Creutzfeldt-Jakob disease with neuroleptic malignant syndrome

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Abstract

Creutzfeldt – Jakob disease (CJD) is a rare neurodegenerative disease with complex clinical manifestations. Neuroleptic malignant syndrome (NMS) is a complication of antipsychotic medications which are used to treat neuropsychiatric symptoms of CJD. We present a case of a 51-year-old woman with CJD who developed NMS after being prescribed quetiapine.

Case Report

Creutzfeldt-Jakob disease with neuroleptic malignant syndrome

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Key Clinical Message: Neuroleptic malignant syndrome associated with quetiapine in a patient with Creutzfeldt-Jakob disease.

Abstract: Creutzfeldt – Jakob disease (CJD) is a rare neurodegenerative disease with complex clinical manifestations. Neuroleptic malignant syndrome (NMS) is a complication of antipsychotic medications which are used to treat neuropsychiatric symptoms of CJD. We present a case of a 51-year-old woman with CJD who developed NMS after being prescribed quetiapine.

Keywords: Creutzfeldt-Jakob disease; neuroleptic malignant syndrome; magnetic resonance imaging; electroencephalography.

Introduction

Prion diseases are a group of rare neurodegenerative diseases that are caused by infectious abnormally structured and shaped proteins - prions - which impose their structure onto nearby normal prion proteins, thereby propagating and causing progressive cell damage and death [1]. Creutzfeldt – Jakob disease (CJD) is the most common human prion disease and has a prevalence of 1 new case per 1 million individuals each year worldwide and usually presents in the 7th decade of life [2]. Sporadic CJD (sCJD) accounts for up to 85-95% of CJD cases, while other genetic and acquired forms are far less common, accounting for 5-15% and less than 1% of cases, respectively [3].

CJD is a clinically heterogeneous disease but typically presents with rapid cognitive and neuropsychiatric deterioration. The most common clinical presentation is rapid cognitive decline progressing to dementia;

other manifestations include behavioral abnormalities, myoclonus, pyramidal/extrapyramidal signs, cerebellar symptoms and higher cortical dysfunction (i.e., aphasia, apraxia, acalculia, agraphia, neglect), which are seen in about half of all reported cases [4; 5; 6]. Clinical picture, in combination with cerebrospinal fluid (CSF), electroencephalography (EEG), and brain magnetic resonance imaging (MRI) studies form the basis of in vivo diagnosis of CJD; histopathological confirmation, however, still remains the gold standard for diagnosing definite CJD (Table 1). MRI is a very valuable tool in detecting signal abnormalities suggestive of CJD in an appropriate clinical context, approaching a sensitivity of 91% and a specificity of 95% [7].

Unfortunately, CJD is incurable and universally fatal, usually progressing rapidly over 6 to 12 months.

Neuroleptic malignant syndrome

Neuroleptic malignant syndrome (NMS) is a life-threatening neurologic complication, arising as an idiosyncratic reaction to medications that block D2 receptors [8]. Clinically it is characterized by fever, extrapyramidal symptoms (mainly rigidity), impaired consciousness, and dysautonomia. NMS is not dose-dependent and can occur at any time during treatment with antipsychotic drugs, however usually presents within the first two weeks. The incidence is up to 2,4% among patients receiving these drugs, while mortality (mostly as a result of autonomic complications), is reported to be up to 20% [9]. Hypertonia and subsequent rhabdomyolysis lead to leukocytosis and serum creatine kinase (CK) elevation, which are the main laboratory derangements seen in NMS [10]. NMS usually exhibits no distinguishing features on MRI. It is thought that a variety of factors, including concomitant infections, acute neurologic diseases or substance abuse may predispose to NMS [11].

In this case report we present a rare case of a patient with sCJD who developed NMS.

Table 1. Criteria for probable sporadic Creutzfeldt-Jakob disease [12].

Neuropsychiatric disorder + positive RT-QuIC in CSF or other tissues **OR** Rapidly progressive dementia; and at least 2 ou

CJD - Creutzfeldt-Jakob disease; RT-QuIC - real-time quaking-induced conversion; CSF - cerebrospinal fluid; EEG - electroencephalography; MRI - magnetic resonance imaging.

