CREUTZFELDT-JAKOB DISEASE: RECENT OBSERVATION AND DISCUSSION OF TWO CLINICAL CASES

GRACI DANIELA*, ALBA GIOVANNI*, BORSSELLINO GASPAR*, MANDRACCHIA RICCARDO*, CUTRÒ MARIO*, TRIGONA ANGELO*, ROSA MARIA GAGLIO*, AVALRELO ROSA*, GURGONE GIACOMO*

*Medicine Department, Operative Unit of Neurology- ASP 1 Agrigento, (Italy) - ° Radiology Department, ASP 1 Agrigento, (Italy).

ABSTRACT

Introduction: Creutzfeldt-Jakob Disease (CJD) is a prion disease that has a wide range of clinical presentations. The diagnosis of CJD is a highly challenging issue, as clinical manifestations should be considered along with electroencephalography (EEG), cerebrospinal fluid examination (CSF), Magnetic Resonance Imaging (MRI) and serum analysis.

Cases presentation: we describe two cases of CJD, come to our observation in the same period. In first patient clinical features suggested the diagnosis of Heidenhain’s dementia, a rare variant of sporadic CJD, occurring in a 71-year-old woman. She succumbed to the disease within 8 weeks of onset of symptoms and diagnosis was pathologically confirmed. Second patient, a 56-year-old housewife, referred with mood disorders and presenting dementia, ataxia, myoclonic jerks, carried point mutation V210l at codon 210 of the Prion Protein (PRNP) gene. In both patients protein 14-3-3 in CSF was detected, EEG showed bilaterally periodic sharp and slow-wave discharges, and MRI findings revealed cortex hyper-intensity (“ribbon-sign”) in DWI and T2W sequences.

Conclusions: Our two cases are interesting because the beginning was atypical, namely with visual disturbance previous for several months the definite clinical picture in one case, and in the other with misleading psychiatric disorders.

Key words: Transmissible Spongiform Encephalopathies, protein 14-3-3, periodic sharp wave complexes, prion protein.

DOI: 10.19193/0393-6384_2016_3_81

Received June 30, 2015; Accepted January 02, 2016

Introduction

Prion diseases, or Transmissible Spongiform Encephalopathies (TSE), are infectious neurodegenerative diseases occurring in humans and animals with an invariably lethal outcome. The aggregation of aberrantly folded prion protein into large amyloid plaques and fibrous structures, associated with neuro-degeneration, are until today the basic mechanisms supposed.

The most common human prion disease is the Creutzfeldt-Jakob Disease (CJD), of which three subtypes are been described: infectious, sporadic, familial. All CJD subtypes have been successfully transmitted to primates by ingestion or inoculation of brain tissue, thus fulfilling one of the main characteristics of TSE diseases.

The transmitted or infectious group consists of “Kuru”, iatrogenic CJD, and new variant CJD (described in the United Kingdom since 1996 and more likely related with bovine spongiform encephalopathy in cattle or BSE). Approximately 85% of all human prion diseases are actually sporadic forms of CJD, with a reported incidences of 0.4-1.8 cases per million people per year. There is not association for sporadic CJD with a mutant allele of PRNP gene, nor there is any epidemiological evidence for exposure to a TSE agent through
contact with people or animals infected\(^{(1)}\). Nevertheless, heterozygosity (Met/Val) at PRNP codon 129 appears to be associated with a lower risk and/or prolonged incubation time\(^{(5)}\).

Familial TSE are associated with an autosomal dominant PRNP gene alteration and accounts for 10%-20% of all cases in humans. Familial TSE includes familial CJD, Gerstmann-Sträussler-Scheinker (GSS) syndrome, and fatal familial insomnia (FFI). In addition to point mutations in the PRNP gene, insertions in the OR region of the PRNP gene have been associated with this degenerative brain diseases\(^{(1)}\).

In this article we report two cases of CJD, both admitted in the same period, to emphasize inconstant clinical manifestation of the disease and diagnostic difficulties it cause. The first patient is an autopsy proven sporadic CJD, initially characterized by visual cortical symptoms rapidly progressive, in the setting of a relatively normal ophthalmologic examination. Genetic analysis showed no germ-line mutations on chromosome 20 at PRNP gene, and was diagnosed as Heidenhain’s variant, a rare presentation of sporadic CJD.

Second patient likely falls under the category of familial CJD because genetic analysis revealed a single mutation of the PRNP gene, although a clear familial history is not present. Early complaints were prevalent psychiatric disorders and behavioral changes, but the clinical picture was suggestive of neurological background from the beginning.

