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Case Report

PROLONGED COURSE OF CREUTZFELDT-JAKOB DISEASE WITH EXCESSIVE CENTRAL NERVOUS SYSTEM DEGENERATION

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SUMMARY – In Slovak genetic Creutzfeldt-Jakob disease patients with E200K mutation in the prion protein gene the mean duration of clinical stage is significantly shorter in methionine homozygous than in methionine/valine heterozygous patients (3.70±2.00 *vs.* 7.84±7.30 months). An atypical prolonged course (13 months) of Creutzfeldt-Jakob disease complicated by malignant neuroleptic syndrome in a 48-year-old methionine homozygous carrier of E200K mutation is reported. Progression was documented by computed tomography, magnetic resonance imaging, functional-biochemical magnetic resonance spectroscopy, and electroencephalography. Post mortem neurohistologic findings confirmed the definitive diagnosis of Creutzfeldt-Jakob disease and revealed severe reduction of cerebral and cerebellar cortex with almost complete depletion of neuronal cells. The possible explanation of unusual duration of the disease in genetic Creutzfeldt-Jakob disease is discussed. The importance of early diagnosis and timely therapeutic intervention (when effective treatment becomes available) sufficiently preceding the development of irreversible degenerative changes of the central nervous system is emphasized.

Key words: *Creutzfeldt-Jakob syndrome – genetics; Prions diseases – diagnosis; Prions genetics; Central nervous system – degeneration; Case report*

Introduction

Creutzfeldt-Jakob disease (CJD) is known to be the most common human transmissible spongiform encephalopathy (TSE)[1]. The degenerative central nervous system (CNS) disorder occurs with an incidence of 0.5-2.0/million/year all over the world. Familial cases have never exceeded 10%-15%, however, genetic testing of the prion protein gene (PRNP) performed in sporadic cases revealed a disease specific mutation in some of them[2]. Annual sporadic CJD incidence is 1.0/million all over the world[3]. The occurrence of CJD in Slovakia shows some characteristic features, i.e. geographic clustering of genetic cases carrying a CJD specific mutation in the PRNP gene at codon 200 (E200K mutation)[4]. They account for up to 74.2% of all Slovak CJD patients, 53.7% of them typical familial cases. Moreover, 64% of these E200K carriers are methionine homozygous at codon 129 of the PRNP gene[5]. Methionine homozygosity at codon 129 is not only a recognized risk factor in sporadic, iatrogenic, genetic and variant CJD[3,5-8], but also significantly accelerates the clinical course of genetic CJD. The mean duration of the disease in CJD E200K methionine homozygous patients is significantly shorter compared with methionine/valine heterozygous cases (3.70±2.00 *vs*. 7.84±7.30), therefore a clinical

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course exceeding 1 year in such a case is atypical and deserves attention.

Case Report

A 48-year-old male was admitted to the Department of Psychiatry in September 2000 for the developement of depressive psychosis with paranoid features. The condition emerged markedly 14 days prior to admission. Treatment with antidepressant and neuroleptic drugs was introduced. On day 10 of treatment, the patient developed symptoms of malignant neuroleptic syndrome (MNS), including qualitative and quantitative consciousness disturbance, oculogyric crises, extrapyramidal rigidity, hyperpyrexia, vegetative instability, paralytic ileus and metabolic disequilibrium. High blood levels of creatine kinase were documented.

Treatment with neuroleptic and antidepressant drugs was discontinued and complex symptomatic treatment was supplemented with intravenous administration of amantadine sulfate and methylprednisolone (total dose 2000 mg amantadine sulfate and 2500 mg methylprednisolone for 5 days). Meanwhile the patient was transferred to the metabolic intensive care unit (ICU), where the metabolic and cardiovascular equilibrium was achieved. Then the patient was transferred to the Department of Neurology. At that time the patient was stuporous, with persistent oculogyric crises. These attacks persisted for four weeks, although extrapyramidal rigidity gradually disappeared.

The following circumstances raised suspicion of TSE as the possible pathomorphologic substrate: incomplete improvement of MNS, complementary patient's history (episodic memory failures, behavioral and personality changes for 4 months prior to admission), and electroencephalographic (EEG) findings (burst-suppression pattern).

