Revisiting the Heidenhain Variant of Creutzfeldt-Jakob Disease: Evidence for Prion Type Variability Influencing Clinical Course and Laboratory Findings

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Abstract. The Heidenhain variant defines a peculiar clinical presentation of sporadic Creutzfeldt-Jakob disease (sCJD) characterized by isolated visual disturbances at disease onset and reflecting the early targeting of prions to the occipital cortex. Molecular and histopathological typing, thus far performed in 23 cases, has linked the Heidenhain variant to the MM1 sCJD type. To contribute a comprehensive characterization of cases with the Heidenhain variant, we reviewed a series of 370 definite sCJD cases. Eighteen patients (4.9%) fulfilled the selection criteria. Fourteen of them belonging to sCJD types MM1 or MM1+2C had a short duration of isolated visual symptoms and overall clinical disease, a high prevalence of periodic sharp-wave complexes in EEG, and a marked increase of cerebrospinal fluid proteins t-tau and 14-3-3 levels. In contrast, three cases of the MM 2C or MM 2+1C types showed a longer duration of isolated visual symptoms and overall clinical disease, non-specific EEG findings, and cerebrospinal fluid concentration below threshold for the diagnosis of “probable” CJD of both 14-3-3 and t-tau. However, a brain DWI-MRI disclosed an occipital cortical hyperintensity in the majority of examined cases of both groups. While confirming the strong linkage with the methionine genotype at the polymorphic codon 129 of the prion protein gene, our results definitely establish that the Heidenhain variant can also be associated with the MM 2C sCJD type in addition to the more common MM1 type. Likewise, our results highlight the significant differences in clinical evolution and laboratory findings between cases according to the dominant PrPSc type (type 1 versus type 2).

Keywords: Dementia, molecular typing, neurodegenerative diseases, occipital cortex, prion diseases, prion protein

INTRODUCTION

Creutzfeldt-Jakob disease (CJD) belongs to the human transmissible spongiform encephalopathies or prion diseases, a group of neurodegenerative disorders characterized by tissue deposition of a misfolded form
of the cellular prion protein (PrPSc). Despite their relative rarity, prion diseases show a wide spectrum of clinical and pathological phenotypes. Accordingly, the clinical presentation of sporadic CJD (sCJD) includes a wide range of neurological signs of cortical, subcortical, or cerebellar origin, either isolated or in various combinations [1–4]. Different strains of prions, likely enciphered by alternative conformations of PrPSc, are considered the main cause of this phenotypic diversity [5]. In addition, the host variability in the prion protein gene and two PrPSc profiles (type polymorphic codon 129 (methionine, M or valine, V) distinctive clinic-pathological features largely correlate at the molecular level with the genotype at the polymorphic codon 129 (methionine, M or valine, V) in the prion protein gene and two PrPSc profiles (type 1 and type 2) distinguishable by the size of the protease K-resistant core of the protein (21 and 19 kDa, respectively). More precisely, with only minor exceptions, each phenotypic variant or “type” of sCJD results from a specific codon 129 genotype/PrPSc type combination (e.g., MM1, VV1, MM2, VV2, etc.). Most significantly, two types with distinctive histopathological features in the cerebral cortex and in the thalamus have been linked to the rare MM2 molecular combination and designated accordingly (MM2-cortical or MM 2C and MM2-thalamic or MM 2T). Finally, mixed types, comprising clinical-pathological features of two pure types, especially involving the co-existence of MM1 and MM 2C, have also been recognized [9, 10]. One of the most peculiar clinical presentations of CJD occurs in the so-called Heidenhain variant, which is characterized by isolated visual symptoms including poor vision, disturbed perception of colors or structures, and optical distortions as well as hallucinations without any ocular disease. The fact that visual symptoms may persist in isolation for weeks without cognitive decline or motor signs and sometimes causing diagnostic difficulty makes the Heidenhain variant of particular clinical interest. Indeed, affected patients sometimes present to ophthalmologists and are subjected to needless ocular interventions with risks of onward transmission [11]. Originally, Heidenhain ascribed to CJD the severe histopathological changes to include severe neuronal loss with glial reaction or status spongiosus found in the occipital cortex of two patients with a pre-senile form of rapidly progressive dementia presenting with prominent visual disturbances despite normal disc and fundus examination [12]. Since 1954, similar cases have been described, most often as small case series [11, 13–18] or individual case reports [19–37] and referred to as the Heidenhain variant of CJD [38]. To date, molecular and histopathological analyses have been performed in 23 cases with this clinical presentation, and the large majority (22 out of 23) belonged to the MM-MV1 sCJD type [11, 13, 16, 34, 35]. In a single case, however, the Heidenhain variant has also been linked to the MM 2C type, which has widened the molecular basis and histotype classification of this peculiar clinical phenotype [29]. To contribute a comprehensive clinical, histopathological, and molecular characterization of cases presenting with the Heidenhain variant, we here provide the results of a review of a series of 370 definite sCJD cases, including the detailed description of three peculiar cases of the Heidenhain variant belonging to the rare MM 2C and MM 2C+1 sCJD types.

