Creutzfeldt–Jakob disease in the Republic of Sakha (Yakutia)

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Creutzfeldt–Jakob disease (CJD) is a rare neurodegenerative disease caused by the accumulation of the pathological isoform of prion protein. The classic clinical presentation of CJD is characterized by rapidly progressive dementia, ataxia, myoclonus, and akinetic mutism at the terminal stage of the disease. Of the instrumental techniques, brain magnetic resonance imaging plays a leading role in clinical practice.

The authors followed up 4 patients with probable CJD in the Republic of Sakha (Yakutia) in 2014 to 2019. All the patients had approximately the same age (50–60 years) at disease onset and onset with non-specific cerebral symptoms. However, the subsequent development of rapidly progressive dementia and other characteristic features might suggest CJD. The patients were found to have characteristic neuroimaging signs as hyperintensity of the caudate nuclei and pulvinars in the fluid-attenuated inversion recovery (FLAIR) and diffusion weighted imaging (DWI) modes to form the typical signal of hockey sticks, as well as hyperintensity of the gray matter in the DWI mode (the symptom of the «Venus necklace»). In 3 patients, the disease ended fatally within a year of its onset. The fourth patient with a disease duration of 6 months is being supervised at home.

The authors reason that the diagnosis of CJD is now insufficient due to the similarity of its clinical symptoms at the onset with other disorders, including cerebrovascular and neurodegenerative diseases.

Keywords: *prion diseases; Creutzfeldt–Jakob disease; dementia; myoclonus; spongiform encephalopathies.*

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Creutzfeldt–Jakob disease (CJD) is a rare neurodegenerative disease, that belongs to transmissible spongiform encephalopathies. It is caused by a pathological isoform of prion protein PrP^{Sc} [1, 2]. There are about 1–2 CJD cases per 1 million people [3, 4]. Clinical presentation of CJD includes rapidly progressive dementia, ataxia, myoclonus and akinetic mutism at the terminal stage of the disease [5]. The latest diagnostical criteria of CJD were established in 2015 (Table 1) [6].

CJD accounts for 85% of all prion encephalopathies and occurs in all ethnic, gender and age groups. CJD is characterized by high contagiousness and inevitable death [1, 7]. CJD is classified by its clinical presentation and etiology: sporadic (sCJD, 85%), familial CJD (fCJD, 10–15%), iatrogenic CJD (<1%) and variant CJD (vCJD, <1%) [1, 8].

As sCJD is the most common form in the older age group (on average, 67 y.o.), there are reports of sCJD mimicking some rapidly progressive neurological diseases in this age group. According to the researches, sCJD may also mimic stroke [9], acute peripheral neuropathy [10], hyperparathyroidism [11], various forms of primary dementia [12, 13], encephalitis [13], primary aphasia [14], mental illness [15] and motor disorders [13, 16].

Given this, we introduce clinical reports of probable CJD diagnosed from 2014 to 2019 in the Sakha (Yakutia) Republic.

Case Report 1

Patient G., *female, 53 y.o., Yakut ethnicity. The patient was from Vilyuysky District and was admitted to the neurological department on the 10th of February 2014. In November 2013, she noted episodes of severe dizziness and impaired gait. She was examined by a paramedic and received vascular and nootropic therapy without any positive effect. In December 2014, the patient had complaints about mental slowing, impaired speech (dysarthria), ataxic gait, limb weakness, so she required assistance in walking. As severe cognitive impairments progressed, she didnXt recognize her relatives. Pelvic disorders, such as urinary and fecal incontinence, also appeared. On the 16th day of hospitalization, generalized tonic-clonic seizures debuted. The day after, she was transferred to the intensive care unit due to respiratory failure.*

The patient had no hereditary neurological diseases. In recent years before the first symptoms, she had been living with her daughter and hadnXt been working. In 1992, she had a blood transfusion due to postpartum complications. After the transfusion, she had been complaining of constant weakness and headaches.

