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CASUISTIC PAPER

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Rapidly progressing dementia as a manifestation of the Creutzfeldt-Jakob disease: an analysis of two cases

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ABSTRACT

Introduction. Creutzfeldt-Jakob disease (CJD) is a rare and fatal neurodegenerative disease of the central nervous system which is caused by an infectious protein called prion. Multiple forms of CJD have been classified including sporadic (more than 90% cases), familial, iatrogenic and variant type of disease. CJD, especially in its early stages, is a highly challenging illness to diagnose.

Aim. Article aims to present cases of Creutzfeldt-Jackob disease with early symptoms of rapidly progressing dementia at the initial stage of CJD.

Description of the cases. This paper describes two cases of patients with suspected CJD with a history of rapidly progressive dementia admitted to the Department of Neurology, MSWiA Hospital in Rzeszów.

Conclusion. Despite the fact that CJD is an incurable illness and there is no cure guaranteeing recovery, it is important to make the right diagnosis. Assay of 14-3-3 protein in cerebrospinal fluid is a sensitive and specific marker which is helpful in the diagnosis of CJD. The only relevant method of correctly confirming a diagnosis of this disease is by performing a brain biopsy.

Keywords. 14-3-3 protein, brain biopsy, cerebrospinal fluid, Creutzfeldt-Jakob disease, EEG, prion

Introduction

Creutzfeldt-Jakob disease (CJD) is a peculiar disease that can not only have a genetic background or occur sporadically, but it can also have an infectious character.[1]

Creutzfeldt-Jakob disease was described for the first time in 1920 by H.G. Creutzfeldt from Breslau (Wroclaw) University.[2] It is the most common of the prion diseases, with a prevalence equal to 1-1.5 per 1,000,000 inhabitants.[1] However, CJD diagnosis is the first diagnosis in only 35% of the patients who probably have the disease.[3]

CJD is caused by the transformation of the normal cellular prion protein (PrP), which is observed on the cell membranes in human and animal subjects, to ab-

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normal. It has been discovered that the PrP^{c} prion (as *cellular*) is an infectious factor, which undergoes conversion into a proteinase-resistant PrP^{d} (as *disease*) or PrP^{Sc} (as *scrapie*) protein. The PrP protein codes the PRNP gene on the short arm of the 20th chromosome.[4] The disease phenotype as well as the susceptibility of its sporadic form is influenced mostly by the 129 codon of the PRNP gene coding methionine or valine. A vast majority of individuals suffering from the iatrogenic and sporadic forms are considered homozygotes in the 129 codon while sporadic heterozygotes suffer from the disease after a significantly longer latent period. There are also reports of the isolation of a proteinase-sensitive PrP protein from CJD patients which may undermine the theory of the prion being the only etiological factor.[5,6] The following subtypes can be distinguished, based on aetiology:[7]

- Spontaneous (sporadic) – *s*CJD
- Familial (genetic) – *f*CJD
- Iatrogenic (induced) – *j*CJD
- Variant – *v*CJD

The most common form of this disease in Poland, as well as worldwide, is *s*CJD in approximately 90% of all cases.[1,7] The prevalence is equal to 0.9 per million inhabitants. There have been no *v*CJD cases reported in Poland so far.[1] The characteristic clinical image of the disease consists of rapidly progressing dementia, myocloni, visual impairment, cerebellar disturbances, pyramidal or extrapyramidal symptoms, akinetic mutism, characteristic EEG records and 14-3-3 protein presence in the cerebrospinal fluid, when the disease duration is less than 2 years.[3,9] Nonspecific prodromal symptoms occur in 10-30% of patients and include weakness, sleep disorders (insomnia or hypersomnia), eating disorders, or depression.[3,10,11] In the course of the disease, extrapyramidal and cerebellar symptoms dominate over pyramidal. All of the mentioned symptoms rarely occur simultaneously and their order of appearance as well as co-occurrence is largely dependent on the disease subtype. The disease always results in death. It is known that 90% of patients die within a year from the appearance of first symptoms.[12] Due to a heterogeneous clinical image, the following clinical criteria of CJD diagnosis have been developed:[13]

I – rapidly progressing dementia

II - myocloni
- visual impairment
- pyramidal/extrapyramidal symptoms
- akinetic mutism

III – characteristic EEG record (periodically occurrence of sharp and slow waves)

IV – in the magnetic resonance image: a hyperintensive signal in the caudate nucleus and the putamen or in at least 2 areas of the cerebral cortex (temporal, parietal or occipital) in the diffusion-weighted imaging (DWI) or in the fluid-attenuated inversion recovery (FLAIR) – the examination should be conducted using a high field device (min. 1.5 T).

Possible CJD – I + two group II symptoms + duration time lower than years.