Clinical picture was predominated by hyperkinesias of the right upper and both lower extremities, paradoxically with only mild 'cogwheel' phenomenon in the limb flexor muscles. These hyperkinetic attacks had no EEG correlates. Tonic grasp reflex on the right hand was also present. Furthermore, we repeatedly evoked Babinski's phenomenon followed by bilateral complex three-flexion response (ankle, knee and hip joints). The tonic oculogyric crises were provoked by painful stimuli and accompanied by an altered respiration pattern, intense perspiration and pale face. In the final stage of the disease (months 10-13 apart from the initial symptoms) the patient was deeply comatose, Glasgow Coma Scale (GCS) 3. There was no reaction to painful stimuli, the eyeballs were deviated to the left without any pupil light reaction but with persistent corneal reflex bilaterally. The upper limbs remained constantly in extension and lower limbs in flexion posture with marked spastic resistance. In general view the patient was cachectic. During the hospital stay, intermittent airway and urinary infections were repeatedly treated with antibiotics. Apnea episodes with very superficial respiratory movements were observed in the last three weeks of the disease course. Death occurred suddenly as a consequence

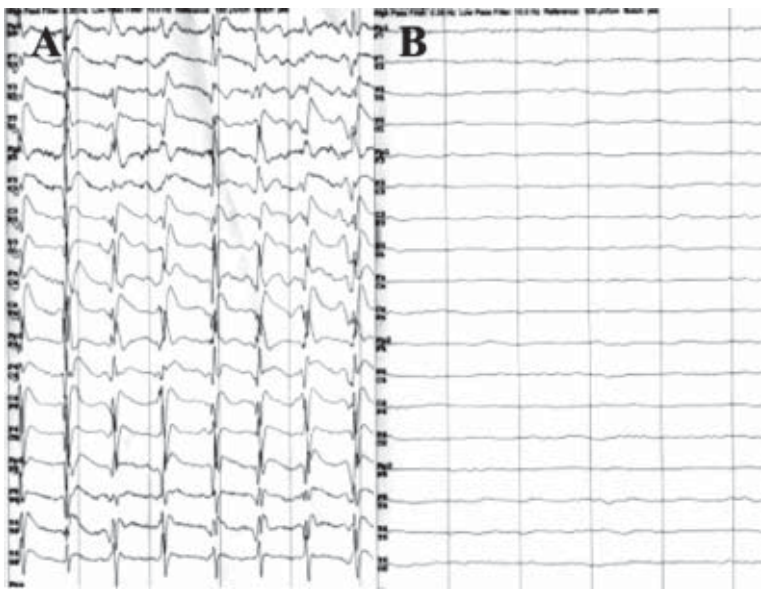


Fig. 1. 'Burst suppression pattern' characteristic of Creutzfeldt-Jakob disease: (A) generalized periodic 1.5 Hz discharges of polyphasic sharp wave or spike-slow wave complexes on flat background activity; (B) terminal stage of the disease with flat low voltage activity with very sporadic dispersed fast unsharp theta waves occurring mainly in the left frontocentral region.

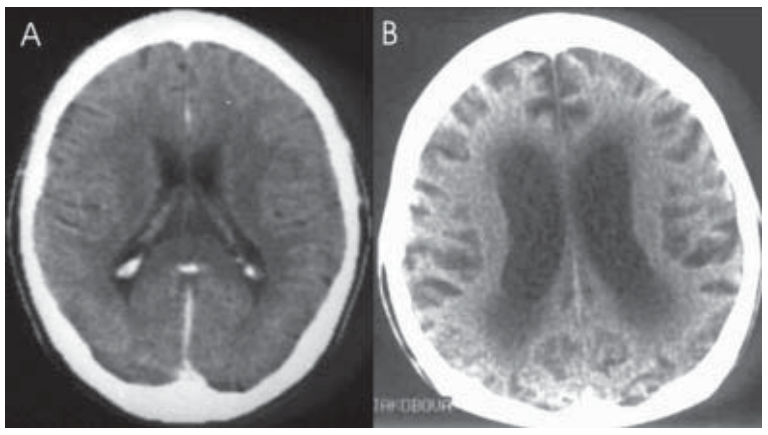


Fig. 2. Computed tomography scans showing mild brain atrophy without any visible pathologic changes of the brain tissue, with marked progression (A) and marked brain atrophy in the final stage of the disease course (B).

of respiratory and cardiovascular CNS center failures in the night, 9 months of hospital admission and 13 months of the onset of clinical symptoms and signs.

