The value of magnetic resonance imaging in the early diagnosis of Creutzfeldt-Jakob disease – own experience

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Summary

Background:
Creutzfeldt-Jakob disease (CJD) is a rare progressive neurodegenerative disorder, caused by the deposition of the pathological isoform of prion protein PrPsc in the central nervous system. The classic triad of symptoms consists of: rapidly progressive dementia, myoclonus and typical electroencephalographic findings (intermittent rhythmic delta activity and periodic sharp wave complexes). Detection of 14-3-3 protein in the cerebrospinal fluid plays an important diagnostic role as well. Magnetic resonance (MR) images of the brain have been recently incorporated into the diagnostic criteria of sporadic Creutzfeldt-Jakob disease.

Case Report:
MR examinations were performed in a 65-year-old man and a 54-year-old woman with delusional disorder and cognitive dysfunction, respectively. Diffusion restriction (hyperintense signal in DWI) was shown in the cortex of the left parietal and occipital lobe in the first patient and symmetrically in the cortex of both cerebral hemispheres except for precentral gyri in the second one. In both cases, the first examinations were misread, with the suspicion of ischemic infarcts as the first differential diagnosis. Consultations and subsequent MR examinations in which lesions in subcortical nuclei appeared allowed for a diagnosis of probable CJD. In the first case it was confirmed by clinical picture, EEG and finally – autopsy. In the second case, EEG was not typical for CJD but the clinical course of the disease confirmed that diagnosis.

Conclusions:
The authors present the cases of two patients with characteristic MR images that allowed early diagnosis of probable Creutzfeldt-Jakob disease before the characteristic clinical picture appeared. Early diagnosis is nowadays important for the prevention of disease transmission and in the future – hopefully – for early treatment.

Key words: Creutzfeldt-Jakob disease (CJD) • magnetic resonance imaging (MRI)

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Background

Creutzfeldt-Jakob disease (CJD) is a rare progressive neurodegenerative disorder, caused by the deposition of the pathological isoform of prion protein PrPsc in the central nervous system. The incidence of CJD is 1/1000000/year. Sporadic CJD accounts for over 90% of all cases. The remaining 10% includes familial, iatrogenic and variant CJD. The onset of the disease is usually around the age of 60 with the life expectancy of 6–24 months after diagnosis. Histopathological examination reveals the atrophy of neurons and subsequent proliferation of astrocytes and formation of vacuoles in neuropil, leading to spongiform degeneration (status spongiosus).

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and periodical sharp wave complexes. Detection of 14-3-3 protein in the cerebrospinal fluid is of much diagnostic significance. Magnetic resonance (MR) images of the brain have been recently incorporated into the diagnostic criteria of sporadic Creutzfeldt-Jakob disease. Typical features of MRI images in the presented patients allowed an early diagnosis of probable CJD prior to the characteristic clinical manifestation.

Case Report

Case 1

A 65-year-old male, a butcher, was admitted to hospital on February 2, 2009 with suspected stroke after two days of persisting speech disturbance. History revealed: controlled arterial hypertension, ischemic heart disease, left bundle branch block, ventricular extrasystoles, recurrent phlebitis of the lower limbs (treated with oral anticoagulant chronically). A mild degree of aphasia, discrete right-sided hemiparesis with hypoaesthesia and bilateral hearing loss were found on neurological examination. The laboratory tests were normal. There were no pathological lesions on brain CT. A logopedic therapy was implemented – slowly withdrawing aphasia and improving verbal contact was observed. On the 3rd day of hospital stay, delusions of reference as well as hypochondriac delusions appeared. Neuropsychologist consultation revealed a mild degree of sensory aphasia (difficulties in understanding complex sentences and distinguishing between similar-sounding words, slight difficulties with naming), anxiety, depressed mood and symptoms of delusional disorders. Psychiatrist consultation: organic delusional disorder. Treatment with pernazine was introduced leading to gradual reduction of productive symptoms. Brain MRI performed on the 9th day of hospital stay showed restricted diffusion (increased signal on DWI; Diffusion-Weighted Imaging) in the left occipital and parietal cortex (Figure 1). FLAIR (Fluid Attenuated Inversion Recovery) sequence demonstrated slightly increased signal from these cortical areas. Additionally, focal lesions of ischemic origin were found. A (false) diagnosis of acute ischemic lesions in left hemisphere was made. The patient was discharged from hospital with partial recovery, being diagnosed with ischemic stroke. He was re-admitted after 3 weeks due to regression in verbal contact, general weakness and aggressive behavior. Brain CT and laboratory tests were normal. The patient stayed at the Department of Psychiatry with the diagnosis of delirium overlapping dementia. Treatment with Tiapridalum was introduced. The regression in verbal contact progressed until a complete lack of verbal contact. The clinical manifestation also included dysphagia, right-sided paresis, sphincter disturbance and akinetik mutism. EEG revealed abnormal activity with rhythmical sharp-and-slow wave complexes (PLED), spike- and polyspike-wave complexes during the whole examination. Intravenous treatment was initially introduced: diazepam, phenytoin, valproic acid. Despite the treatment, consciousness alterations progressed. Consecutive EEG examination showed abnormal activity with sharp-and-slow wave complexes and triphasic sharp-waves through the entire recording. Changes were located predominantly in the left hemisphere. Subsequent brain DWI MRI did not reveal changes in the area demonstrated on the previous study, whereas signal intensification was demonstrated in the caudate and lenticular nuclei, also visible in T2-weighted images in the FSE (fast spin echo) sequence and FLAIR (Figure 2). The description of the previous MRI examination of the head was verified in which changes demonstrated by DWI sequence were limited to the area of the posterior cortex of the left hemisphere, both peripherally and parasagittally, and did not fit any particular artery supply. There was no edema of the affected cortex and the radiological signal was less intensive as it would be in case of an acute stroke. Hence, images were not characteristic for acute ischemia. Basing on MRI and clinical manifestation, Creutzfeldt-Jakob disease was suggested. The patient died 5 days later (i.e. March 25, 2009) due to cardiovascular and respiratory failure. Autopsy showed anatopathological features of acute ischemia of the affected cortex.