Neurological examination: the patient had paresis of the gaze to the left. Pseudobulbar palsy. No active movements in the lower extremities; myoclonic twitches on the shoulder joints level. A mixed (pyramidal and extrapyramidal) type of increased muscle tone in the extremities. The left plantar reflex. Severe ataxia. Positive meningeal symptoms. Akinetic mutism.

MRI revealed a symmetric lesion of the basal nuclei (putamen, caudate nucleus, thalamus, globus pallidus, cerebral peduncles on both sides), parasagittal cortical sections (mainly frontal), medial areas of the temporal lobes, cerebellum atrophy. According to the data, CJD was suggested.

Video-EEG monitoring detected bioelectrical signs of severe organic changes of the brain, severe slowing of the cortical rhythm and periodic bilateral complexes of sharp waves.

There was leukocytosis up to $20{,}6\times10^9$/L. The cerebrospinal fluid analysis was normal. Cardiac arrest occurred on the 21st day of the hospitalization. The autopsy was not performed.

Case Report 2

***Patient P.**, male, 59 y.o., Yakut ethnicity. The patient was from Churapchinsky District and was admitted to the neurological department on the 26th of January 2016. He suffered from arterial hypertension and frequent headaches since 2012. In September 2013, due to an acute loss of vision (he was a driver), he got into a car accident, hit his head and had a short-term loss of consciousness. After the accident, the patient developed dizziness and impaired gait, became slow, uncommunicative, apathetic, forgetful. He complained of insomnia and lost interest in hunting, which was his hobby. From September 2015, sleep disturbances increased, as night episodes of hyperhidrosis with a feeling of heat were disturbing. In November 2015, he was hospitalized to the Churapchinsky District Hospital due to increased shakiness and a debut of dysarthria. During the treatment, swallowing disorders appeared, the patient became unable to talk, pelvic disorders developed. The air ambulance service transferred the patient to Yakutsk in a critical condition. Blood pressure was 123/92, heart rate was 92 per min. Neurological examination: consciousness was rated as obtundation, the patient was able to perform simple tasks. Speech impairment. Increased muscle tone of extrapyramidal type. Tetraparesis. Anisoreflexia, S>D. Positive meningeal symptoms. Myoclonus in the limbs. As the condition progressively worsened, 6 days later he was put on artificial lung ventilation, a tracheostomy tube and a nasogastric tube were also installed. MRI brain tomograms revealed the signs of damage to the basal nuclei (caudate nuclei, putamen) and the cortex of frontoparietal lobes on the right, deposition of hemosiderin in the right temporal lobe, calcifications of the head of the caudate nucleus on the right, cystic-gliotic changes of the insular cortex on the right.*

Video-EEG monitoring detected pronounced diffuse changes and focal activity in the right anterior temporal lobe (TIRDA). Blood analysis revealed leukocytosis.

Shortly after the discharge from hospital, the patient died. The autopsy was not performed.

Case Report 3

***Patient E.**, male, 58 y.o., Yakut ethnicity. The patient was from Suntarsky District and was admitted to the neurological department on the 12th of January 2017.*