Case presentation

A 51 year-old woman was transferred from the regional hospital to the Neurology department of the University hospital due to over a two week history of an advancing speech abnormalities characterized by difficulty in retrieving words and producing structured sentences, involuntary repetition of the same words or phrases. Most common diagnosis of acute cerebrovascular event was ruled out after normal CT scan. Due to Covid-19 pandemic and strict quarantine rules, family members were not allowed to visit the patients in the hospital, which made gathering anamnestic facts rather difficult. Recurrent expedient phone call conversations with patient's family members revealed that first symptoms were noticed about three months prior hospitalization. She had trouble concentrating and had impaired short-term memory which resulted in her doing same actions repeatedly (e.g. bringing multiple cups of coffee or meals to her husband), she did not answer questions sensibly and looked mildly confused.

Past medical history was significant for hypertension. Otherwise the patient was physically active and worked as an accountant.

At the time of hospitalization, neurological examination revealed disorientation in space and time. She seemed noncritical of her condition, had inadequate emotions (e.g. kept smiling or laughing at questions about her health), and was unable to follow commands on neurological examination. She had severe sensorimotor aphasia and could not tell her name or formulate her complaints. Palilalia, echolalia, apraxia, acalculia, agraphia were present. The rest of the examination was unremarkable: cranial nerves, motor and sensory systems were intact, no pathologic or primitive reflexes were found. There were no signs of either extrapyramidal or cerebellar dysfunction and no myoclonus.

Patient used valsartan/hydrochlorothiazide and metoprolol for her hypertension. There was no reported alcohol, illicit drug use or possible contact with chemicals or heavy metals.

On the day of the admission, brain magnetic resonance imaging (MRI) did not show any signs of ischemia, tumor or other possible structural cause of her symptoms.

Patient underwent a broad investigation for differential diagnosis - tests were performed to rule out encephalopathy of various origin, i.e., hepatic, renal, thyroid, vitamin deficiencies, and any possible vascular, infectious, paraneoplastic, and autoimmune etiology of the previously mentioned symptoms. Laboratory tests included a complete blood count, a comprehensive metabolic panel, vitamin B12, folates, thyroid-stimulating hormone, which were all unremarkable. Tests for sexually transmitted diseases (i.e. syphilis and HIV), borreliosis, tick-borne encephalitis, onconeural and antineuronal antibodies were negative. Lumbar puncture was performed in order to eliminate neuroinfection as a possible diagnosis; CSF analysis did not show any pleocytosis, while glucose and protein levels were within normal limits.

Neuropsychological testing with Mini-Mental State Examination (MMSE) and a clock drawing test returned scores of 0, showing significant impairment of cognitive functions including short-term memory, attention, concentration, writing, reading, calculating, and constructional praxis.

In the course of the next 2 weeks she suffered severe cognitive decline, could no longer eat or go to the bathroom on her own, and replied with one-word nonsensical answers.

On day 15 in the Neurology department, a second brain MRI was performed. It revealed very subtle cortical T2W/FLAIR hyperintensities, best appreciated in the right parietal cortex, and subtle but more extensive abnormalities on diffusion-weighed imaging, showing signs of diffusion restriction in both the cortical and deep grey matter, including bilateral cortical regions (best appreciated in the right parietal and left parieto-occipital cortices), caudate nuclei, and anterior putamina (Figure 1). MRI findings were suggestive of typical sCJD, with possible (but less likely) differential diagnoses including autoimmune encephalitis and other systemic encephalopathies of various etiologies.

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Figure 1. MRI features suggestive of sCJD**.** Axial T2-weighted FLAIR images (a) show very subtle cortical hyperintensities, best appreciated in the right parietal cortex (grey arrow). Axial diffusion-weighted images (b) show subtle but more extensive bilateral hyperintensities in multiple cortical regions (best appreciated in the right parietal and left parieto-occipital cortices), caudate nuclei, and anterior putamina (white arrows), with corresponding slight hypointensities on apparent diffusion coefficient maps (c) representing true diffusion restriction (black arrows).

Patient then developed psychomotor agitation, sleep disturbance, severe confusion, and was caught trying to jump out of the window. She was started on quetiapine 50 mg once daily and lorazepam 1 mg before sleep to alleviate neuropsychiatric symptoms. Over the next week she developed fever of over 40°C, muscular rigidity of all extremities, muscles of mastication and jaw, as well as autonomic instability including high blood pressure, tachycardia, profuse diaphoresis, and sialorrhea. Blood and urine laboratory tests, chest and abdominal imaging revealed no signs of possible infectious processes. Serum creatine kinase (CK) level was elevated 1225 IU/l (normal 0-145 IU/l). With most infections being ruled out, the likely diagnosis was NMS. Antipsychotic drugs were immediately discontinued and specific treatment for muscular rigidity with dopamine agonist bromocriptine was started. Further supportive care was started with intravenous fluids to maintain volemia, antipyretics and cooling blankets to reduce hyperthermia, trihexyphenidyl to manage extrapyramidal symptoms; doses of antihypertensive drugs were increased.

