct EEG findings in CJD are periodic sharp wave complexes (PSWCs). In the advanced stage of the disease, PSWCs are usually generalized but can be asymmetric, lateralized, or focal in the early stages (Levy et al., 1986; Steinhoff et al., 2004).

Although CJD clinical presentation is usually typical, sometimes non-specific symptoms may be observed at the disease onset and persist for a certain period, leading to misdiagnosis. For example, isolated progressive speech impairment suggestive of PPA can mimic more common causes of PPA such as FTLD and AD. A more

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detailed evaluation of the clinical presentation, neuroimaging, and neurophysiology studies can be useful for providing timely and precise diagnosis.

We describe a case of sporadic CJD, which manifested with PPA syndrome, with a specific pattern of focal PSWCs observed on EEG that evolved gradually over the time of the disease, requiring differential diagnosis with focal non-convulsive status epilepticus.

2. Case report

A 58-year-old woman developed word-finding difficulties, anxiety, sleep disturbances, and reduced interest in everyday activities, which gradually worsened over the time of eight months. Due to a prominent speech disorder the patient was referred to a neurology department for ruling out early signs of frontotemporal dementia. Her family history was otherwise normal except for her father suffering from alcohol abuse and committing suicide.

Clinical examination. At her first referral to the clinic, the patient was anxious, emotionally labile, with a low mood and preserved criticism. Neurological examination revealed only slight postural hand tremor (more pronounced on the right) and slight limb-kinetic apraxia in both hands. Neuropsychological examination revealed mild aphasia, attention deficit, and executive disfunction. Her speech was non-fluent with pauses and lack of frank agrammatism. She had some difficulties with phrases repetition and comprehension of complex sentences. Naming, reading and semantic were unimpaired. With aphasia being the most prominent deficit, a preliminary diagnosis of primary progressive aphasia (PPA) was suggested. According to Gorno-Tempini diagnostic criteria (Gorno-Tempini et al., 2011) this disturbance was close to logopenic variant of PPA (lvPPA), but considering prominent reduction of the spontaneous speech output the diagnosis of dynamic aphasia was also discussed.

Laboratory testing. Blood cell count and blood biochemistry were unremarkable. Blood tests revealed folic acid deficiency for which folic acid supplements were prescribed. Vitamin B12 serum levels and thyroid hormones were normal. Serum tests for antineuronal antibodies (Hu, Yo-1, CV2, PNMa2, Ri, AMPH) were negative, as well as NMDA-R antibodies.

Neuroimaging and EEG. The patient underwent structural brain MRI, which was unremarkable. EEG recorded during wakefulness and sleep showed posterior dominant normal alpha rhythm (9.5 Hz) and intermittent mild polymorphic theta-slowing over the left frontotemporal region. Occasionally slowing was replaced by groups of sharp waves (~2 Hz) of higher amplitude, some of them having triphasic morphology, spreading to the right frontopolar region. These waves were interpreted as PSWCs. When the patient was alert or talking sharp waves would disappear. They were also much less prevalent in sleep (Fig. 1).

Disease follow-up. Since focal sharp waves in a patient with speech disturbances are found in rare cases of aphasic status epilepticus, the patient was started on levetiracetam 500 mg/day with gradual dosage titration up to 1000 mg/day. Nevertheless, at that moment the possibility of CJD could not be completely ruled out because of PSWCs on EEG, although they were focal. Over the following four weeks the patient's condition worsened: she developed bradykinesia, gait and limb ataxia, decreased speech fluency with severe comprehension problems, and reduced criticism.

Second EEG was performed, which demonstrated decreased posterior dominant rhythm and its slowing to 7.5 Hz, spreading of focal slowing to the right hemisphere, with some waves having triphasic morphology. Typical PSWCs persisted in the left frontotemporal region (Fig. 2).

In order to exclude possible adverse effects of levetiracetam therapy, it was discontinued. Two weeks later (almost ten months after disease onset), the condition of the patient further deteriorated: she understood only simple instructions, was able to turn her head towards the sound of her name, answered questions only using monosyllabic words. She also had visual hallucinations. Neurological examination revealed down gaze palsy, difficulties with visual fixation and smooth pursuit, dystonic posture in both hands, arm levitation sign on the right, distal myoclonus in the arms, severe gait ataxia, and truncal titubation. Repeat brain MRI showed hyperintensity of the gray matter of the cerebral cortex in the central gyri, temporal lobes, as well as of the heads of the caudate nuclei (more pronounced in the left hemisphere) in DWI (Fig. 3, B). Retrospective analysis of the DWI sequence in the previous brain MRI revealed the same but less pronounced changes (Fig. 3, A).