MATERIAL AND METHODS

This study has been conducted with the highest respect for each participant according to the Declaration of Helsinki [39].

Patients

Three hundred and seventy cases with a definite diagnosis of sCJD were selected based on available medical records including a detailed description of the clinical evolution of symptoms and signs from onset. The case series included all sCJD phenotypic variants described to date in a relative proportion fairly representing their current reported incidence in the Caucasian population [3, 9, 40]. Three hundred and fifteen subjects were Italian patients referred to our laboratory for diagnosis from 2003 to 2013, while the remaining 55 were part of a previously published case series [9]. All the Italian cases were also part of the National CJD Registry in Rome, which collects data of all suspected CJD patients aiming to ascertain all cases with definite or probable disease in Italy. The presence of clinically suspected patients is notified to the reference center by their treating physicians, mainly neurologists. Most suspected patients are also examined by a neurologist of the surveillance unit at the reporting hospital, and copies of patients’ medical records are collected. For case selection, we combined the information recorded in the two available databases (Bologna and Rome) to search for cases presenting visual symptoms at onset. Subsequently, only patients suffering from isolated, non-transient, visual symptoms of cortical/subcortical origin at disease onset were
diagnosed with the Heidenhain variant. Visual symptoms included at least one of the following: blurred vision, visual field restriction, vision loss up to cortical blindness, disturbed perception of colors or structures, optical hallucinations, and visual agnosia. Duration of visual symptoms was calculated based on the timing of appearance of associated neurological symptoms, as reported in the available medical records. Results of electroencephalographic (EEG) recordings were classified into three categories: periodic sharp-wave complexes (PSWCs), paroxysmal discharges (PDs), and diffuse non-specific slowing. When available, cerebrospinal fluid (CSF) biomarker assays included the measurement of total tau (t-tau) protein concentration by quantitative Elisa (INNOTEST® hTAU Ag, Innogenetics) and the semiquantitative detection of protein 14-3-3 by western blotting, performed as previously described [41]. In particular, two CSF controls (with a weak or a strong 14-3-3 signal, respectively) were loaded in duplicate in every gel together with the CSF samples to be analyzed. The immunoreactivity signals were rated as negative, ambiguous, or positive on the basis of optical densitometric (OD) comparison with the weakly positive control as follows: the 14-3-3 signal was classified as negative when the 14-3-3 band OD was lower than the control; ambiguous (i.e., weakly positive) when the 14-3-3 OD was up to two times higher than the control, and positive when it was at least two times higher than the control. The latter decision point was chosen as optimal after an analysis of the test predictive value at different densitometry value ranges in a large series (>1000) of CSF samples from subjects with suspected CJD (unpublished data). Finally, cerebral magnetic resonance imaging (MRI) studies were reviewed when available. According to currently accepted clinical diagnostic criteria for sCJD [42], high signal abnormalities in caudate nucleus and putamen or at least two cortical regions (temporal-parietal-occipital) either in diffusion-weighted imaging (DWI) or fluid attenuated inversion recovery (FLAIR) sequences was considered “typical,” while non-specific findings included signal abnormalities suggesting gliosis, microvascular changes, or atrophy.