Probable CJD – I + at least two symptoms from group II or III, or I + at least two symptoms from groups II + IV, or possible disease + 14-3-3 protein presence in the cerebrospinal fluid.

Definitive CJD – diagnosis of typical histopathological changes and/or PrP^{Sc} deposits as a result of a neuropathological brain examination (biopsy/autopsy).

Description of the case report

Case I

Patient C.K., a 73-year-old male pensioner, was admitted to the Neurology Department due to increased speech impediments, balance disorders, involuntary limb movements, rapidly progressing dementia and double vision sensation. The initial symptoms, which occurred two months earlier, included balance and cognition disorders (at the time the patient was admitted to the Neurology Department and was diagnosed with mild cognitive disorders and cerebellar ataxia). The symptoms underwent significant intensification between the hospitalizations. Furthermore, the medical history included hypertension and type 2 diabetes. At the time of admission, the patient was conscious and demonstrated psychomotor slowness as well as disartric, slow and quiet speech. The physical examination revealed a slight 'central' paresis of the right facial mimic muscles, slightly increased muscular tension in the right limbs, significant limb and torso ataxia, marked myocloni in the upper and lower limbs, medium frequency resting tremor of the upper limbs intensifying with a slight (including vocal) stimulus, right-sided Babinski sign and ataxic, broad-based gait in a bent-back position (impossible independently). Firstly, an MRI with contrast was performed which revealed atrophy of the cerebral cortex and cerebellum and hyperintensive (in T_2-weighted images) paracentral sections of the temporal lobes which did not clarify the reason for the neurological state. Dementia features with distinctive bradyphrenia were observed during the psychological examination. Correct records were obtained in the EEG examination conducted twice. In the differential diagnostics, the prion disease (cerebrospinal fluid was collected to determine the presence of the 14-3-3 protein – positive result) as well as the parkinsonism plus syndrome (lack of clinical improvement after the withdrawal of levodopa and clonazepam) were taken into account. During the hospitalization, the patient's state deteriorated rapidly with the occurrence of sleepiness, verbal contact cessation, the occurrence of global anxiety, intensification of limb and facial myocloni, the appearance of choreic move-

ments, limitation of eyeball side and upward mobility, the appearance of release symptoms, significant increase of muscular tension (pyramidal stiffness) and the appearance of a both-sided Babinski sign. Furthermore, obstructions of the digestive system, fever and pneumonia appeared. The patient died on the 15th day of the hospitalization. A brain autopsy examination was conducted which confirmed the diagnosis of a CJD-type spongiform encephalopathy.

Case II

Patient M.R., a 78-year-old female resident of a Nursing Home, was admitted to the Neurology Department due to a paresis of the right limbs persisting for a few days. According to the available documentation, in the past the patient went through an ischemic stroke of the right hemisphere which resulted in a left-sided hemiparesis; furthermore, the intelligence collected from the Nursing Home staff mentions a rapidly progressing dementia within the period of two months. At the time of admission, the patient demonstrated psychomotor slowness and maintained basic verbal contact (basic information on oneself); the physical examination revealed the following deviations from the normal state: approximately 3 cm neck stiffness, shallowed left nasolabial fold, spastic tetraparesis (more intense on the right side), right ankle clonus and left-sided Babinski sign. The conducted examinations (CT and MRI of the head) revealed a cortical-subcortical brain atrophy as well as symmetrically hyperintensive periventricular changes (in the T_2-weighted MRI images) in the form of degenerative lesions of white matter with overlaying ischemic, angiogenic changes. No fresh pathological foci were found. During hospitalization, several episodes of simple motor seizures of the right limbs were observed. The patient's state deteriorated rapidly with the occurrence of fluctuating consciousness and the myocloni of the lower right limb.

A spinal puncture was conducted obtaining a normal pressure cerebrospinal fluid which was of correct composition. The twice-conducted EEG record revealed periodic, occurring every 1s, discharges of sharp-slow-wave complexes and slow waves. Cerebrospinal fluid was collected again and was positively tested for the presence of the 14-3-3 protein. The patient was discharged to the Nursing Home with severe consciousness disorders, weak reactions to pain stimuli, spastic tetraparesis, right ankle clonus and a lack of plantar reflexes. Further fate of the patient is not known. The clinical characteristics of the patients are given in Table 1.