Laboratory testing for the 14–3-3 protein in the CSF was not available, so, according to the 1998 World Health Organization (WHO) criteria (World Health Organization, 1998), taking into account rapidly progressive dementia, ataxia, myoclonus, extrapyramidal and visual symptoms, typical EEG findings, a diagnosis of probable CJD was made. No mutations in the coding sequence of the *PRNP* gene were found, so a diagnosis of CJD sporadic variant appeared more likely.

In the closest followed period, dysphagia, mutism, and inability to walk developed gradually. The patient received palliative care at home. She died 34 months after disease onset. Full timeline of symptom progression, clinical examinations, and performed EEG and MRI studies is presented in Fig. 4.

3. Discussion

Although classic CJD phenotype usually includes rapidly progressive dementia and typical movement disorders, in some cases disease onset with isolated focal neurological deficit is observed. For instance, isolated cerebellar ataxia (Jellinger et al., 1974), isolated vision impairment (Kropp et al., 1999), cortical deafness (Tobias et al., 1994), auditory agnosia (Orimo et al., 2000), pure motor upper limb weakness (Obi et al., 1996), and aphasia (Mandell et al., 1989) have been described as first clinical manifestations of CJD.

Aphasia is a common neurological symptom observed in sporadic CJD, occurring in 40–60 % of all CJD cases (Lundberg, 1998). Nevertheless, isolated aphasia at the onset of the disease is rare and occurs only in around 1 % of CJD (El Tawil et al., 2017). Onset and progression of speech disorders may vary. Kirk et al. reported acute stroke-like manifestation of the disease (Kirk and Ang, 1994), while Johnson et al. described a case with slowly progressive (for more than 3 years) lvPPA (Johnson et al., 2013). Another rare primary presentation of sporadic CJD is a subacute manifestation of expressive aphasia with focal epileptiform activity which has been interpreted as nonconvulsive status epilepticus (Mahboob et al., 2018).

In overall, clinical presentation and speech disturbances pattern in our patient were similar to those reported before. Eight months since disease onset clinical manifestations reflected left frontal cortex and basal ganglia involvement (non-fluent aphasia, tremor, limb-kinetic apraxia). Nevertheless, the speech impairment pattern may also refer to a more widespread neurodegenerative process with left posterior perisylvian area and parietal lobe involvement. Asymmetric pathological features of EEG and brain MRI also point to this location.

Slow predominant progression of speech impairment over the time course of eight months in our case led to the incorrect preliminary diagnosis of PPA syndrome due to frontotemporal dementia and lack of proper alertness to the visual analysis of MRI specific sequences. Later we observed global cognitive decline with