Figure 1. Patient no. 1. MRI no. I. DWI hyperintensity of the cortex of the posterior part of the left cerebral hemisphere.

Figure 2. Patient no. 1. MRI no. II, 5 weeks after no. I. FLAIR sequence. Hyperintense signal intensity in the caudate nucleus and striatum bilaterally.
myocardial infarction of the posterior wall and generalized atherosclerosis of a moderate degree. Neuropathologically disseminated lesions of vascular origin (perivascular lacunes, arterial and venous thrombosis) as well as spongiosic lesions typical for spongious encephalopathy were seen both in frontal lobes and cerebellum. Positive immunohistochemical test with PrP antibody (3F4, DAKO) confirmed definite diagnosis of Creutzfeldt-Jakob disease (Figure 3).

Case 2

A 54-year-old female, with academic education, generally healthy, presented to a general practitioner because of a substantial weight loss (10 kg within 1 year) and undefined worsening of disposition and functioning. Additional tests were not explanatory (blood test, ESR, CRP, markers of liver and kidney function, thyroid hormones, vitamin B12 level; Borreliosis test was negative, gastroscopy did not reveal any abnormality). During subsequent two months (i.e. since July 2010) some disturbances of everyday activity appeared: the woman was losing orientation easily, she had difficulties with assessing time, had problems with dressing up. On the other hand, she easily performed her home chores and continued her hobby, she drove a car. Neuropsychological assessment in November 2010 revealed significant cognitive impairment, mostly considering visuo-cognitive functioning: impaired visuo-spatial memory, severe constructional apraxia, acalculia, agraphia as well as impaired executive functions. Patient’s cognition ability was assessed by Mini-Mental State Examination (MMSE). She scored 27 points (backward spelling version was used due to acalculia). Her verbal and social functioning was markedly good. There were no abnormalities found in neurological examination apart from cognitive disturbances. Brain MRI was performed (outside our hospital) which showed hyperintense signal from the cortex of both hemispheres on FLAIR and DWI sequences (Figure 4). The interpretation indicated differential diagnosis between hypertensive encephalopathy, drug side effect and initial phase of ischemic stroke. Radiologist in our center suggested CJD. Subsequent MRI study revealing – apart from cortical lesions – discrete changes in the right caudate nucleus and both thalami (Figure 5) sustained this suspicion. In order to confirm the diagnosis, EEG examination was performed: with a slower basic rhythm, numerous theta waves and some delta waves synchronizing the activity were noted. Sharp-and-slow wave complexes were also recorded (changes were not typical for CJD). Lumbar puncture was performed for 14-3-3 protein detection – with negative result. During the follow-up visit in May 2011, neurological decline was noted – left-sided extrapyramidal signs appeared with periodic involuntary dyskinetic movements in lower extremities. The neuropsychological assessment revealed an aggravation of previously observed disturbances, verbal memory impairment appeared. MMSE score was 18. The patient required permanent help in everyday functioning due to increasing difficulties with orientation in space and planning complex activities.

Discussion

The typical triad of symptoms includes: rapidly progressive dementia, myoclonus and typical electroencephalographic findings (periodic sharp-and-slow wave complexes). These are clinical and electroencephalographic symptoms occurring in advanced stages of the disease and forming diagnostic criteria of probable CJD, as determined in 1998 by WHO [1]. Definite diagnosis of CJD requires histopathological examination.

Figure 3. Patient no. 1. Immunohistochemical examination. Spongiform changes and perivascular pattern of PrP-immunoreactive depositions. Basal ganglia – putamen. PrP ×400.

Figure 4. Patient no 2. MRI no. I. DWI. Hyperintense signal intensity of the cerebral cortex bilaterally. Sparing of the precentral gyri.