Cases presentation

**Case 1**

A 71-year-old right handed woman presented progressive loss of vision over the course of few months. An ophthalmologist evaluated her and the visual disturbance was blamed on her initial eye cataract. In the same period her daughter noticed forgetfulness, gait uncertain, impaired attention and orientation, and some difficulty in word finding.

On examination, she was alert but not oriented for space. She performed simple calculations, and comprehended verbal commands, and demonstrated normal praxis. She was fluent, and she could repeat normally. Visuo-spatial testing revealed difficulty copying a cube and to drew a clock.

Patient described her visual disturbances as difficulty in the depth perception and objects shape distortion. Further, she complained of insomnia and anxiety. Confrontation visual fields examination revealed a left superior quadrant scotoma and a partial right superior quadrant scotoma. Pupils were reactive; ocular motility and fundus examinations were normal. Deep tendon reflexes were symmetrical and the plantar response was flexor. There were not increased tone or pathological movements, strength and sensation were normal. Coordination testing showed no dysmetria in both the upper and lower extremity, and axial ataxia.

An extensive workup, including complete blood count, coagulation, serum chemistry, autoimmunity, thyroid profile, was normal. Two EEG examinations demonstrated a slow background activity with periodic sharp wave complexes (PSWC). Although PSWC were no repeating typically every 0.5-1 sec, EEG was considered suggestive for suspected prion encephalopathy. Therefore a cerebrospinal fluid analysis was performed, which excluded any inflammatory process or infection but confirmed the presence of the 14-3-3 protein. Further, a peripheral blood sample was collected and sent for detection of mutations of the gene PRNP. No DNA mutation was established and the patient was found to carry the Met/Met allelo-type at codon 129.

A cerebral magnetic resonance imaging (MRI) was performed two weeks before entering our hospital, and a new control performed during recovery confirmed the same picture: presence in restricted diffusion, FLAIR and T2 weighted imaging, of hyper-intense “gyriform” band on right temporal and occipital cortex (figure 1), or “cortical ribbon sign”. No increased signal involving striatum and thalamus was noted.

![Figure 1: Magnetic Resonance Imaging coronal (A) and axial (B) FLAIR sequence were highly suggestive for diagnosis, revealing the “cortical ribbon sign” in the right temporo-occipital cortex (white arrow). Same intensity abnormality is noted, more attenuated, in the parietal region of the left hemisphere. Basal ganglia and thalamus are spared.](image-url)
Based on clinical and radiological findings, and a positive 14-3-3 protein test in CSF, patient was discharged as probable sporadic CJD. For leading symptoms of cortical visual defects and the most pronounced radiological changes in the temporal and occipital lobes, the case was classified as “Heidenhain’s variant”. First described in 1929 by Heidhenhain, this entity is a rare dementia rapidly progressing in which prominent visual disturbances constitute the initial symptoms. As reported in literature, neuronal loss, gliosis and vacuolization are most prominent in the occipital lobes.6)

The patient died two months after with unremitting progression of cortical blindness, mental deterioration and a-kinetic mutism. The patient’s family gave informed consent for post-mortem studies. At autopsy, the brain was grossly unremarkable, except for mild atherosclerosis in the circle of Willis. Microscopic examination revealed spongiform changes and gliosis throughout the cerebral cortex, basal ganglia, thalamus, and cerebellum. Immunohistochemical analysis of cerebral tissue showed positive staining of prion protein deposits, and Western blot analysis demonstrated the presence of protease resistant prion protein type1. Therefore patient was classified as sporadic CJD type MM1.

Case 2

A 56-year-old previously health woman was hospitalized with imbalance and gait disturbance, lasting for one month. According to her family, she had suffered from mild personality disturbance and depression attributed to death of a daughter several months before, unsuccessfully treated with antidepressants. Her medical history was unremarkable except for gallstones.

On examination the patient was disoriented in both time and space; recent memory and attention were decreased and she responded slowly with speech difficulty. Increased tone in the arms was present, with rigidity and cog-wheeling. Coordination testing revealed truncal and appendicular ataxia, mild dysmetria with nystagmus, and unsteady standing with her feet together. Deep tendon reflexes were increased in both the upper and lower extremities bilaterally. A few days later she developed spontaneous and startle myoclonic jerks of the four limbs, as well as agitation and psychotic changes.

