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 PrP 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 46-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; Prion disease – diagnosis; PrP gene; Central nervous system – degeneration; Case report

Introduction

Creutzfeldt-Jakob disease (CJD) is known to be the most common human transmissible spongiform encephalopathy (TSE). 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 them1. Annual sporo-

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radic CJD incidence is 1.0/million all over the world1. 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)2. They account for up to 74.2% of all Slovak CJD patients, 53.7% of them typical familial cases. Moreover, 6.4% of these E200K carriers are methionine homozygous at codon 129 of the PRNP gene3. Methionine homozygosity at codon 129 is not only a recognized risk factor in sporadic, iatrogenic, genetic and vari-

ant CJD11-14, but also significantly accelerates the clinical course of genetic CJD. The mean duration of the disease in CJD E200K methionine homogyous patients is significantly shorter compared with methionine/valine heterozygous cases (3.70±2.00 vs. 7.84±7.30), therefore a clinical
course exceeding 1 year in such a case is atypical and de-

Case Report

A 48-year-old male was admitted to the Department of Psychiatry in September 2000 for the development of depressive psychosis with paranoid features. The condi-
tion emerged markedly 14 days prior to admission. Treat-
ment with antidepressant and neuroleptic drugs was in-
roduced. On day 10 of treatment, the patient developed
symptoms of malignant neuroleptic syndrome (MNS),
including qualitative and quantitative consciousness dis-
turbance, oculogyric crises, extrapyramidal rigidity, hyper-
pyrexia, 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 methylprednis-
olone for 5 days). Meanwhile the patient was transferred
to the metabolic intensive care unit (ICU), where the met-
abolic and cardiovascular equilibrium was achieved. Then
the patient was transferred to the Department of Neuro-
logy. At that time the patient was stuporous, with persis-
tent oculogyric crises. These attacks persisted for four
weeks, although extrapyramidal rigidity gradually disap-

The following circumstances raised suspicion of TSE
as the possible pathological substrate: incomple-

Clinical picture was predominated by hyperkinesias of
the right upper and both lower extremities, paradoxically
with only mild “cogwheel” phenomena in the limb flexor
muscles. These hyperkinetic attacks had no EEG corre-
lates. Tonic grasp reflex on the right hand was also present.
Furthermore, we repeatedly evoked Babinski’s pheno-
menon followed by bilateral complex three-flesion 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 coma-
tose. Glasgow Coma Scale (GCS) 3. There was no reac-
tion 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 con-
stantly 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 antibiot-
ic. Apnea episodes with very superficial respiratory move-
ments were observed in the last three weeks of the dis-
ease 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 polyspike sharp
wave or spike–slow wave complexes on flat back-
ground activity; (B) terminal stage of the disease
with flat low voltage activity with very sporadic
dispersed fast sharp theta waves occurring
mainly in the left frontocentral region.](image)
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 alpha 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 spectroscopy (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 codons 200 mutation (E200K) and codon 129 methionine homozygosity.

Autopsy revealed enormous brain and cerebellar atrophy. Histo-pathologic examination performed in formalin fixed and paraffin embedded brain tissue revealed strik-
ing neuronal loss. In neocortical areas, disappearance of the
typical laminar structure caused by extensive loss of neu-
rons throughout the gray matter thickness was recorded
(Fig. 4a). Pathologic findings were also evident in the cer-
ebrohum, 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 hyper trophy and proliferation of
astrocytes were observed in all examined structures. Inter-
estingly, the spongiform changes were rare, they disap-
ppeared due to severe structural changes of the neuropil.
Generalized, extensive neuronal loss and severe astrocite-
ric 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 se-
verity and extent of CNS degeneration. The duration of
the disease differed significantly from the average dura-
tion in Slovak CJD E208K patients. 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 sulfare, one can recollect reports analyzing the
effect of amantadine hydrochloride on CJD. Although sev-
eral trials of amantadine in CJD patients proved disap-
pointing for ultimate deterioration and death, some au-
thors report that treatment with amantadine hydrochlo-
ride was followed by prolonged survival. According to

Fig. 4. Histology. (A) Cerebral cortex (HE, X250): severe loss of neurons, the whole grey matter is dominated by hypertrophic astocytes
(arrow); (B) cerebellar cortex (HE, X250): striking changes in the granular layer (severe loss of Purkinje’s cells and proliferated Berg-
mann’s glia) and extremely reduced cells in the granular layer resulted in atypically, pathologically altered structure of the cerebellar cortex;
(C) cerebellar cortex in genetic CJD (FLAVK 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 monoclonal
antibodies in the granular layer. (Eva Mirosa, M.D., Ph.D., Institute of Preventive and Clinical Medicine, Bratislava, Slovak Repub-
lie).
Terezs et al., 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 sulphate 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 generic 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 the correct 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 comput- ed 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 clinical cases, could contribute to better knowledge, easier clinical diagnosis and in perspective to early treatment of the genetic subgroup of CJD.

References
Sažetak

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


Srednje trajanje kliničkog stadija u slovackih bolesnika s genetskom Creutzfeldt-Jakobovom bolesti s mutacijom E200K u genu prionskog proteina (PRNP) iznažajno je kraće u bolesnika homozigotnih za metionin nego u onih heterozigotnih za metionin i valin (3,70±2,00 prema 7,84±7,50 mjeseci). Opoziv se atipičan produljeni tijek (15 mjeseci) Creutzfeldt-Jakobove bolesti komplikiran malignim neurolepšćim sindromom u 48-godišnjeg nositelju mutacije E200K homozigotnog za metionin. Pregresija je dokumentirana komputeriziranom tomografijom, magnetskom rezonancijom, funkcionolal biokemijskom spektroskopijskom magnetskom rezonancijom i elektoencrenofotografijom. Neurohistolohski nalazi pri obdobju potvrđeni su definitivnu dijagnozu Creutzfeldt-Jakobove bolesti i otkrili teško smanjenje cerebralnog i cerebelarnog kortika uz gotovo potpun nestanak neuronnih stanica. Raspravljalo se o mogućem objašnjenju neurolepšćenog trajanja bolesti u slučaju genetske Creutzfeldt-Jakobove bolesti. Naglašava se važnost rane dijagnoze i terapijske intervencije (kad učinkovita terapija bude dostupna), koje će dostatno prehoditi razvoju zapuštenih irreversibleb in degenerativnih promjena središnjega živčanog sustava.

Ključne riječi: Creutzfeldt-Jakobov sindrom – genetika; Prionne bolesti – dijagnoza; Genetika prionne; Srediništii živčani sustav – degeneracija; Prions dijagnoza.