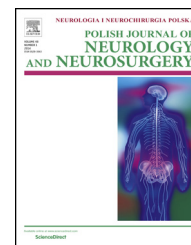


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## Case report

# The Heidenhain variant of Creutzfeldt–Jakob disease and concomitant tau pathology: A case report

Edvard Ehler<sup>a,\*</sup>, Michael Pipka<sup>a</sup>, Alena Meleková<sup>a</sup>, Petra Mandysová<sup>b,a</sup>,  
Silvie Johanidesová<sup>c</sup>, Radoslav Matěj<sup>e,f</sup>, Robert Rusina<sup>c,d</sup>

<sup>a</sup>Department of Neurology, Regional Hospital Pardubice, Czech Republic

<sup>b</sup>Faculty of Health Studies, University of Pardubice, Pardubice, Czech Republic

<sup>c</sup>Department of Neurology and Centre of Clinical Neuroscience, First Faculty of Medicine, Charles University in Prague and the General University Hospital, Prague, Czech Republic

<sup>d</sup>Department of Neurology, Thomayer Hospital, Prague, Czech Republic

<sup>e</sup>Department of Pathology and Molecular Medicine, Thomayer Hospital, Prague, Czech Republic

<sup>f</sup>Department of Pathology, First Faculty of Medicine, Charles University in Prague and the General University Hospital, Prague, Czech Republic

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## ABSTRACT

The Heidenhain form of Creutzfeldt–Jakob disease (CJD) is a rare CJD variant with predominantly visual symptoms in the early stages. Clinical manifestations of metamorphopsia, hemianopia and Balint's syndrome correlate with the involvement of the posterior cortical regions. A 71-year old healthy and very active man was admitted because of impaired visual acuity, hemianopia, and gait disturbance progressing over one week. MRI found typical cortical hyperintensities in the occipital regions while rhythm slowing and sharp waves were seen in the occipital regions on EEG. Protein 14-3-3 was detected in the cerebrospinal fluid. Postmortem neuropathology revealed typical histopathological changes consistent with CJD. Moreover, we found deposits of phosphorylated tau protein in the limbic regions that met the criteria for primary age-related tauopathy (PART); representing an additional and interesting finding in our case.

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## 1. Introduction

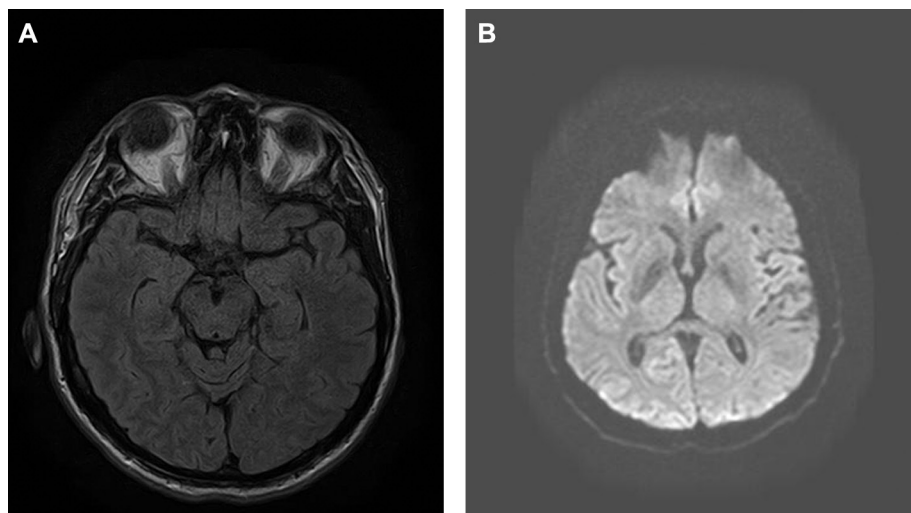
Creutzfeldt–Jakob disease (CJD), the most common human prion disease, is a rare degenerative and invariably fatal brain disorder. Currently, four forms of the disease have been

identified: sporadic, familial, accidentally transmitted (iatrogenic), and variant CJD [1]. The Heidenhain variant describes any case of CJD, although it is mainly associated with the sporadic form, in which visual symptoms are significant in the early stages [2]. This variant should be considered part of the differential diagnosis involving patients presenting with

\* Corresponding author at: Department of Neurology, Regional Hospital and Faculty of Health Studies, University of Pardubice, 44 Kyjevská, 532 03 Pardubice, Czech Republic. Tel.: +420 466014701.

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**Fig. 1 – MRI findings: absence of noticeable hippocampal and temporal atrophy in FLAIR sequences (A); visible occipital and frontal cortical hyperintensities with a normal signal in the basal ganglia in diffusion-weighted imaging (DWI) (B).**

confusion and visual hallucinations of unclear etiology. The Heidenhain variant can be definitively diagnosed using clinical history, EEG, brain MRI, presence of protein 14-3-3, and postmortem brain pathological findings [3].