**Molecular studies and CJD histotype classification**

To exclude cases carrying mutations and to determine the genotype of PRNP polymorphic codon 129, we conducted a molecular analysis in all cases as previously described [40]. We performed PrPSc typing and sCJD histotype classification according to established methodology and consensus criteria [8, 43]. Specifically, we analyzed at least four brain regions (middle temporal gyrus, parietal cortex, occipital cortex, and thalamus) for PrPSc typing and at least eight (middle frontal gyrus, middle temporal gyrus, parietal cortex, occipital cortex, basal ganglia, hippocampus, thalamus, and cerebellum) for histotyping.

**RESULTS**

Among the 370 cases examined, 70 (18.9%) had visual symptoms at onset, but in many case, they were not isolated. Therefore, only 18 (4.9%) cases fulfilled the criteria for the Heidenhain variant (Tables 1 and 2). Molecular and histopathological analyses demonstrated that the cases belonged to four sCJD types: MM1 (10 cases), MM 1+2C (5 cases), MM 2+1C (2 cases), and MM 2C (1 case).

**MM1**

Mean age at the onset was 70.7 ± 7.8 years (range 57–80), mean duration of isolated visual symptoms was 1.6 ± 0.5 months (range 1-2), and mean total disease duration was 4.2 ± 2.1 months (range 2.5–10). According to frequency, visual symptoms included the following: disturbed perception of structures and/or colors (i.e., metamorphopsia, micropsia, dyschromatopsia) (80%), visual field restriction (60%), loss of vision (40%), blurred vision (30%), optical hallucinations, and optical anosognosia (20%). EEG examination revealed PSWCs in eight patients (80%), whereas PDs or a diffuse non-specific slowing were observed in one case each (10%). Fluid attenuated inversion recovery (FLAIR) and DWI brain MRI sequences were performed in four patients. They showed a typical (parietal and occipital, and/or basal ganglia) hyperintensity on FLAIR and/or DWI sequences in three (50%), a hyperintensity confined to the left parietal lobe in one, and were unremarkable in the other one. CSF 14-3-3 protein was positive, and t-tau markedly elevated (range 2335–2522 pg/ml) in all patients analyzed (five and two, respectively). Histopathological examination and PrPSc typing revealed the typical features of sCJD MM1 in all cases [44].

**MM1+2C**

Mean age at the onset of symptoms was 66.6 ± 9.4 years (range 54–80), mean duration of isolated visual symptoms was 1.5 ± 0.5 months (range 1–2.5), and
Table 1
Clinical features of patients with the Heidenhain variant of sCJD