Efficacy of NMS treatment was only partial as the patient still showed signs of subfebrile fever, dysautonomia and muscle hypertonia, although CK levels normalized.

During the next two weeks her neurological condition worsened. She had exaggerated, startled responses to louder noises or sudden touch (hyperekplexia), developed akinetic mutism, and lost all voluntary motor function; a nasogastric tube had to be placed due to dysphagia.

On the 30th day of hospitalization another follow-up MRI was performed. It showed persistent and slightly more pronounced bilateral diffusion restriction in multiple cortical regions, caudate nuclei, and anterior putamina, with similar subtle cortical T2W/FLAIR hyperintensities (Figure 2). MRI findings continued to be suggestive of typical sCJD with slight progression of signal abnormalities even on short-term follow-up.

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Figure 2. MRI features suggestive of sCJD with slight progression of signal abnormalities. Short-term follow-up axial T2-weighted FLAIR images (a) show similar subtle cortical hyperintensities, again best appreciated in the right parietal cortex (grey arrow). Axial diffusion-weighted images (b) and apparent diffusion coefficient maps (c) show persistent and slightly more pronounced bilateral diffusion restriction in multiple cortical regions, caudate nuclei, and anterior putamina (white and black arrows).

Follow up awake EEG revealed pathologic diffuse slowing of background activity and bilateral periodic polyphasic sharp wave complexes, dominating in right frontal-temporal area (Figure 3).

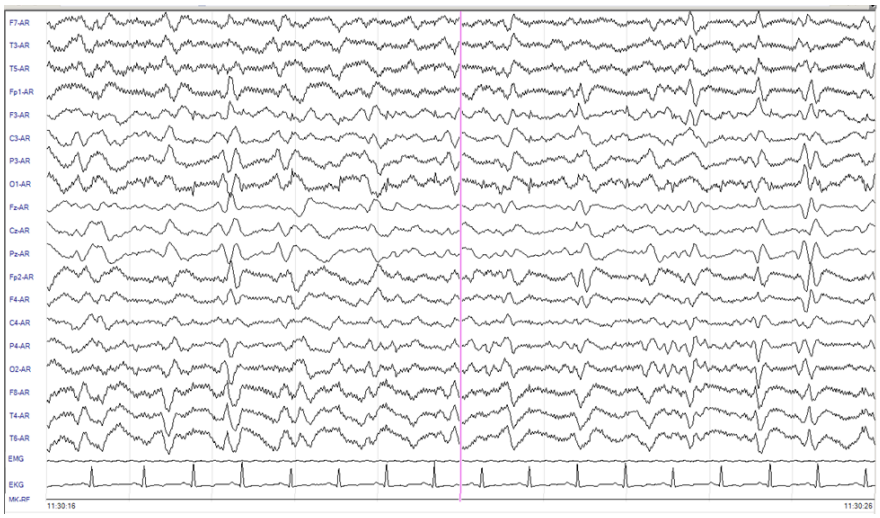

Figure 3. Diffuse slowing of background activity. Bilateral periodic polyphasic sharp wave complexes, dominating in right frontal-temporal area.

The patient was diagnosed with probable sporadic CJD as she met the Centers for Disease Control and Prevention Diagnostic Criteria for probable sporadic Creutzfeldt-Jakob disease based on: 1) rapidly progressive dementia followed by development of myoclonus (hyperekplexia), extrapyramidal signs and akinetic mutism; 2) typical EEG findings of periodic sharp wave complexes; 3) brain MRI findings of diffusion restriction in multiple cortical regions (best seen in the right parietal and left parieto-occipital cortices), bilateral caudate nuclei, and anterior putamina; alternative diagnoses were excluded.

The patient was transferred to the palliative care unit 35 days following admission. Three months later she died of pulmonary embolism. Autopsy was carried out, and immunohistochemical examination demonstrated abnormal prion protein deposition in the acquired grey matter specimens (brainstem). The abnormal prion

protein deposition was in the form of synaptic diffuse labelling without any micro-plaques or larger plaque-like deposits or filamentous labelling in the white matter. Histopathological changes were compatible with prion disease, confirming the diagnosis of definite CJD. For exclusion of a genetic form, genetic testing for mutations in the PRNP gene were warranted, but unfortunately could not be performed.