An EEG performed as part of the routine evaluation, disclosed periodic tri-phasic wave complexes of moderate amplitude, distributed in both hemispheres. A MRI was performed which revealed on DW images (figure 2) bilateral increased signal in the striatum involving the putamen and the caudate nucleus, and a fine hyper-intense band on left parietal and occipital cortex.

Figure 2: Radiological features in second patient. Magnetic Resonance Imaging on T2 FLAIR sequences shows (A) bilateral and symmetrical abnormal signal in the putamina and caudate nuclei, without involvement of the thalami, and DWI sequence shows (B) the “cortical ribbon sign” (white arrow) in the parieto-occipital left cortex.

FLAIR images confirmed the presence of increased signal in the basal ganglia and in the periventricular white matter.

There was no evidence of autoimmune or rheumatic diseases: anti-thyroid peroxidase (anti-TPO), rheumatoid factor, antineutrophil cytoplasmic antibody (ANCA), antinuclear antibody (ANA), anti-Ro, anti-La, anti Smith antibodies (anti-SM), anti-DNA double helix, negative; cancer: chest, abdomen and pelvis Computed Tomography normal, tests for alpha fetoprotein, CA 125, CA-15-3, TPA, and protein serum electrophoresis all normal; endocrine-metabolic conditions: normal Thyroid Stimulating Hormone (TSH), Free Thyroxine (FT4), parathyroid hormone (PTH), vitamin B12, folic acid, iron, ferritin, transferrin, electrolytes, homocysteine; neither evidence of renal and liver function or vascular abnormalities.

After these observations, associated to the clinical picture of sub-acute cognitive decline, myoclonus, extra-pyramidal and cerebellar signs, we requested the 14-3-3 protein be tested in CSF, in which was effectively present. Genetic analysis revealed a point mutation at codon 210 of the PRNP gene on chromosome 20, causing the Val210Ile protein mutation.
Therefore, a diagnosis of probable familial CJD was made. During her hospital stay the illness progressed rapidly over the next days with outstanding cognitive impairment, serious ataxia with impossibility to gait and standing, dysphagia, incontinence of urine, progressive immobility leading to dependency, and mutism. She remained in the same state for eight weeks, and died after six weeks of discharge. Autopsy was refused.

Discussion

Clinical presentations of CJD are variable, depending on the stage of disease. A majority of patients demonstrate, as our observed cases, rapidly progressing mental decline, ataxia, and sometimes visual disturbances, within a few weeks to several months. Of course the relatively recent signaled new variant of CJD(7) perhaps related to BSE, has increased the attention on patients presenting with sudden onset of dementia. Moreover, CJD is an extremely challenging disease to diagnose especially in its very early stage. The clinical symptoms are relatively nonspecific, and overlap with other more frequent dementia disorders. Despite efforts to establish definite criteria, a definitive diagnosis of CJD still requires a brain post-mortem autopsy and/or the presence of pathological prion protein(8).

As observed in our cases, the EEG pattern of PSWC on a disorganized background activity associated with a progressive dementia can suggest the diagnosis of sporadic CJD. However, the characteristic EEG findings are seen in only 66% of patients, and have a reported specificity of 74%(9).

In the case 1 EEG was supportive for diagnosis considering the atypical initial clinical presentation with visual disturbances. Without a doubt, Heidenhain’s variant of sporadic CJD is even more challenging to diagnose during initial phase in which there are only visual symptoms. Visual disturbances include decreased visual acuity, peripheral visual field defects, tunnel vision, hemianopia, metamorphopsia, achromatopsia, palinopsia, optical hallucinations, cortical blindness, and Anton syndrome(10). These patients are commonly seen by ophthalmologists first, and visual loss is sometimes attributed to a preexisting ocular condition, such as cataract, or a somatoform disorder(11). Almost all cases of Heidenhain’s variant are homozygous for methionine at codon 129 of the PRNP gene, such as our patient, but the significance of this association remains unclear(12).

Detection of 14-3-3 protein in CSF, a signal of neuronal loss, is analogously considered supportive to diagnosis, according the WHO diagnostic criteria(13). The presence of this protein in the CSF has reported to have higher sensitivity and specificity (94% and 84%) than using only the detection of PSWC in EEG, and improves the sensitivity of clinical diagnosis in addition to EEG(14). EEG has been shown to be positive in only a subset of sporadic CJD patients, and typically PSWC are detected late in the disease and the median time to positive EEG is around 12 weeks(15).