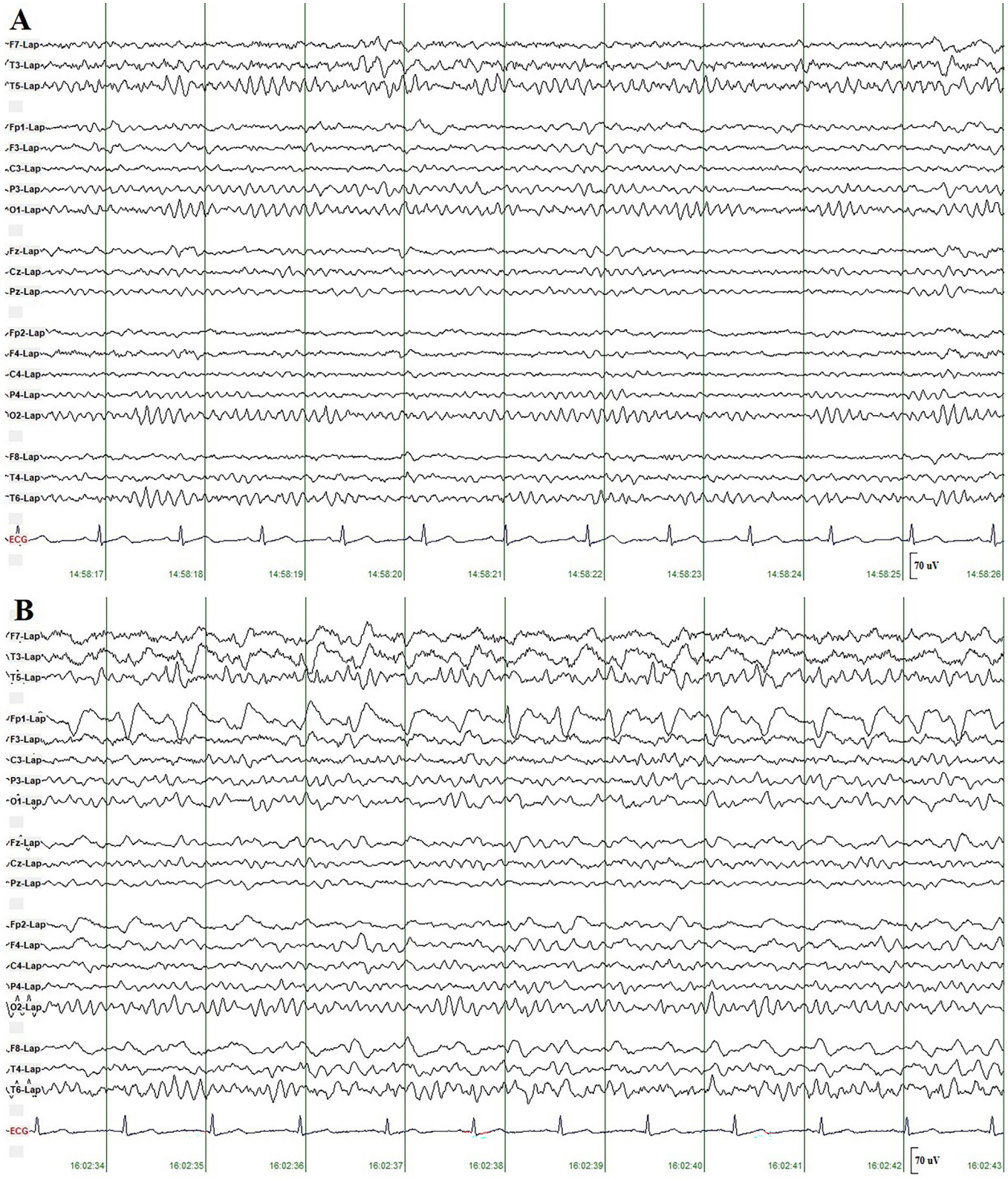

Fig. 1. EEG performed upon admission (Laplacian montage). (**A**) Preserved posterior dominant alpha-rhythm (frequency of 9.5 Hz) with intermittent polymorphic slowing in the left frontotemporal region. (**B**) Periodic sharp wave complexes (PSWCs) in the left frontotemporal region with the highest amplitude at Fp1 electrode. Bandpass filters: 0.5–70 Hz.