Electroencephalography (EEG) – The first EEG recording (October 2000) showed irregular, mainly asynchronous slow theta, occasionally delta activity (especially over the right frontocentroparietal region) with only sporadic alfa waves. The second recording was obtained four days later, showing generalized periodic (0.6 Hz) bursts of polyphasic sharp waves and spikes with right frontocentroparietal maximum occasionally followed by a slow wave in a flat (suppressed voltage) background. The next recording taken one week later showed complete 'burst suppression pattern' (generalized periodic 1.5 Hz discharges of polyphasic sharp wave or spike-slow wave complexes on flat background activity) characteristic of CJD. Such complexes were present throughout the recording (Fig. 1a). The last EEG recording represented terminal stage of the disease with flat low voltage activity with very sporadic dispersed fast, unsharp theta waves occurring mainly in the left frontocentral region (Fig. 1b).

Brain imaging methods (computed tomography, magnetic resonance imaging) on admission (4 months of clinical complaints) revealed very mild brain atrophy without any visible focal pathologic changes of the brain tissue (Fig. 2a) followed by marked atrophy progression with time (Fig. 2b).

Magnetic resonance spectrosopy (MRS) 11 months after the onset of symptoms revealed marked loss of vital neurons in the brain tissue with signs of cell membrane decomposition (Fig. 3).

Cerebrospinal fluid (CSF) analysis showed physiologic composition (the 14-3-3 protein was not tested). Common biochemical tests in blood tissue did not reveal any pathologic changes.

DNA analysis of the PRNP gene detected CJD specific codon 200 mutation (E200K) and codon 129 methionine homozygosity.

Autopsy revealed enormous brain and cerebellar atrophy. Histopathologic examination perfomed in formalin fixed and paraffin embedded brain tissue revealed strik-

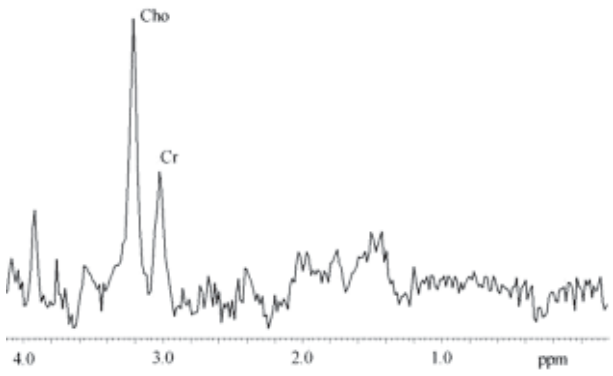


Fig. 3. Magnetic resonance spectroscopy (MRS) through the white matter right parietal window. A brain tissue volume of 2x2x2 cm was analyzed. The spectrum obtained is considered basically different from the normal MRS spectrum because of the N-acetylaspartate peak absence at 2.02 ppm. The marker is a neurochemical sign of functional neurocytes, therefore excessive neurocyte shortage is to be presumed. In addition, in the spectrum obtained the choline (Cho) signal is markedly expressed compared to creatine (Cr) signal. A relatively increased Cho signal indicates protoplasmic membrane catabolism. In MRS conclusion there is a marked loss of vital neurons in the brain tissue with protoplasmic cell membrane decomposition.