Protein 14-3-3 was found in CSF of patient 1, considered a sporadic CJD, and in patient 2 considered a familial CJD in relation to point mutation of the gene PRNP, even if an investigation about family history resulted negative. A number of CSF biomarkers have been reported in CJD, including 14-3-3, tau, S100b, neuron-specific enolase, phosphorylated tau and abeta, but the majority of available data are related to 14-3-3 and tau proteins(16). Both these biomarkers support clinical diagnosis in sporadic CJD, although low levels in CSF are reported in some atypical CJD variant(17). Biological variables such as long disease duration, young age at onset, type 2 pathogenic prion protein and heterozygosity at codon 129 genotype of the PRNP gene are all associated with low biomarker levels(17).

MRI changes detected in CJD patients are supposed correlated with spongiform changes seen at autopsy(18). Initial reports described a pattern of hyper-intensity in the basal ganglia on T2 weighted imaging(19). After the introduction of FLAIR and DWI sequences, cortical signal changes are become an important radiological feature for CJD diagnosis. Pattern of isolated cortical involvement consists of high signal intensity in the insula, in the cingulate and superior frontal gyri, and in the cortical areas near the midline. In patients with dementia who have the described cortical changes, the suspicion of sporadic CJD should be raised even without involvement of the structures of the deep grey matter(20). In a study two major lesion patterns were identified by DWI and FLAIR sequences: cortex and basal ganglia involvement and isolated cortex involvement(21).

In the latter case, the cortex involvement was widespread (at least 3 regions affected in 89% on DWI) and usually included the frontal and parietal lobes (78%). The isolated cortical hyper-intensities, seen in one third of the patients, should be recognized as a frequently occurring pattern on the MR.
imaging, which might be characteristic of atypical disease variants with a slowly progressive course\(^{26}\).

Then an isolated cortex involvement on DWI and FLAIR sequences should lead to suggestion of sporadic CJD, even if the disease course is only slowly progressive\(^{21}\). Furthermore, no significant differences between these two patterns were observed concerning EEG, CSF findings and codon 129 genotype distributions.

Isolated cortical lesions were detected in case 1, with preferential involvement of the posterior cortex that provides a clinical-anatomical correlation with patient’s visual disturbances. However, the clinical course was very fast with disease duration short.

In case 2, DWI and FLAIR sequences showed high signal intensity in cortex and symmetrically in basal ganglia, well correlating with a rapid disease course. Indeed, basal ganglia abnormalities on T2WI are reported to correlate with rapidly progressive dementia and short disease duration, whereas in patients lacking of this finding the onset of dementia is supposed delayed and the disease course prolonged\(^{22}\). However, single disease variants determined by codon 129 genotype of the PRNP gene and the molecular sub-type of prion protein may be supposed to influence both disease duration and basal ganglia lesions on MR imaging\(^{23,24}\). DWI has pointed out its diagnostic value in respect to conventional MRI because can reveal increased signal in basal ganglia as well as in cortical regions in the early stages of the disease\(^{25}\). Further, DWI showed a sensitivity and specificity of 100% in patients with autopsy-proven CJD, and clearly superior in the diagnosis of cortical changes\(^{26}\), probably dependent by spongiform degeneration which contribute to alter the molecular motion of water\(^{27}\).

As a result of recent data indicating high sensitivity and specificity of DWI and FLAIR, diagnostic criteria for pre-mortem diagnosis of sporadic CJD include also MRI findings. MRI is valuable in the assessment of suspected CJD patients, both excluding other disorders but also demonstrating features considered typical of human prion disease. A multicenter international study\(^{28}\) has provided a rationale for utilizing MRI findings, even early in the illness and to overcome the limitations of EEG and CSF analysis. “Optimum” in the diagnostic accuracy is obtained when either at least two cortical regions (temporal, parietal or occipital) or basal ganglia display a high signal in FLAIR or DW imaging.

In conclusion both our cases were diagnosed pre-mortem with probable CJD. Disease was histopathologically confirmed in one of them, diagnosed as Heidenhain’s variant. This case is instructive because isolated visual disturbances preceding obvious mental deterioration may be misdiagnosed with non-neurological disorders. Second case instead is remarkable for the only psychiatric disturbances at beginning. Even if psychiatric symptoms are present in the early stage of CJD\(^{29}\), a misleading fact was the death of patient’s daughter previous to mood and behavior disturbance onset. In both cases EEG was suggestive of the diagnosis, but protein 14-3-3 positive in CSF in conjunction with quickly progressing dementia and MR imaging were essentials for a correct diagnosis.

References


Corresponding author
DR GRACI DANIELA
Ospedale S. Giovanni di Dio
c/da Consolida
92100 Agrigento
(Italy)