| N° | Gender | Age  | Visual symptoms (VS) | VS duration (mo) | Other symptoms | Disease duration (mo) |
|----|--------|------|----------------------|------------------|----------------|----------------------|
| 1  | F      | 54   | Visual field restriction, loss of vision, disturbed perception of colors or objects, hallucinations | 2.5              | Delirium, confusion, disorientation, pyramidal signs, akinetic mutism | 5                     |
| 2  | M      | 63   | Blurred vision, visual field restriction | 2                | Aphasia, ataxic gait, stiff reflexes, myoclonus | 4                     |
| 3  | M      | 67   | Blurred vision, visual field restriction, vision loss up to cortical blindness | 1.5              | Cognitive disturbances, abnormal behavior, myoclonus, tremor, pyramidal signs, akinetic mutism | 5                     |
| 4  | M      | 80   | Blurred vision, disturbed perception of colors or structures, hallucinations | 1                | Ataxia, disorientation | 4                     |
| 5  | M      | 69   | Blurred vision, vision loss | 1                | Dysthria, myoclonus, cognitive and gait disturbances | 2.5                   |
| 6  | F      | 70   | Blurred vision, vision loss up to cortical blindness, disturbed perception of colors or structures | 2                | Ataxia, cognitive decline, myoclonus, akinetic mutism (several months with parenteral nutrition in vegetative state) | 10                    |
| 7  | F      | 80   | Disturbed perception of colors or objects, optical anosognosia | 1.5              | Cognitive decline, cerebellar and pyramidal signs, seizures, myoclonus, akinetic mutism | 5                     |
| 8  | M      | 78   | Distorted perception of structures, optical hallucinations | 1.5              | Ataxia, dysarthria, apraxia, involuntary movements, ataxia | 3.5                   |
| 9  | M      | 69   | Visual field restriction, vision loss, optical hallucination (palinopsia) | 2                | Pyramidal signs, myoclonus, abrupt stupor, coma | 4                     |
| 10 | F      | 64   | Blurred vision, disturbed perception of objects (comitans anosognosia) | 1.5              | Myoclonus, memory loss, disorientation, ataxic gait, akinetic mutism | 2.5                   |
| 11 | F      | 77   | Visual field restriction, vision loss up to cortical blindness, optical anosognosia | 1                | Myoclonus, ataxic apraxia, disorientation | 3.5                   |
| 12 | F      | 63   | Visual field restriction, vision loss up to cortical blindness, disturbed perception of objects (distortion) | 2                | Memory loss, aphasia, weakness, myoclonus | 3.5                   |
| 13 | M      | 57   | Visual field restriction, blurred vision, disturbed perception of objects | 2                | Dementia, myoclonus, rigidity, seizures, coma | 3                     |
| 14 | F      | 79   | Distorted perception of colors and objects, visual field restriction | 2                | Ataxia, myoclonus, dementia, aphasia, coma | 4                     |
| 15 | F      | 70   | Distorted perception of colors or objects, visual field restriction | 1                | Ataxic gait, ideomotor apraxia, dysphonia, memory loss, myoclonus, rigidity, ataxic state | 3                     |
| 16 | F      | 70   | Vision loss, disturbed perception of colors or structures, optical anosognosia | 6                | Ataxia, dysphonia, dysphagia, cognitive disturbances, pyramidal signs | 26                    |
| 17 | M      | 54   | Optical hallucination, environmental agnosia | 12               | Dorsal dementia, pyramidal signs, disorientation, psychosis | 44                    |
| 18 | M      | 48   | Blurred vision, visual field restriction, vision loss up to cortical blindness | 2.5              | Dysthria, dysphagia, disorientation, myoclonus | 6                     |
Table 2

| N° | sCJD Type       | Brain MRI                                      | EEG (timing) | CSF 14-3-3 (test result) | t-tau (pg/ml) | Timing |
|----|----------------|-----------------------------------------------|--------------|--------------------------|---------------|--------|
| 1  | MM 1+2C        | Parietal and occipital hyperintensity on DWI  | PSWCs (1.5)  | Ambiguous               | 5600          | 2      |
| 2  | MM 1+2C        | Normal (routine MRI)                          | PSWCs (2.5)^a| Positive                 | 6459          | 2.5    |
| 3  | MM 1+2C        | Bilateral frontal atrophy (routine MRI)       | PSWCs (2)    | Positive                 | NA            | 2      |
| 4  | MM 1+2C        | Parietal and temporal+BG hyperintensity on DWI| PSWCs (2)    | Positive                 | 3990          | 2      |
| 5  | MM 1+2C        | White matter signal alterations               | PSWCs (1.5)  | Positive                 | 7579          | 1.5    |
| 6  | MM1            | Parieto-occipital and basal ganglia hyperintensity on DWI| PSWCs (1.5)^a| Positive             | 2522          | 0.5    |
| 7  | MM1            | Non-specific (routine MRI)                    | PSWCs (3)    | Positive                 | NA            | 1.5    |
| 8  | MM1            | Non-specific                                  | PSWCs (1.5)  | Positive                 | 2335          | 0.5    |
| 9  | MM1            | Non-specific (routine MRI)                    | PSWCs (1.5)  | Positive                 | NA            | 2      |
| 10 | MM1            | Parietal and occipital hyperintensity on FLAIR and DWI| PSWCs (1.5)  | Positive                 | NA            |        |
| 11 | MM1            | Normal (routine MRI)                          | PSWCs (2)    | Positive                 | NA            | 2      |
| 12 | MM1            | NA                                            | PSWCs (2)    | NA                       | NA            | NA     |
| 13 | MM1            | Right parietal atrophy (routine MRI)          | PSWCs (2)^a  | NA                       | NA            | NA     |
| 14 | MM1            | Left parietal hyperintensity on FLAIR and DWI | Generalized slowing (3) | Positive | NA | 3 |
| 15 | MM1            | Non-specific vascular signs (routine MRI)     | PSWCs (2.5)^a| NA                       | NA            | NA     |
| 16 | MM 2C+1        | Normal (routine MRI)                          | Generalized slowing (9,13) | Ambiguous | NA | 9, 13 |
| 17 | MM 2C+1        | Parietal and occipital hyperintensity on FLAIR and DWI| Generalized slowing (6,8,11,13,20) | Ambiguous | 1070 | 6 |
| 18 | MM 2C          | Parietal and occipital hyperintensity on FLAIR and DWI| Generalized slowing (3.5,6) | Ambiguous | 1140 | 3 |