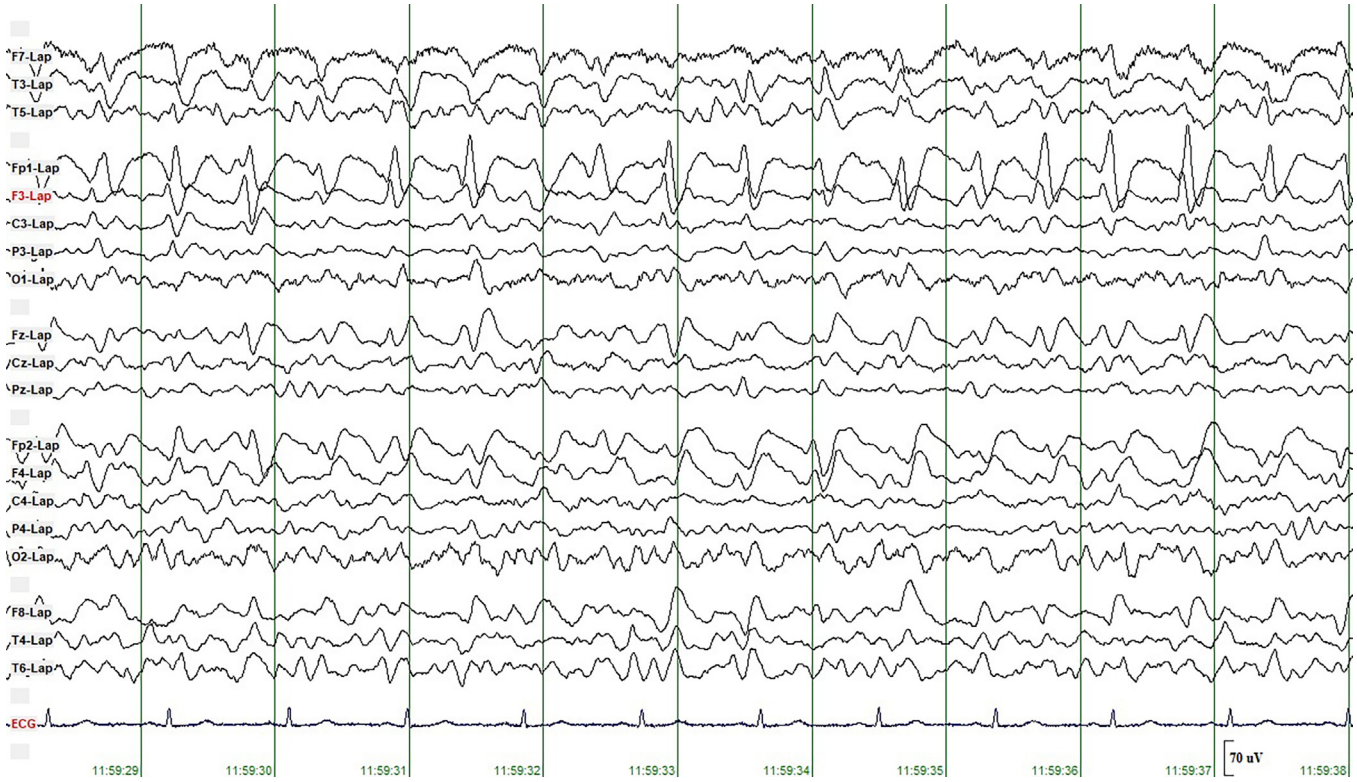

Fig. 2. Second EEG (performed four weeks after the first EEG). Periodic sharp wave complexes (PSWCs) with the highest amplitude in the left frontal region with further spreading of focal slowing to the right frontal region, triphasic waves, and alpha rhythm slowing to 7.5 Hz. Bandpass filters: 0.5–70 Hz.

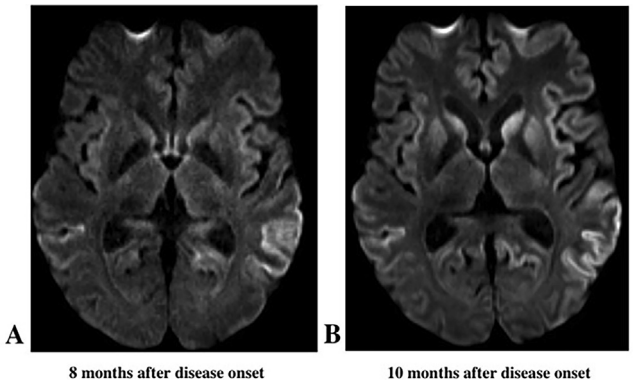

Fig. 3. DW brain MRI at disease onset when only focal neurologic deficit (PPA syndrome) was observed (**A**), and later when typical clinical manifestations of CJD appeared (**B**).

progression to dementia and mutism, with signs of cerebellum, left occipital-parietal cortex (levitating movement in the hand, posterior variant) and basal ganglia (dystonia) involvement, which, along with consistent MRI and EEG findings, confirmed the hypothesis of CJD.

EEG findings, as well as their evolution over time, play a crucial role in the diagnosis of CJD. Various EEG abnormalities ranging from intermittent or continuous slowing, frontal intermittent rhythmic delta activity (FIRDA) to triphasic waves and PSWCs during the course of CJD have been described so far (Wieser et al., 2006). These EEG patterns are nonspecific**,** and only PSWCs have certain diagnostic significance. In a patient with rapidly progressing dementia, cerebellar, pyramidal and other neurological signs, appearance of PSWCs in EEG support the diagnosis of probable CJD according to the WHO criteria (World Health Organization, 1998).

Serial EEG studies (Ayyappan and Seneviratne, 2014; Hansen et al., 1998) demonstrate that mild background slowing or FIRDA is most often found upon disease onset, with more typical PSWCs appearing later on. Shin et al. showed that periodic patterns are irregular at the onset of the disease; rhythmic sharp waves, typical regular periodic discharges and triphasic waves emerge with further disease progression (Shin et al., 2017). As CJD advances, and the patient develops akinetic mutism, EEG can become low-voltage or show various deep coma patterns, including alpha-coma (Asai et al., 2001). Thus, EEG findings in CJD largely depend on the clinical stage of the disease.