He had been suffering from paroxysmal dizziness with prolonged remissions for 5 years. Previously, the patient had undergone treatment in the internal disease department with episodes of dizziness, nausea, and vomiting several times. The symptoms started to progress from the fall of 2016 when dizziness became constant with paroxysmal exacerbations. It was often accompanied by nausea and repeated vomiting. Sleep disturbances of inversion type appeared. In November 2016, his wife noticed that the patient started to consume alcohol. In December 2016, dizziness and shakiness increased, which was accompanied by repeated vomiting, so he was treated in the internal disease department of the district hospital. On the 17th of December 2016, anxiety, inadequate speech, inappropriate behavior and a psychotic reaction developed: the patient was agitated and shouted that «there was an explosion». Then he began complaining about the «unreality» of what was happening and also had deja vu episodes. He expressed the idea, that «the neurons and axons were locked in his body». Then he suddenly became aggressive, tried to leave the hospital, because the medical staff «poisoned him with psychotropic substances». The episode of psychosis was stopped, as the antipsychotic treatment was given. Later, apathy and disorientation arose, the patient couldn't recognize his acquaintances. As muscular rigidity and postural instability debuted, he couldn't walk without extraneous support. In January 2017, he completely lost his self-care skills within a week: he wasn't able to walk, eat and talk on his own. He was examined by a psychiatrist at home and encephalopathy with severe cognitive impairment was diagnosed. From the 12th of January, myoclonus of the head and left arm developed; the patient was subsequently admitted to the neurological department in Yakutsk. The condition was serious. Neurological examination: the patient was lying with his eyes closed in a «frog» pose. There was no productive contact. He did not carry out tasks and did not answer questions. A grimace of pain on his face. Blepharospasm. The right nasolabial fold was smoothed. Trismus of masticatory muscles. Pseudobulbar palsy. Myotatic arm reflexes were enhanced, leg reflexes normal. Abdominal reflexes were reduced. There was no paresis. Myoclonus in the left extremities. Diffuse muscle stiffness. Coordination tests were not performed. Neck stiffness. Positive Kernig's sign 70° on both sides. Cheekbone percussion symptom was positive on both sides. Positive plantar reflexes on both sides. Positive symptoms of Schaeffer, Gordon on both sides. Pathological phenomena, such as focal periodic FIRDA complexes, were detected on EEG. CSF was normal. Brain MRI showed restriction of the diffusion coefficient of gray matter in the frontotemporal lobes and basal nuclei on both sides. Moderate hyperintensity in the medial sections of both thalami. MRI conclusion: selective damage to the gray matter of the brain. There was more evidence of a neurodegenerative disease (CJD), than of a metabolic disorder (Fig. 1). There was a telemedicine consultation with the Research Center of Neurology (Moscow) experts, who agreed with the proposed diagnosis. The fatal outcome occurred after the patient's discharge from hospital. The autopsy was not performed.

Table 1. Proposed updated diagnostic criteria for CJD*

A	B	C	D
Rapidly progressive dementia	1. Myoclonus 2. Visual or cerebellar signs 3. Pyramidal/extrapyramidal signs 4. Akinetic mutism 5. VV2 genotype with predominant ataxia without myoclonus at the early stage 6. MV2 genotype with disease duration >12 months at the early stage 7. MM2 genotype & temporal lobe changes on MRI without basal ganglia involvement 8. VV1 genotype & young age at onset (<50 yrs), slowly progressive disease with frontotemporal dementia	1. Periodic sharp wave complexes (PSWCs) on electroencephalography (EEG) 2. Positive 14–3-3 CSF assay 3. MRI high-intensity signal abnormalities in caudate nucleus &/or putamen on DWI or FLAIR imaging	Routine investigations that do not indicate an alternative diagnosis
* Probable CJD = (A) + at least 2 of (B [criteria 1–4]) + positive result on at least 1 of (C) + (D). Possible CJD = (A) + at least 2 of (B) + absent (C) + absent (D). Definite CJD = diagnosed by standard neuropathological techniques; and/or immunocytochemically; and/or CDI-confirmed PrP; and/or positive RT-QuIC of CSF or nasal brushings.			