Discussion

While Creutzfeldt-Jakob disease has a multifaceted clinical presentation that differs based on which areas of the brain are most affected, rapidly progressive cognitive decline is a particularly typical finding. Thus, the differential diagnosis should always include conditions that manifest with a syndrome of rapidly progressive dementia. Primarily, certain treatable and/or reversible diseases, such as paraneoplastic and autoimmune encephalitis, viral encephalitis, metabolic encephalopathy, HIV, and Lyme disease should be considered [13]. Primary CNS lymphoma, vasculitis, and intravascular lymphoma can also lead to rapidly progressive dementia. MRI is usually helpful in confirming or excluding these diagnoses. Mitochondrial encephalopathy with lactate acidosis and stroke-like episodes (MELAS) can have some clinical features overlapping with CJD, however it presents in a younger population and appears on imaging as multifocal cortical-subcortical lesions resembling strokes of various ages with typical elevated lactate on MR spectroscopy [14]. Other dementias such as Alzheimer's disease, dementia with Lewy bodies, frontotemporal dementia, corticobasal degeneration, and progressive supranuclear palsy usually progress less quickly and on imaging are characterized by atrophy in a generalized or specific distribution, without the extensive diffusion restriction typically found in CJD [15].

In our case the patient's rare main condition (sCJD) was complicated by what we assume to be an infrequent process of a completely different etiology (NMS, a complication of antipsychotic medication), which made the differential diagnosis after its onset more difficult. Various predisposing factors, including organic brain diseases, are postulated to exert influence on the development of NMS [16]. Therefore, we might hypothesize that structural changes in the brain (particularly in the caudate nuclei and putamina) caused by CJD could have contributed to a disruption of nigrostriatal pathways and a decrease in dopaminergic activity, which could have resulted in a hypersensitivity to antipsychotic drugs and therefore a predisposition to develop NMS.

The risk of NMS may increase with extrapyramidal disorders such as PD [17]. This type of neuroleptic sensitivity is broadly described in patients with dementia with Lewy bodies (DLB), hence additional studies are essential to differentiate these conditions to avoid false positive diagnosis of CJD, as was shown in a case series by Lemstra et al., in which they described 12 patients with autopsy-confirmed DLB who had been clinically suspected to suffer from CJD; however, our case shows that a manifestation of neuroleptic sensitivity can also occur in CJD [18].

According to Yang et al. study of 173 sCJD cases, extrapyramidal symptoms were noticed in over 77% of patients and were the second most frequent symptom after progressive dementia. [19].

Diffusion restriction (which correlates with spongiform changes detected on autopsy) in the basal ganglia (particularly caudate nuclei and putamina) is found in a great proportion of CJD cases, although to our knowledge there are no other reports about CJD and NMS co-existing [20; 21]. We emphasize the diagnostic dilemma of this case: whether persisting extrapyramidal hypertonia, reduced consciousness, and dysautonomia after treatment of NMS were residual symptoms of incompletely resolved NMS, or a consequence of the inevitable progression of CJD.

Disease duration in presented case was about five months. According to the collaborative study of human transmissible spongiform encephalopathies, mean survival time of sCJD is 7,3 months, median - 5 months [22]. Unfortunately, we cannot confidently affirm whether shortened survival time and fast progression of the disease was due to NMS. There is limited amount of data concerning the survival time in patients with CJD. Younger age, female sex, clinical manifestation of cerebellar symptoms, pseudo-periodic sharp-wave complexes on EEG and presence of various biomarkers in CSF were reported to be factors of longer survival time [23; 24].

Conclusions

In conclusion, this case report shows that patients with CJD who receive antipsychotic medications can develop NMS. Further research is needed to investigate whether CJD is a predisposing factor for developing NMS, or is their co-existence merely a coincidence.

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Author contribution: Julija Čiauškaitė, Ieva Puleikytė and Simonas Jesmanas collected the data from the medical record and drafted the manuscript; Giedrė Jurkevičienė and Daiva Rastenytė supervised the drafting of the manuscript; Antanas Vaitkus was the patient's treating physician. All authors reviewed, edited, and agreed on the final version of the manuscript.

Data availability statement: Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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