Our patient's EEG recorded at different stages of CJD is remarkable in the light of a specific clinical presentation of the disease. Early in the disease, a pattern of focal sharp wave complexes was observed. Focal sharp wave EEG activity in a patient with persisting speech disturbances can be interpreted as aphasic status epilepticus – rare focal type of nonconvulsive status epilepticus (NCSE). There are few publications reporting patients with CJD clinically and electrophysiologically resembling NCSE, including cases of predominant speech disturbances at the time of first referral to the clinic (Cohen et al., 2004; Mahboob et al., 2018; Ng et al., 2014; Shapiro et al., 2004). In these cases, after antiseizure therapy did not lead to any clinical improvement, further diagnostic tests and disease course confirmed the diagnosis of CJD. In most of the reported cases, aphasic status epilepticus lasted from several hours to a few days. No history of previous seizures, slow progression of speech disturbances over the course of several months, disappearance of discharges on EEG during talking and sleep argued against the possible epileptic origin of aphasia in our case.

EEG was performed in nine of previously published cases of CJD with isolated aphasia at the time of presentation. Diffuse (El Tawil

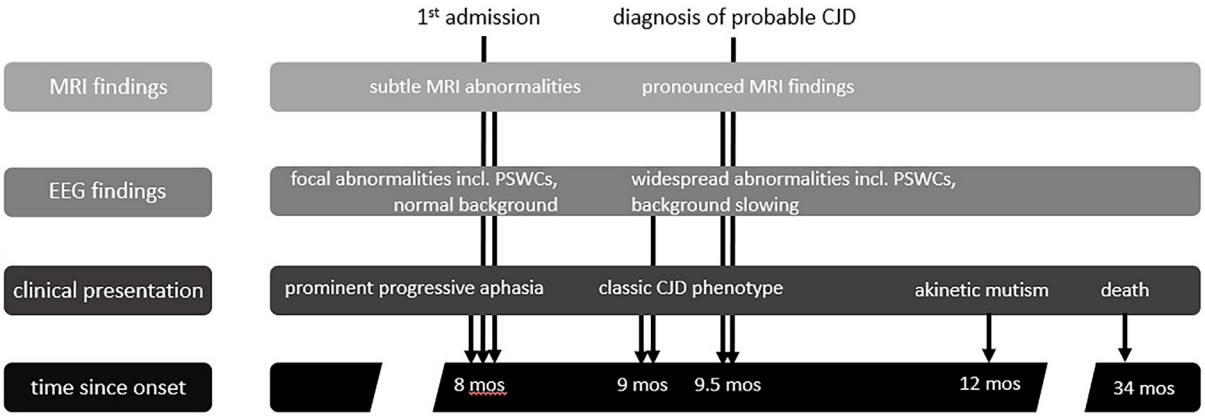

Fig. 4. Timeline of the clinical case. Abbreviations: CJD - Creutzfeldt-Jakob disease, EEG - electroencephalography, mos - months, MRI - magnetic resonance imaging, PSWCs - periodic sharp wave complexes.

et al., 2017; Ghorayeb et al., 1998; Song et al., 2010) or focal slowing (Hillis and Selnes, 1999; Johnson et al., 2013; Martory et al., 2012; Terrin et al., 2017) was noted in seven patients, and in two cases EEG demonstrated focal PSWCs (Mandell et al., 1989; Stark et al., 2007) with diffuse or focal slowing of background activity. In our case, first EEG was performed at the time of isolated speech impairment, showing mostly normal background activity and well-preserved posterior dominant rhythm alternating with epochs exhibiting focal PSWCs, sometimes spreading to nearby regions. It is particularly noteworthy that PSWC were maximal over the left frontopolar region, at a certain distance from structural changes visualized by brain MRI. It could be argued that PSWC were generated by less damaged brain regions.

Although EEG abnormalities were focal, taking into account their highly specific morphology, maximal prevalence in relaxed wakefulness, decrease in sleep, a diagnostic hypothesis of CJD was suggested. Second EEG performed four weeks later, when cognitive and neurological impairment was clinically apparent, showed further deterioration, diffuse background slowing, more sustained PSWC spreading to the contralateral hemisphere. Second MRI was also consistent with CJD progression, demonstrating more prominent hyperintensity of the cortical grey matter and basal ganglia.