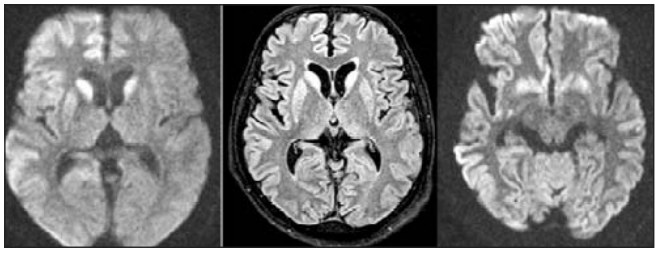

Fig. 1. *Patient E. brain MRI shows the hyperintensity in the caudate nuclei (FLAIR, DWI sequences) and pulvinar thalamic nuclei (FLAIR) that is called a Tdouble hockey stickУ sign. DWI sequence identifies hyperintensity of the right hemisphere cortex (the cortical ribbon sign).*

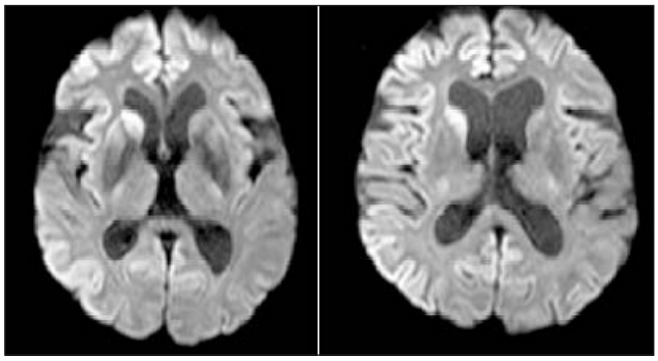

Fig. 2. *Patient B.Xs brain MRI. Hyperintense signal on the right caudate nucleus and the right hemisphere cortex (DWI sequence).*

Clinical Report 4

***Patient B.**, female, 65 y.o., Russian ethnicity. The patient was from Olyokminsky District and was admitted to the neurological department on the 5th of September 2019. In July 2019, the relatives noted that she was forgetful and got easily distracted: she didn't remember why she came to the kitchen, started to skip medications, etc. She was diagnosed with encephalopathy by a neurologist. Despite the therapy, memory disorder was progressing, as the patient forgot what she had been doing in the last 1–2 days. A week after, a gait abnormality and non-systemic dizziness abruptly appeared, without nausea or vomiting. The patient became lethargic and sleepy. A stroke was suspected, so she was urgently hospitalized to the internal disease department of the district hospital due to an increased blood pressure up to 190/100 mm Hg. During the treatment, the blood pressure was stabilized, but dizziness, instability and gait disorders persisted. Memory decline grew, she was disorientated in space: she could not find her ward, the bathroom, her bed in the ward. She didn't recognize her relatives. In September 2019, urinary incontinence arose, and she became unable to walk without assistance. According to the patient's son, for many years until 2017 she had been raising livestock. But she did not consume raw meat and there was no livestock mortality on the farm. In 1986 she had an ectopic pregnancy and blood transfusion was carried out. There was no hereditary neurological pathology.*

On admission the patient's condition was of moderate severity. Neurological examination: the patient was calm but seemed confused. The answers were poor («yes–no» type). She was disoriented in dates and locations. Convergence was insufficient on both sides. Mild dysarthria. Swallowing was normal. Urinary incontinence. Pseudobulbar palsy. There was no paresis. Myotatic reflexes were equal but exaggerated. Astasia-abasia. There were no meningeal signs. On the 5th day of the hospitalization, urinary retention with infection added. On the 11th day, acute swallowing disturbance debuted. Then decerebrate rigidity with an increased muscle tone in the extremities and extensors of the neck, myoclonus in abdominal muscles and the left arm, akinetic mutism developed.

The brain MRI revealed hyperintensity of the right parietal lobe cortex and basal nuclei (more intensive on the right), which was similar to CJD but required a differentiation (Fig. 2). EEG detected a diffuse slowdown of the main activity. General and biochemical analyses of CSF were normal. The patient was discharged from hospital to be followed-up by a local physician.