Figure 5. Patient no 2. MRI no. II, 5 weeks after no. I. DWI. Discreetly increased signal intensity in the thalami appeared.
According to the Polish regulations, autopsy in patients with CJD is compulsory. This is in accordance with the Act of 5 December 2008, article No. 33, section 2, point 6 [2] on preventing infections and contagious diseases in humans.

It was repeatedly suggested in the literature to include typical DWI MRI findings of Creutzfeldt-Jakob disease (restricted diffusion in the cerebral cortex and subcortical structures) in the criteria allowing the clinical diagnosis [3–5]. Other authors suggested to generally include MRI manifestation into the diagnostic criteria, due to the fact of characteristic involvement of caudate nuclei and putamen in familial CJD [6].

Most recently revised CJD criteria include – apart from clinical manifestation, EEG findings and cerebrospinal fluid test – also MRI study findings. Sporadic CJD criteria (sCJD) were adjusted regarding MRI study (Table 1) and have become mandatory in that form since 2010 [7]. Criteria proposed by University of California, San Francisco (UCSF) for CJD diagnosis based on MRI findings are presented in Table 2 [8].

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### Table 1. Diagnostic criteria for sCJD according to the National Creutzfeldt-Jakob Disease Surveillance Unit in Edinburgh.

| Category | Criteria |
|----------|----------|
| **I** | Rapidly progressive dementia |
| **II** | Myoclonus, Visual or cerebellar disturbance, Pyramidal/extrapyramidal dysfunction, Akinetic mutism |
| **III** | Characteristic EEG activity (periodic appearance of sharp-and-slow wave complexes) |
| **IV** | MRI – hyperintense signal in DWI or FLAIR sequence within caudate nucleus and putamen or at least from two areas of the cerebral cortex (temporal, parietal or occipital) |
| Possible CJD | I + two symptoms from group II + duration of disease <2 yrs |
| Probable CJD | I + at least two symptoms from group II and III or I + at least two symptoms from group II and IV or possible CJD + 14–3–3m protein in cerebrospinal fluid |
| Definite CJD | Typical histopathological changes or/and PrPSc on brain examination (biopsy or autopsy) |

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### Table 2. MRI criteria for CJD diagnosis presented by the University of California in San Francisco (UCSF) in 2010.

| Category | Criteria |
|----------|----------|
| **Definite CJD** | Hyperintense signal on DWI > FLAIR with: Typical presentation: cingulate gyrus, striatum and >1 gyrus of neocortex (often precuneus, angular gyrus, superior or middle frontal gyrus) Additional criteria of subcortical structure involvement: Striatum with antero-posterior gradient Subcortical hyperintensity on ADC map Additional criteria of cortical involvement: Asymmetric involvement of neocortex in midline or of cingulate gyrus Spared precentral gyrus Cortical hypointense edging on ADC map Only from cortex (>3 gyri). See additional criteria as above |
| **Probable CJD** | Unilateral involvement of striatum or cortex (< or =3 gyri). See additional criteria above Bilateral involvement of striatum or postero-lateral thalami. See additional criteria above. |
| **Probably not CJD** | Increased signal on FLAIR/DWI in limbic areas, appearing physiologically (e.g. insula, anterior part of cingulate gyrus, hippocampus), no changes on ADC map Hyperintense signal on DWI due to artifacts. See below. Abnormalities on FLAIR>DWI. See below |
| **Definitely not CJD** | Normal MRI Abnormalities of different type than in CJD |
| **Other MRI features** | Long courses of sCJD (>1 year) — MRI may reveal significant brain atrophy with loss of hyperintense signal on DWI. To differentiate between abnormal signal from artifacts, a particular sequence should be repeated in different planes (e.g. transverse and coronal). |

ADC – Apparent Diffusion Coefficient.
In the first patient, MRI of the brain enabled the diagnosis of CJD basing on DWI sequence (UCSF criteria) on the 9th day from symptom onset. In case of the second patient, with much slower progression, the diagnosis was possible in the 2nd month from the onset of neurological symptoms. That period could have been even shorter if MRI studies had been performed earlier on. Clinical criteria of probable CJD, from 2010, were fulfilled by the first patient after 7 weeks from symptom onset (dementia, pyramidal signs, akinetic mutism + MR images), and after 10 months from neurological manifestation onset in case of the second patient (dementia, cerebellar and extrapyramidal symptoms + increased signal on DWI from brain cortex).

Brain MRI became an important tool for early diagnosis of CJD. The shortest period presented in literature from symptom onset to the appearance of characteristic radiological features on MRI was 3 weeks [9]. MRI sensitivity in CJD diagnosis is estimated to be as high as 96% with specificity of 93% [8]. For comparison, 14-3-3 protein detection in CSF has a sensitivity of 86% and specificity of 68% [according to some authors even 94% and 84%, respectively [10]], and EEG has a sensitivity of up to 64% and specificity of 91% [11].

Early diagnosis is nowadays very important for preventing disease transmission, and probably in future – as assumed – for early treatment implementation.

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