In the reported cases (Cohen et al., 2004; El Tawil et al., 2017; Ghorayeb et al., 1998; Hohler and Flynn, 2006; Johnson et al., 2013; Katsikaki et al., 2021; Kirk and Ang, 1994; Kobylecki et al., 2013; Mandell et al., 1989; Martory et al., 2012; Stark et al., 2007), the disease duration from onset to death in CJD manifesting with isolated aphasia varied from two months to six years, accounting for less than six months in half of all patients (Fig. 5). It is noteworthy that all the described cases form two 'clusters' with a relatively short disease duration (typical of CJD) and longer disease duration, respectively. Those cases with a longer disease duration were characterized by a substantially longer period with aphasia being the only disease manifestation. One can suggest that in these cases of longer disease duration, a longer period of isolated aphasia can probably lead to a differential diagnosis with other conditions characterized with PPA, such as FTD. Our case can be attributed to the second group, since the time from disease onset to classical CJD presentation took almost 10 months. Thus, it can be assumed that a slowly progressive and atypical monosymptomatic course of CJD usually results in a diagnostic delay, with

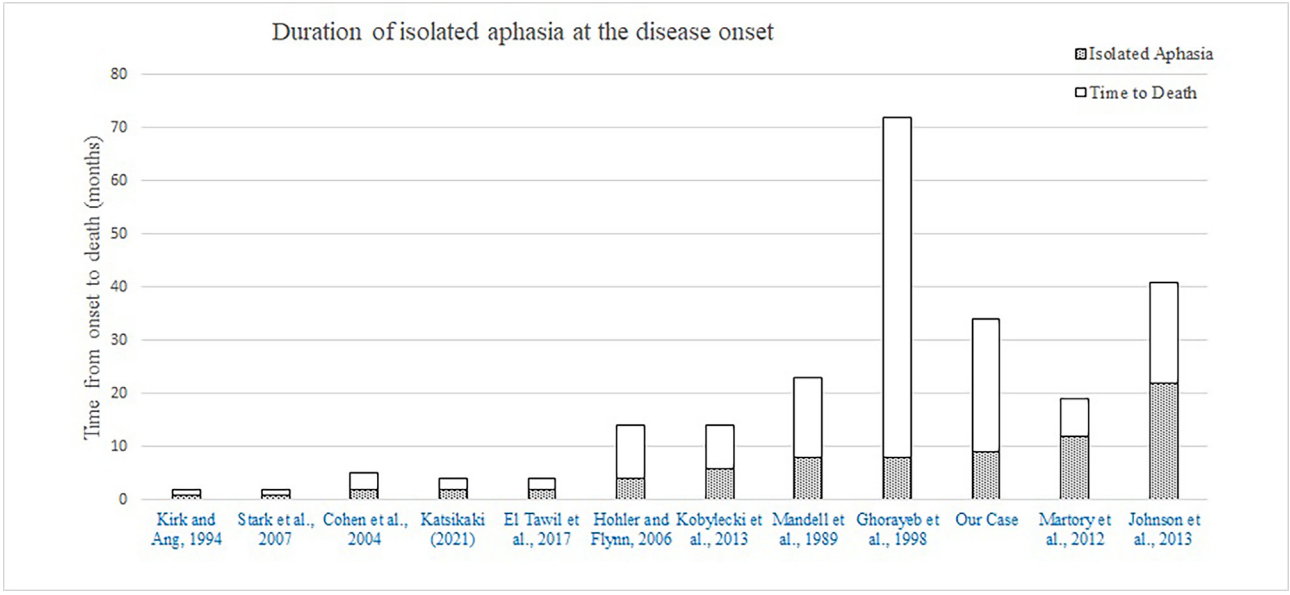

Fig. 5. Duration of isolated aphasia (months) at the disease onset and time to death in patients with Creutzfeldt-Jakob disease from published cases.

EEG and DW-MRI performed early in the disease making a significant contribution to a more accurate and timely diagnosis.

4. Conclusion

In summary, our case demonstrates an atypical course of CJD presenting with isolated speech impairment over the period of nine months, which resulted in the initial diagnosis of frontotemporal dementia. After focal PSWCs were revealed on EEG, a possible diagnosis of CJD was suspected, which was later confirmed by clinical follow-up, repeated MRI and EEG. In our case, EEG evolution in CJD was unusual, with focal PSWCs preceding diffuse EEG abnormalities. This could be due to a focal pathological lesion in a limited part of the brain at the earlier stages of the disease. FTD and CJD have different prognoses, and timely diagnosis is important for providing proper clinical management. Therefore, we suggest that the diagnostic workup in patients with isolated slowly progressing speech impairment should include not only brain MRI, but also wake and sleep EEG.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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