Discussion

Based on the clinical symptoms, outcomes from EEG and MRI as well as a positive result in 14-3-3 analysis, the abovementioned cases of patients were diagnosed with CJD. A very rapidly progressive dementia is a dominant symptom of CJD and it reveals initial symptoms appeared two months before and very distinctive ones occur in the last week prior to admission.[14] Similarly as in the CJD case described by Yegya-Raman et al. as well as Hamlin et al. cerebrospinal fluid analysis was positive for protein 14-3-3.[9,15-17] Other markers of CJD in the cerebrospinal fluid also include S-100 protein, neuron-specific enolase, or tau. Analysis of tau is considered as a more sensitive and specificity marker in the diagnosis of CJD than 14-3-3 protein. However, combination of determination of tau and 14-3-3 is used as the most efficient marker for the diagnosis of CJD.[17] Recently, there have been reports of a supravital definitive CJD diagnosis on the basis of the amplification of the pathological prion protein from the cerebrospinal fluid with 80% sensitivity and 100% specificity.[6] However, study by Peckeu et al. based on autopsy of 1572 patients with CJD, showed that induction of analysis of 14-3-3 protein caused an increase in the diagnostic sensitivity to 82% and a decrease in the specificity to 75%.[18]

Myoclonus is another important and cardinal symptom for the diagnosis of CJD which occurs in 80-100% of the patients, particularly in the advanced stages of the disease.[19] One of presented cases featured an incorrect periodic EEG record. Literature data shows that EEG criteria

Table 1. Patient characteristics

Age	Sex	Clinical symptoms	Initial diagnosis	MRI	EEG	14-3-3 protein	Biopsy	Times of symptoms
73	M	Sudden significant deterioration of the overall state, speech disorders, involuntary limb movements, rapidly progressing dementia, double vision sensation	Neuro-infection	Cerebral and cerebellar atrophy, hyperintensive paracentral sections of the temporal lobes in T2-weighted images	Recording within norm limits	Present	Disease confirmed	21days
78	F	Paresis of the right limbs	Vascular incident	Supratentorial hyperintensive periventricular changes (in the T_2-weighted MRI images) in the form of degenerative lesions with overlaying angiogenic changes	Discharges of sharp-slow-wave complexes and slow waves occurring periodically approximately every 1 second	Present	Not conducted	16 days

are positive in above 60% of the CJD patients.[20] Magnetic resonance imaging is a helpful tool in the clinical diagnosis of CJD with solid sensitivity and reliable specificity.[21] It is worth mentioning that the MRI examinations did not reveal the characteristic changes in first case. Lack of a description of characteristic changes in the MRI image in CJD may also result from the fact that the such hyperintensive changes in the basal ganglia and the thalamus can be observed in the T_2-weighted images only in certain types (type 1 MM1/MV1, type 2 VV2, type 3 MV2; the rest do not show typical changes). It is also worth mentioning that the image unusualness, the disease rarity and close coordination with the radiologist is of significant importance.[22,23] In the second case the image is the closest to the characteristic change (cortical damage and damage in the proximity of subcortical nuclei) similar to the case described by Kojima.[24,25] Our patients had no history of the disease in family. Evaluation of brain tissue obtained by biopsy or autopsy by neuropathologists is the only way to confirm a diagnosis of CJD.[26] In case of disease, histopathological evidence of neuronal, glial and spongiform damages are revealed.[21]

It was possible to confirm the disease by brain autopsy in only one case; the second patient was discharged from the hospital and it was not possible to convince the family to consent to an autopsy following the patient's death, should it occur outside the facility. In the first case, it is possible to diagnose a probable CJD. The most serious doubts arise in relation to the second case, however, despite the lack of the most typical symptoms and according to the applicable Edinburgh criteria, it is possible to make a probable (rapidly progressing dementia + pyramidal/extrapyramidal symptoms and akinetic mutism + MRI image) or at least possible (without MRI, but the symptoms last less than two years) diagnosis. The greatest problem in making a definitive diagnosis is the lack of the families consent for the autopsy following a discharge from the hospital. Currently, there is no effective method of disease treatment or slowing, therefore the observation and diagnostics should be conducted thoroughly, as a probable diagnosis inclines the inevitability of treatment failure. Furthermore, relaying such information to the family needs to be supported by substantial evidence.

Summarizing, Creutzfeldt-Jakob disease is generally a diagnostic challenge for physicians because symptoms are similar to rapidly progressing dementias, so physicians should have a comprehensive understanding of CJD. It is important to carry out more detailed and sensitive tests to support an early clinical diagnosis, even before the onset of specific clinical manifestations.

Conclusion

In case of a rapidly progressing dementia with apparent neurological symptoms, CJD should be considered. Obviously, the clinical symptoms covered in the diagnosis criteria may appear in various fully-developed neurodegenerative diseases, however a very rapid progression suggests CJD (with the rare exceptions of slow-progression cases e.g. heterozygotes of the PRNP gene 129 codon).

The most characteristic additional examination results rarely occur simultaneously, therefore their lack should not constitute a decision to cease the CJD-oriented observations such as the characteristic periodic EEG record occurs mainly in MM1 homozygotes and MV1 heterozygotes in the PRNP gene 129 codon (type 1 *s*CJD) which constitute approximately 40% of CJD cases.

A clearly lower recognizability in Poland, compared to Europe, may result from the fact that the disease is not diagnosed.

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