*routine MRI not including DWI and FLAIR sequences; ^months after onset of symptoms; EEG recording/s performed earlier in the clinical course did not show PSWCs; NA, not available; see text for other abbreviations.

Mean disease duration was 4.1 ± 1 months (range 2.5–5). Cortical visual symptoms included blurred vision (80%), visual field restriction (60%), vision loss (60%), image distortion (40%), and optical hallucinations (40%). EEG recording revealed PSWCs in all patients (100%). Brain MRI with FLAIR and DWI sequences was positive in two subjects (66%) and non-specific in one (33%). CSF analysis of protein 14-3-3 was positive in four patients (80%) and ambiguous in one (20%), while t-tau was markedly elevated in all four patients (range 3990–7579 pg/ml) that were tested. Histopathological examination and PrPSc typing revealed the typical features of sCJD MM1 except for the presence of clusters of large vacuoles associated with perivascular and coarse PrP deposits mainly in the cerebral cortex or thalamus. Consistently, PrPSc type 1 was detected by western blotting in all areas analyzed, whereas PrP^{B} type 2 was only seen focally in the cerebral cortex and/or in the thalamus as a relatively minor co-occurring type.

**MM2C+1**

Patient #16, a 70-year-old female, presented with a subacute loss of visual acuity associated with visuospatial distortion and a mild campimetric deficit. After three months of isolated visual disturbances, she developed gait difficulties and a rapidly progressive cognitive impairment. Six months later, her difficulties were followed by cerebellar signs (ataxia, dysmetria), myoclonus, dysphagia, and dysphonia. EEG recording showed a non-specific generalized slowing, routine brain MRI was normal, while the 14-3-3 protein test was ambiguous. The patient progressed to akinetic mutism after 21 months of clinical course and died five months later. Histopathological examination and...
Fig. 1. Distinctive histopathology and regional distribution of PrPSc in patient #16 (MM 2C+1). (A) Spongiform change characterized by large, confluent vacuoles (H&E stain) and (B) perivascular and coarse PrP deposits (PrP immunohistochemistry) in the occipital cortex; (C) mixed type of spongiform change with large, confluent vacuoles intermixed with smaller vacuoles in the striatum (H&E stain); (D) spongiform change characterized by small, fine, microvacuoles (H&E stain) and (E) synaptic pattern of PrP deposition in the cerebellum (PrP immunohistochemistry).

PrPSc typing revealed all the distinctive features of sCJD MM 2C+1. In particular, spongiform change comprised either large, confluent vacuoles correlating with perivascular and coarse PrP deposits or relatively small interspersed vacuoles associated with a synaptic pattern of PrP staining (Fig. 1A–E). As typically seen in sCJD MM 2C+1, the cerebral cortex was predominantly affected by the former type of spongiosis, whereas the cerebellum only showed the latter type (Fig. 1A,D). PrPSc typing revealed the co-occurrence of types 1 and 2 in all regions analyzed but the cerebellum (Fig. 1F). Consistent with histopathological findings, the amount of PrPSc type 2 was higher than that of type 1 in most samples from the cerebral cortex, in contrast to the cerebellum, where only a relatively low amount of type 1 is seen. While the amount of PrPSc type 2 is higher than that of type 1 in most samples from the cerebral cortex, subcortical gray matter structures show either a similar amount of the two proteins or a predominant accumulation of type 1.