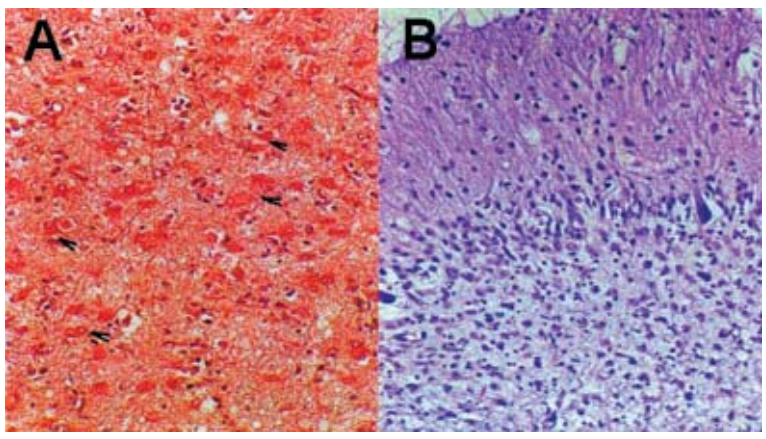
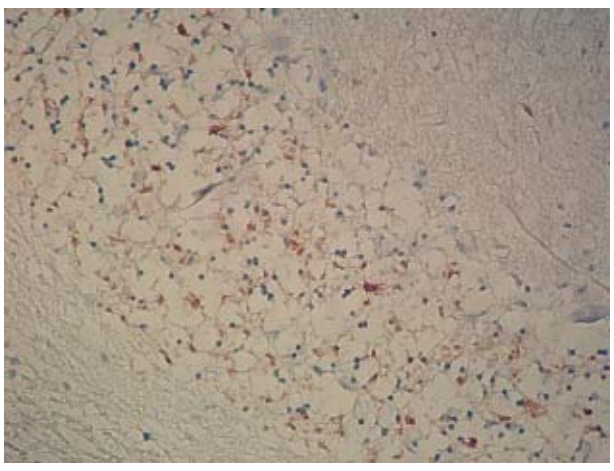


Fig. 4. Histology. (A) cerebral cortex (HE, X250): severe loss of neurons, the whole grey matter is dominated by hypertrophic astrocytes (arrows); (B) cerebellar cortex (HE, X250): striking changes in the ganglial layer (severe loss of Purkinje's cells and proliferated Bergmann's glia) and extremely reduced cells in the granular layer resulted in atypical, pathologically altered structure of the cerebellar cortex; (C) cerebellar cortex in genetic CJD (E200K mutation and methionine homozygosity at codon 129 in the PRNP): severe depletion of neurons in all cortical layers, most striking in the granular layer. Positive pathologic PRNP immunostaining with 3F4 MAb (monoclonal antibodies) in the granular layer. (Eva Mitrová, M.D., Ph.D., Institute of Preventive and Clinical Medicine, Bratislava, Slovak Republic).

ing neuronal loss. In neocortical areas, disappearance of the typical laminar structure caused by extensive loss of neurons throughout the gray matter thickness was recorded (Fig. 4a). Pathologic findings were also evident in the cerebellum, where the molecular layer showed proliferated Bergmann's glia around degenerated Purkinje's cells and extremely reduced granular cells. The cerebellar cortex showed atypical pathologic structure mainly in the 2nd and 3rd layer (Fig. 4b). Surviving neuronal cells in basal ganglia were characterized by a markedly increased amount of lipofuscin. Conspicuous hypertrophy and proliferation of astrocytes were observed in all examined structures. Interestingly, the spongiform changes were rare, they disappeared due to severe structural changes of the neuropil. Generalized, extensive neuronal loss and severe astrocytic reaction without inflammatory changes confirmed the diagnosis of CJD. Immunocytochemistry revealed positive pathologic PRNP immunostaining with 3F4 monoclonal antibodies in the granular layer of the cerebellar cortex (Fig. 4c).



Discussion

The presented case was atypical in comparison to 23 patients diagnosed or consulted till now at our department, in the clinical course, disease duration, and both the severity and extent of CNS degeneration. The duration of the disease differed significantly from the average duration in Slovak CJDE200K patients[5]. One of the possible causes of the patient's atypical prolonged survival is the quality of medical and nursing care at the neurologic ICU, where the patient was hospitalized.

Since the patient was also symptomatically treated by amantadine sulfate, one can recollect reports analyzing the effect of amantadine hydrochloride on CJD. Although several trials of amantadine in CJD patients proved disappointing for ultimate deterioration and death, some authors report that treatment with amantadine hydrochloride was followed by prolonged survival[9-11]. According to

Terzano *et al.*[12], the failure of amantadine to prolong survival significantly in their four patients could be ascribed to the delay in the initiation of therapy. Considering the above mentioned experience, it could not be excluded that besides nursing care the administration of amantadine sulfate also contributed to prolonged survival of the patient presented.

The extremely severe CNS degeneration in our patient clearly demonstrates that even if therapy should become available, irreversible changes of the brain do not allow to restore an acceptable quality of life. To be effective, any treatment should be administered early after the clinical onset of the disease. Due to the limited specific diagnostic methods it is rather difficult in sporadic CJD. At this point, we want to stress the importance of repeated EEG examination in the diagnostic process of CJD.