## 2. Case report

A 71-year old man, previously healthy and very active, was admitted to the neurological department due to visual disturbance, eye field defects, and gait difficulties progressing over one week.

The patient presented having to use two trekking poles to stabilize his gait, which was subject to lateropulsion to the right side. On admission, a perimeter defect was found in the left lower quadrant along with paleocerebellar and left-sided neocerebellar symptoms and binocular vertical diplopia, which worsened while looking to the left. At this time, the laboratory analysis and brain MRI were unremarkable. After 10 days, the patient was discharged with only a mild walking imbalance and left sided hemianopia. Since the patient had recently been diagnosed with hypertension, we attributed his clinical manifestations to probable cerebrovascular circulation impairment.

After one month, the patient was readmitted with progressive and severe visual disturbances and instability (walking was only possible with a walker). The patient described metamorphopsia (visual foggy day combined with visual snow, seeing two oblique pictures as being parallel, distortion of pictures, and mirroring). We observed significant psychomotor slowing, apathy, decreased verbal fluency, significant perseveration of motor tasks and words, and grasping. Left-sided hemianopia with neglect, visual and color agnosia, bilateral direct optic ataxia, simultagnosia, and dressing apraxia were also present.

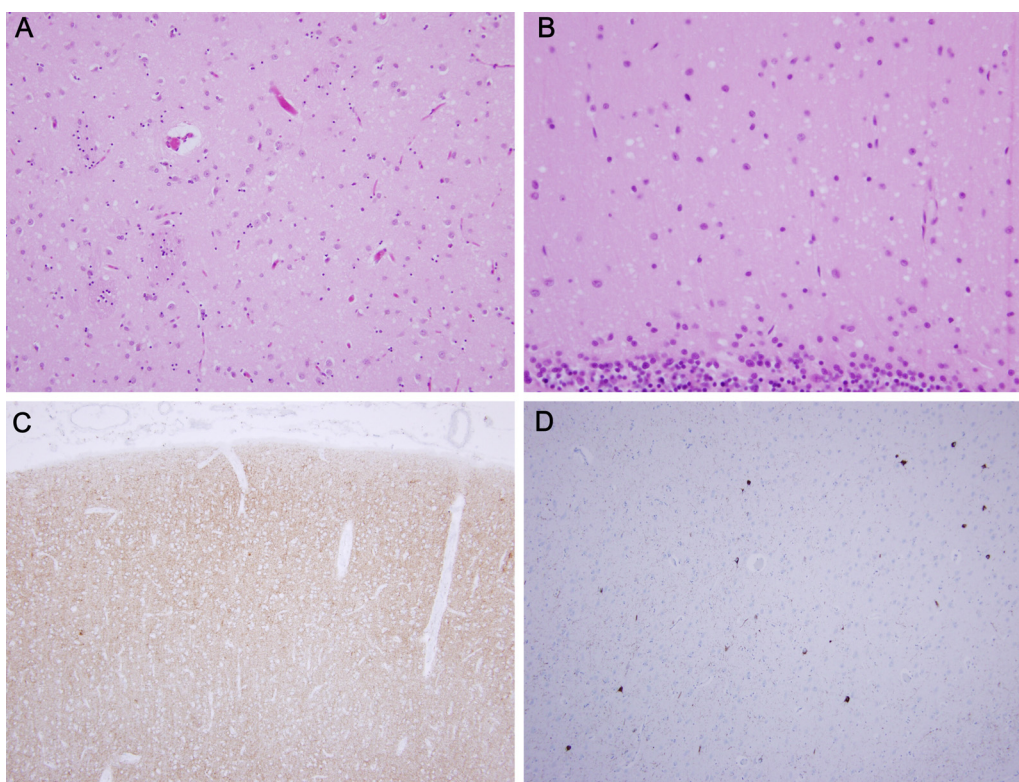
MRI DWI (diffusion-weighted imaging) showed cortical hypersignals in the parietal and occipital lobes (mainly on the right side) (Fig. 1). EEG showed temporal and occipital sharp

waves with a tendency to generalize over a slowed background. Ophthalmological examination revealed worsening of the left-sided hemianopia with progression to the right side and to central retinal regions. Cerebrospinal fluid showed borderline hyperproteinorhachia (0.7 g/L) with positive protein 14-3-3, and very high levels of tau protein (>1200 pg/mL); cytology was normal and inflammatory and paraneoplastic parameters (onconeural antibodies, neurotropic viruses, panel of limbic encephalitides) were negative.

During the following weeks, the patient's mobility progressively worsened, resulting in mixed hypertonus that was mainly limited to the upper extremities with mainly left sided rigidity, hyperreflexia, startle myoclonus, muscle weakness, and ataxia. Visual hallucinations were progressive (structured images of persons and animals produced significant emotional affects). Cognitive and motor impairment rapidly led to severe dementia and increased difficulty in walking, respectively.

The patient was finally bedridden as a result of myoclonus, extrapyramidal rigidity, and akinetic mutism. He died from bronchopneumonia about 6 months after the onset of symptoms.