Patient #17, a 54 year-old male, presented with a six month history of visual hallucinations (he saw ladders, houses, or bikes while driving a digger), environmental agnosia (he failed to recognize the gate entrance of his house while driving), and dyscalculia. At this time, campimetry disclosed left homonymous hemianopsia. A brain MRI showed a diffuse and bilateral hyperintensity in the occipital cortex with partial involvement of both parietal lobes and left temporal lobe in DWI (Fig. 2A–C) and FLAIR sequences. EEG was desynchronized and slow. Neuropsychological evaluation revealed a mild encoding memory deficit, while frontal lobe functions were normal. CSF examination disclosed 1070 pg/ml of t-tau, while the 14-3-3 protein test was ambiguous. The clinical course was slowly progressive; after two years, the patient became disoriented and developed a psychosis with paranoid delusions as well as pyramidal signs. He died after a prolonged lethargic state lasting approximately 15 months. At the neuropathologic examination, status spongiosus associated with severe gliosis and neuronal loss was the predominant finding in the cerebral cortex (Fig. 2D) and striatum. Typical spongiform change with vacuoles of intermediate or large size was only seen focally in relatively preserved areas of the cerebral cortex (Fig. 2D) and striatum. Typical spongiform change with vacuoles of intermediate or large size was only seen focally in relatively preserved areas of the cerebral cortex (Fig. 2D) and striatum. Typical spongiform change with vacuoles of intermediate or large size was only seen focally in relatively preserved areas of the cerebral cortex (Fig. 2D) and striatum. Typical spongiform change with vacuoles of intermediate or large size was only seen focally in relatively preserved areas of the cerebral cortex (Fig. 2D) and striatum. Typical spongiform change with vacuoles of intermediate or large size was only seen focally in relatively preserved areas of the cerebral cortex (Fig. 2D) and striatum. Typical spongiform change with vacuoles of intermediate or large size was only seen focally in relatively preserved areas of the cerebral cortex (Fig. 2D) and striatum. Typical spongiform change with vacuoles of intermediate or large size was only seen focally in relatively preserved areas of the cerebral cortex (Fig. 2D) and striatum.
Fig. 2. Results of neuroimaging, histopathological, and PrPSc studies in patient #17 (MM 2C+1). Brain DWI-MRIs at 12 (A), 16 (B), and 19 months (C) from clinical onset showing a prominent occipital hyperintensity extending to the parietal cortices during the clinical course. (D) Status spongiosus associated with severe gliosis and neuronal loss in the occipital cortex (H&E stain); (E) coarse granular pattern of PrP staining in the occipital cortex (PrP immunohistochemistry); (F) focal spongiform change with vacuoles of intermediate to large size in the temporal cortex (H&E stain); (G) coarse and perivacuolar PrP deposits in the frontal cortex (PrP immunohistochemistry); (H) focal mild spongiform change in the cerebellum (H&E stain); (I) PAS positive, unicentric, amyloid plaque in the molecular layer of cerebellum (PAS stain); (L) plaque-like type of PrP deposition predominantly involving the molecular layer in the cerebellum. All pictures (D-L) in the panel have the same magnification (×100) except for L (×40). (M) PrPSc typing by western blot showing PrPSc 2 in all areas analyzed co-occurring with relatively low amount of PrPSc type 1 in the cerebral cortex, brainstem, and cerebellum. Overall, the PrPSc amount is highest in the cerebral cortex; intermediate in the striatum, thalamus, and cerebellum; and lowest in the hippocampus, hypothalamus, and brainstem.

was associated with a plaque-like type of PrP deposition predominantly involving the molecular layer and correlating with the anatomic distribution of amyloid plaques (Fig. 2L). In addition, foci of synaptic PrP deposits were visible (Fig. 2L). PrPSc typing revealed the presence of PrPSc type 2 in all areas analyzed. The relative amount of the protein was highest in the cerebral cortex of all lobes; lowest in the hippocampus, hypothalamus, and brainstem; and intermediate in the striatum, thalamus, and cerebellum (Fig. 2M). In addition, traces or a relatively low amount of PrPSc type 1 were detected in some samples from the cerebral cortex, brainstem, and cerebellum.