Discussion

The presented cases are the first diagnosed CJD cases in the Sakha (Yakutia) Republic, which is the largest region of Russia. Ii is interesting, that all the patients were from central districts of Yakutia (Churapchinsky, Vilyuysky, Suntarsky, Olyokminsky districts). All of them were approximately of the same age when the disease debuted, and at the onset they presented with non-specific cerebral symptoms, which were associated with cerebrovascular pathology. According to the literature reviews, the first common symptom of CJD is cognitive impairment (especially memory impairment), and only 9% of patients have motor disorders (mainly extrapyramidal ones) [5]. Rarely, visual disturbances in the form of progressive vision deterioration and visual field defects can be the initial symptom of CJD. Such cases are known as the Heidenhain variant [17].

The women's cases contain notes about blood transfusion, so iatrogenic CJD was suggested. It is known, that iatrogenic forms of the disease can be a result of intracerebral electrodes installation, corneal transplantation, transplantation of the dura mater or growth hormone injections [6]. The iatrogenic CJD cases, caused by the growth hormone injection in childhood, were described in 2015 by a group of scientists from the UK. The average age of the patients was 42.7 years. The most common symptoms were ataxia and dysesthesia in the lower extremities, also, pyramidal insufficiency and myoclonus; cognitive function at the debut was preserved. The incubation period was almost 40 years, and the duration of the disease was from 5 to 32 months (mean 14 months) [18].

Patient P. (Case Report 2) had been enjoying hunting, so the disease could be triggered by consuming meat of an infected animal. But due to the long incubation period of CJD, which can last more than 20 years, the pathways of infection in most cases cannot be established.

According to the clinical presentation, these cases are most likely to be sJCD, which is characterized by rapidly progressing dementia, akinetic mutism, cerebellar disorders, extrapyramidal or pyramidal dysfunction, and myoclonus. The duration of the disease, in most cases, was less than 2 years, on average 3–6 months. There may be psychiatric symptoms, including depression, psychosis and sleep disturbances, which could be the only symptom in the debut of the disease, so it could mimic some primary psychiatric disorders [19, 20].

The familial form of CJD is associated with a mutation in the PRNP gene (encodes prion PrP protein) and, according to some reports, is characterized by early onset (29–33 years on average). Other symptoms are the same as with the sporadic form [21].

A brain MRI detects a hyperintense signal from the basal ganglia and cortex in DWI and FLAIR sequences (especially for

sCJD, sensitivity – 96%, specificity – 93%) [22]. A similar picture of the MRI was observed in our patients.

Typical changes in the form of periodic two- and three-phase complexes of acute waves with a 1–2 Hz frequency [23], which were also present on our patientsX EEG, are typical of the late stages of CJD.

The general CSF analysis in CJD may have no pathology, but biomarkers such as protein 14-3-3, protein S100-beta, neuron-specific enolase and tau protein can be detected. However, these proteins are not prion-specific and are considered to be the markers of neuronal damage [24]. The patients' CSF analyses were normal, but detection of protein 14-3-3 was unavailable due to the lack of reagents. PrPSc protein detection in CSF by the RT-QuIC method (Real-time quaking-induced conversion) looks promising, because its sensitivity is 80% and specificity is 100% [25].

The confirmation of the diagnosis is possible only through biopsy or autopsy of the brain, which is a world problem [26]. For example, in Britain autopsies are only performed in a half of all cases [27]. As a result, the epidemiology of CJD can be underestimated due to the lack of pathological researches and diagnostic confusion with other neurodegenerative diseases.

CJD detection can be improved by appropriate epidemiological surveillance, medical awareness of the disease and a sufficient number of neurologists. It is confirmed by studies conducted in Australia: it has been shown that the intensity of epidemiological surveillance can affect the incidence of this rare disease [28, 29].

In conclusion, the monitoring of prion encephalopathies and the identification of possible, probable or reliable cases of CJD with an urgent notification of health authorities and epidemiological surveillance, such as in the United States or Europe, are needed in Russia.

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Conflict of Interest Statement

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