Neuropathological, immunohistochemical, neuro-immunological, and molecular genetic examinations definitively confirmed the final diagnosis: the patient met the criteria for sporadic Creutzfeldt-Jakob disease, MM1 subtype. Spongiform dystrophy and numeric atrophy of neuronal structures accompanied by isomorph reactive astrogliosis was apparent in cortical and subcortical structures (Fig. 2A and B). Immunohistochemistry, which was positive for two monoclonal antibodies against the prion protein, was characterized by diffuse synaptic positivity. Nevertheless, accented perivacuolar, so-called "patchy" positivity was also seen locally. More prominent impairment of the occipital cortex, including the optic region, offered a morphological background for a clinical diagnosis of Heidenhain variant of CJD (Fig. 2C). As an accessory neuropathological finding, deposits of the hyperphosphorylated form of tau protein were found in the



**Fig. 2 – Neuropathology: spongiform encephalopathy of different severity seen in the striatum (A) and cerebellum (B) in standard HE staining (original magnification 100× and 200×). Immunohistochemical positivity of pathological deposits of prion protein in the primary visual cortex (C) using monoclonal anti-PrP antibody clone 6H4 (original magnification 200×) and pathological deposits of hyperphosphorylated tau protein in the hippocampus (D) using monoclonal anti-tau antibody clone AT8 (original magnification 100×).**

hippocampal formation, which meets the criteria for primary age related tauopathy (PART) (Fig. 2D).

### 3. Discussion

Our patient initially presented with visual disturbances and gait instability that rapidly progressed to dementia with rigidity, spasticity, and myoclonus. Our neuropathological examination confirmed sporadic Creutzfeldt–Jakob disease. Clinical manifestations of metamorphopsia, hemianopia, and Balint's syndrome (visual ataxia, simultagnosia, and gaze apraxia) correlated with MRI and neuropathological findings of significant posterior cortical involvement, which was highly suggestive of the Heidenhain variant of CJD. This in turn explained the early deposits of prions in the occipital cortex. Moreover, concomitant hyperphosphorylated tau deposits, mainly in hippocampal areas, which met the neuropathological criteria for primary age-related tauopathy (PART), were an interesting accessory finding.

The Heidenhain variant mainly affects the occipital lobe, producing visual disturbances as well as decreases in visual acuity, metamorphopsia, dyschromatopsia, visual agnosia, homonymous hemianopia, palinopsia, or micropsia, and even cortical blindness [2].

The cognitive profile in CJD is non-specific, with a mixture of cortical and subcortical features. In a recent study of 40 patients with CJD (confirmed post mortem), early manifestations involved the frontal and parietal lobes [4]. Executive dysfunction and speech expression were the first to be affected, followed by parietal lobe impairment (visuospatial impairment and apraxia); semantic memory and processing were relatively preserved. In our patient, early visual manifestations were consistent with severe neuronal cell loss in the posterior areas of the brain, which was confirmed on post mortem (Fig. 2C). With disease progression, severe frontal lobe signs developed, however, memory functions were less affected, in correlation with absent signal increase or atrophy in the mesiotemporal cortex on MRI (Fig. 1A).

The MRI is a valuable tool since it identifies features that are highly specific for CJD. According to a multicenter collaboration for amending clinical diagnostic criteria, MRI findings of either two cortical regions or both the caudate nucleus and putamen on DWI or FLAIR had high sensitivity and specificity in diagnosing sporadic CJD. In the Heidenhain variant, DWI and FLAIR can show prominent cortical hyperintensities in the occipital lobes but not in the basal ganglia [3]. In our patient, similar findings were present (Fig. 1B).

In a recent study [1], only 5% of neuropathologically confirmed CJD cases were identified as the Heidenhain variant.

Mostly commonly, as with our patient, this was linked to the MM1 subgroup.

The pathological accumulation of hyperphosphorylated tau protein in neurons and astrocytes is common in the aging brain. Recently, these conditions have been characterized as primary age-related tauopathy (PART) and, more recently, aging-related tau astroglialopathy (ARTAG) [5]. Despite many neuropathologically based postmortem studies, there is still little evidence regarding clinical correlates of either neuronal or astroglial age-related tau pathology. Moreover, various forms of tau pathology may coexist in the same brain affected by other neurodegenerations and might reflect different pathogenic processes; Kovacs recently described the presence of PART in 69.3% of neuropathologically proven CJD cases [6].

In our patient, however, the clinical relevance of hyperphosphorylated tau protein deposits remains uncertain, at least in the context of rapidly progressive dementia associated with CJD.

#### 4. Conclusion

The Heidenhain variant of Creutzfeldt–Jakob disease is a very rare subtype of a rare disorder; nonetheless, it should be considered in cases with prominent visual disturbances. All atypical cases of neurodegenerative disorders can be verified using systematic and standardized neuropathological investigations.

#### Conflict of interest

None declared.

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#### Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

#### Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.pjnns.2017.01.011](https://doi.org/10.1016/j.pjnns.2017.01.011).

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