MM 2C

Patient #18, a 48-year-old obese and heavy smoker, presented with subacute visual complaints characterized by dazzling from lampposts at night. An ophthalmologic examination revealed an irregular campimetric deficit in the right eye, while visual acuity was normal. After two and a half months, he became disinhibited, sometimes unsettled, and the visual campimetric disturbance progressed to a right homonymous hemianopsia. Neurological examination disclosed optic apraxia and simultanagnosia, psychomotor slowing, and executive function impairment.
Fig. 3. Results of neuroimaging, histopathological, and PrPSc studies in patient #18 (MM 2C). Hyperintensity of occipital cortex in DWI (A and B) and FLAIR (C) sequences. (D) Spongiform change characterized by large, confluent vacuoles diffusely involving the gray matter (H&E stain, occipital cortex). (E) Sparse foci of spongiform change especially involving the middle layers (H&E stain, frontal cortex). (F) Perivascular pattern of PrP deposition in the occipital cortex. (G) Sparse foci of coarse PrP deposits in the frontal cortex. (H) Mild spongiform change characterized by small vacuoles in the cerebellum (H&E stain). (I) Lack of significant spongiform change in the putamen (H&E stain). Pictures (D-I) in the panel have the same magnification (×100). (L) PrPSc typing by western blotting revealing a type 2 pattern of electrophoretic mobility in all regions; PrPSc is overall more abundant in the cerebral cortex (especially in occipital cortex) than in subcortical areas where only traces or a relatively low amount of the abnormal protein are detected.

A brain MRI revealed a hyperintense signal involving the occipital and parietal cortices in both DWI (Fig. 3A,B) and FLAIR (Fig. 3C) sequences. EEG showed a diffuse slowing of background activity. CSF assays revealed 1,140 pg/ml of t-tau, while protein 14-3-3 analyses yielded an ambiguous result. During the following two months, the patient developed cortical blindness, complete spatial and temporal disorientation, amnesia, severe dysarthria and dysphagia, paratonic rigidity, and recurring myoclonic jerks. The patient died of septic shock six months after the onset of visual symptoms. Histopathological examination and PrP immunohistochemistry revealed a perivascular pattern of protein deposition in all cortical areas (Fig. 3F,G). In addition, sparse foci of coarse PrP deposits were present in the thalamus, whereas no immunodeposition
was seen in the cerebellum (data not shown). PrPSc typing revealed a type 2 pattern (Fig. 3L). PrPSc was more abundant in the occipital cortex than in the other cortical or subcortical areas where only traces or relatively low amounts of the protein were detected (Fig. 3L).

**DISCUSSION**

Heidenhain variant defines a peculiar clinical presentation of CJD characterized by isolated visual disturbances, reflecting the early and prevalent involvement of the occipital cortex by the degenerative changes. In our large series of sCJD, the prevalence of Heidenhain variant was 4.9%. This number is quite consistent with that (3.7%) reported by Cooper et al. [11]. However, it is significantly lower than that reported by Kropp et al. (20%) [13] who applied less stringent clinical criteria for the definition of Heidenhain variant (e.g., visual symptoms at onset notwithstanding their being isolated for some time). sCJD is a highly heterogeneous disease caused by prion strains showing distinctive neuronal targeting [45]. Detailed studies of the regional distribution of lesions (the so-called lesion profile) across the spectrum of CJD types have shown that sCJD MM-MV1 (e.g., M1 strain) is associated with significant cortical pathology, and that this is often predominant in the cerebral gray matter [50], has also a good sensitivity which shows a very distinctive type of spongiform change characterized by numerous large and confluent vacuoles. Although the present study focused on t-tau levels (well above the 1200 pg/ml threshold) and above threshold levels of protein 14-3-3 (i.e., positive test) in virtually all cases. Interestingly, analyses of the timing of appearance of PSWCs in the EEG and of a “positive” CSF assay suggest that the latter might be more sensitive than the EEG early in the clinical course (i.e., when patients suffer from isolated visual symptoms). Indeed, while the time of appearance of PSWCs in our series ranged from one and a half to three months after onset, in two cases 14-3-3 and t-tau assays were already positive two weeks after onset (Table 2).