Since personal history may indicate iatrogenic exposure, an early diagnosis is relatively easier in the iatrogenic form of CJD. Even better chances have genetic cases, where detection of the disease specific mutation of the PRNP gene provides an early signal for therapeutic efforts. In the reported patient, differential diagnosis was difficult at an early stage of the disease because of the dominant psychiatric disturbances followed by early development of a malignant neuroleptic syndrome. The genetic testing of the PRNP gene had a decisive importance for ante mortem diagnosis.

A study of 136 Slovak CJD patients and their families shows that about 36% of relatives are asymptomatic carriers of the E200K mutation. The penetrance of the mutation is 59%. Such 'healthy' carriers of E200K were also found in the family of our patient. Decisive factors for the clinical manifestation of the disease in E200K carriers have not yet been fully identified. Besides the mentioned methionine homozygosity as an endogenous risk factor, stress (both physical and mental) appeared to be the triggering factor for the clinical onset of CJD. Since no preclinical test for initial stages of conversion of the normal cellular PRNP to the pathologic PRNP has yet become available, the detection of asymptomatic 'healthy' carriers of E200K mutation is very important. They represent a 'genetic risk group of CJD' excluded from tissue and organ donation. The evidence of CJD specific mutation is useful for both the early diagnosis in case of developing CJD and in the prevention of iatrogenic CJD.

In conclusion, we report on an atypical prolonged clinical course (13 months) of CJD complicated by malignant neuroleptic syndrome in a 48-year-old carrier of E200K mutation with methionine homozygosity at codon 129 of the PRNP gene. Progression was documented by computed tomography, magnetic resonance imaging, functional biochemical magnetic resonance spectroscopy and electroencephalography. The definitive diagnosis of CJD was verified by post mortem neurohistopathology.

Considering recent progress and discoveries in human and animal prion diseases, expectations concerning successful treatment of CJD could be optimistic. Since carriers of CJD specific mutation are best candidates for early and effective treatment, additional data, especially on atypical cases, could contribute to better knowledge, easier clinical diagnosis and in perspective to early treatment of the genetic subgroup of CJD.

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Sažetak

PRODULJEN TIJEK CREUTZFELDT-JAKOBOVE BOLESTI UZ OPSEŽNU DEGENERACIJU SREDIŠNJEGA ŽIVČANOG SUSTAVA

M. Drobný, M.R. Voško, E. Kurča, E. Mitrová, V. Nosá³/₄, B. Pit'hová, D. Trstenský, M. Adamková, D. Šútorová, V. Verchovodková, V. Mlynárik i D. Dobrota

Srednje trajanje kliničkog stadija u slovačkih bolesnika s genetskom Creutzfeldt-Jakobovom bolešću s mutacijom E200K u genu prionskog proteina (PRNP) značajno je kraće u bolesnika homozigotnih za metionin nego u onih heterozigotnih za metionin/valin (3,70±2,00 prema 7,84±7,30 mjeseci). Opisuje se atipičan produljeni tijek (13 mjeseci) Creutzfeldt-Jakobove bolesti kompliciran malignim neuroleptičnim sindromom u 48-godišnjeg nositelja mutacije E200K homozigotnog za metionin. Progresija je dokumentirana kompjutoriziranom tomografijom, magnetskom rezonancom, funkcionalno biokemijskom spektroskopijom magnetskom rezonancom i elektroencefalografijom. Neurohistološki nalazi pri obdukciji potvrdili su definitivnu dijagnozu Creutzfeldt-Jakobove bolesti i otkrili teško smanjenje cerebralnog i cerebelarnog korteksa uz gotovo potpun nestanak neuronskih stanica. Raspravlja se o mogućem objašnjenju neuobičajenog trajanja bolesti u slučaju genetske Creutzfeldt-Jakobove bolesti. Naglašava se važnost rane dijagnoze i terapijske intervencije (kad učinkovita terapija bude dostupna), koje će dostatno prethoditi razvoju zapaženih ireverzibilnih degenerativnih promjena središnjega živčanog sustava.

Ključne riječi: *Creutzfeldt-Jakobov sindrom – genetika; Prionske bolesti – dijagnostika; Genetika priona; Središnji živčani sustav – degeneracija; Prikaz slučaja*