At variance with previous studies, three cases (17%) in our series demonstrated distinctive clinical features and an exclusive or predominant deposition of PrPSc type 2. Indeed, in these patients, the duration of isolated visual symptoms was significantly longer, and the clinical course was more slowly progressive than in MM1 or MM1+2C sCJD types. Two of them had a disease duration longer than two years, while in the third, the relatively mild histopathological changes were observed in all areas, but the occipital cortex also indicated a relatively slow progression. EEG findings, showing a diffuse slowing of background activity without PSWCs, were not distinctive in these patients. Similarly, both 14-3-3 and t-tau analyses revealed pathological values that were below the required threshold for the diagnosis of “probable” CJD [42]. In contrast, typical occipito-parietal hyperintensity on FLAIR and DWI sequences were clearly seen on brain MRI in both patients who underwent these analyses. Thus, the results of laboratory investigations significantly differ between the two sCJD types, which is in agreement with the known different pathophysiology of the disease process (e.g., earlier and more rapidly evolving neuronal dysfunction in MM1) and the significantly different transmission properties (e.g., significantly shorter incubation time and higher transmission rate of MM1 prions) [47, 48, 49] between the two sCJD types. Accordingly, CSF biomarkers (i.e., t-tau >1200 pg/ml and 14-3-3) and EEG abnormalities (i.e., PSWCs), reflecting either a subacute neurodegeneration or a rapidly evolving cortical and subcortical dysfunction, show a higher sensitivity in sCJD MM1. In contrast, the brain DWI-MRI increased signal, which instead correlates with the degree of spongiform change in the cerebral gray matter [50], has also a good sensitivity (or even higher according to our results) in MM2C, which shows a very distinctive type of spongiform change characterized by numerous large and confluent vacuoles. Although the present study focused on...
sCJD, it is worth mentioning that a CJD type with identical or very similar clinical-pathological features and transmission properties of sCJDMM1 has also been described in genetic CJD cases carrying the V210I-129M or the E200K-129 PRNP haplotype [7, 48, 51]. Thus, it is expected that cases with the Heidenhain variant may also occur in genetic CJD. Consistently, isolated visual symptoms at onset have been recently reported in two subjects carrying the V210I-129M PRNP haplotype, which further underlines the importance of genetic testing in all cases of possible and probable CJD, including those presenting with visual signs [54]. Despite its rarity, the Heidenhain variant of CJD remains of clinical relevance. A significant number of patients are initially referred to the ophthalmologist, and misdiagnoses are not uncommon, especially in the early clinical stages as well as in the clinical neurological setting. In addition to ocular diseases, differential diagnosis may include occipital stroke and other neurodegenerative conditions causing a posterior cortical atrophy (PCA) syndrome, including Alzheimer’s disease, dementias with Lewy bodies, and corticobasal degeneration [53, 54]. In agreement with the recent literature, which suggests that phenotypic differences (i.e., different visual symptoms) within PCA cases might most appropriately be judged to represent points on a continuum of variation, we failed to recognize a unitary clinical posterior cortical syndrome among sCJD cases that would justify the proposal of a distinct syndromic subtype of PCA. When PCA is suspected, the clinical course, examination is unremarkable in most PCA cases, it is also unhelpful for the differential diagnosis. Nonetheless, the presence of symmetrical parkinsonism or rapid eye movement sleep behavior disorder (suggestive of Lewy body pathology) as well as asymmetric myoclonus/dystonia (suggestive of corticobasal degeneration) can give clues to the underlying cause of PCA [52]. When PCA is suspected, the clinical course, examination is unremarkable in most PCA cases, it is also unhelpful for the differential diagnosis. In this respect, the findings of the present study highlight the fact that, despite their relative rarity, CJD cases presenting with isolated visual symptoms may belong to different disease variants that are characterized by a distinct profile of laboratory findings. In particular, clinicians should be aware that the Heidenhain variant may also occur in atypical cases showing a relatively slow progression, negative or ambiguous CSF biomarkers results, and lack of specific EEG abnormalities.

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