The Heidenhain Variant of Creutzfeldt-Jakob Disease

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Objective: To investigate whether typical neuropathological and radiological findings can be identified in patients with the clinical diagnosis of the Heidenhain variant of Creutzfeldt-Jakob disease (CJD).

Design: Case study. The clinical symptoms, neuropathological findings, electroencephalograms, magnetic resonance images, and cerebrospinal fluid samples of 14 Heidenhain cases were evaluated. Neuropathological changes were compared with those in a group of 14 patients with ataxia as the leading clinical sign.

Setting: A university hospital, base of the German National Creutzfeldt-Jakob Disease Surveillance Study.

Patients: Medical records of 169 neurologically examined patients with prospectively classified and neuropathologically confirmed CJD were analyzed.

Main Outcome Measure: Difference in neuropathological and radiological findings between patients with the Heidenhain variant and other patients with CJD.

Results: Of 169 patients with confirmed CJD, 20% showed characteristic clinical findings such as blurred vision, visual field restriction, metamorphopsia, or cortical blindness. Disease course of the Heidenhain group, as compared with the group of all patients with definite CJD, was significantly shorter (5.7 months vs 7.5 months; \( P = .02 \), \( t \) test). Neuropathological examination of patients with the Heidenhain variant showed most pronounced changes in the occipital lobe but less damage in the cingulate gyrus and basal ganglia compared with 14 patients with CJD who had ataxia as the leading clinical sign. Eleven (92%) of 12 genetically analyzed Heidenhain cases were homozygous for methionine at codon 129 of the prion protein gene (PRNP). In 9 of 9 cases, the 14-3-3 protein was present. In 7 (78%) of 9 cases, the level of neuron-specific enolase was elevated, with a concentration above 35 ng/mL. Periodic sharp-wave complexes were observed in 11 (78%) of the 14 cases. In 7 (63%) of 11 patients, magnetic resonance images showed symmetric hyper-intensities in the basal ganglia in the \( T_2 \)- and proton-weighted sequence. In 4 of 11 cases the \( T_2 \)- and proton density–weighted images showed a pronounced signal increase confined to the gray matter of the occipital and visual cortex. Isolated atrophy of the visual cortex was noticeable in 2 of 11 cases.

Conclusions: The clinical presentation of the Heidenhain variant of CJD was shown to correlate with the neuropathological findings of gliosis and nerve cell loss. In patients with visual disorders of unclear origin and signs of dementia, the differential diagnosis of a Heidenhain variant of CJD must be taken into consideration.

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Creutzfeldt-Jakob disease (CJD) is a rare neurodegenerative human disorder with an incidence of 1 case per 1 million population per year. It was described by Creutzfeldt\(^1\) and Jakob\(^2\) early in this century for the first time. Case reports by Creutzfeldt and Jakob and other authors led to the finding that CJD represents a new disease group, known as spongiform encephalopathies. In most cases, the disease occurs sporadically, but a small proportion of cases are genetically determined. Various mutations of the prion protein (PrP) gene (PRNP) underlie the latter group of familial CJD cases.\(^3\) In a small number of additional cases, iatrogenic transmission by dura mater and corneal grafts\(^4\) or by treatment with pituitary-derived growth hormones was identified.\(^5,6\) The prion hypothesis of an ex-planatory model is currently favored by the majority of researchers. Even though it has not yet been possible to detect a virus,\(^11,12\) a viral origin cannot be excluded definitely.\(^13\)

According to the specific clinical picture and the neuropathological findings, CJD can be divided into different sub-
PATIENTS AND METHODS

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Since 1993, suspected cases of CJD have been reported to the German CJD Surveillance Unit. Based on the reports of the referring physicians and the results of clinical examination and pathological findings, patients were classified according to Masters et al[27] as having "confirmed," "probable," or "possible" CJD. Neuropathologically proved CJD cases were considered confirmed. Probable CJD was diagnosed in patients with a history of rapidly progressive dementia of less than 2 years' duration, typical periodic sharp-wave complexes in the electroencephalogram (EEG), and at least 2 of the following signs: myoclonus, visual and/or cerebellar symptoms, pyramidal or extrapyramidal signs, and akinetic mutism. Patients with the above signs but without a typical EEG were diagnosed as having possible CJD. Medical records of 169 confirmed cases in the period from June 13, 1993, to October 31, 1997, were analyzed for the clinical signs and symptoms. The criteria for the diagnosis of the Heidenhain variant were predominant visual impairments at onset of the disease, consisting of deterioration of vision, blurred vision or visual field restriction, vision loss up to cortical blindness, disturbed perception of colors or structures, optical hallucinations, and optical anosognosia.

Statistical analysis was performed with the SPSS package (version 7.5 for Windows; SPSS Inc, Chicago, Ill).

NEUROPATHOLOGICAL EXAMINATION

As complete neuropathological samples were not obtained from all referred patients by the Reference Center for Spongiform Encephalopathies, different parts of cortical regions, basal ganglia, and cerebellum obtained at autopsy from 14 patients with Heidenhain variant were analyzed in a standardized neuropathological examination. For comparison, brain tissue from 14 patients with pathologically proved CJD with ataxia at onset was examined neuropathologically.

Formalin-fixed tissue was decontaminated for 1 hour in concentrated formic acid according to the instructions of Brown et al[28] and embedded in paraffin. Microtome sections were cut at 2 μm and mounted on silanized slides. Immunohistochemical staining was performed after depurification and pretreatment of the mounted sections by hydrolytic autoclaving in 2-mmol/L hydrochloric acid for 30 minutes at 121°C. A monoclonal antibody against a synthetic peptide corresponding to amino acids 138 to 152 of the human PrP (GoI38) was used. After 18 hours of incubation with the primary antibody at 4°C, a standard alkaline phosphatase anti-alkaline phosphatase (APAAP) technique was used for detection. The slides were counterstained with hemalum. Histological examination was performed by 2 investigators (S.K. and W.J.S.-S.) who were blinded to the clinical data. The degree of spongiform change of the molecular layer, astrocytic gliosis, and loss of granular cells were estimated semiquantitatively on a scale ranging from 0 to 4 in hematoxylin-eosin–stained sections. The pattern of immunohistochemical PrP staining was classified according to Kitamoto et al[29] in a diffuse fine and coarse granular pattern ("synaptic type"), a plaquelike pattern, and plaques visible on hematoxylin-eosin staining.

Spongiform changes, gliosis, and nerve cell loss were classified semiquantitatively for each section (0-4 points, assigned for no change or mild, moderate, severe, or maximal changes [status spongiosus], respectively). The average of semiquantitatively measured pathological changes in 14 cases compared with controls was calculated for each section. A mean of spongiform changes, gliosis, and nerve cell loss was calculated in each case. A lesion profile was drawn, placing the location of the section at the x-axis and the average value of pathological changes along the y-axis of a 2-axis graph.

GENETIC ANALYSIS

Genetic examination was performed by one of us (O.W.) in 12 cases of the Heidenhain variant. Genomic DNA was purified from buffy coat by means of the QIAamp Blood Kit (Qiagen GmbH, Hilden, Germany). The coding region of PRNP was amplified by the polymerase chain reaction (PCR) with the primers 895W (CGCAAGCTTGAACTC-TGACATTCTCCTCCTT) and 896W (TTCGAATTTCTCC- CCTCAAGCTGGAAAAG) as described by Nicholl et al[31] groups. Apart from mutations known to cause genetic prion diseases, polymorphisms in the PRNP are detected by genetic analysis. It was possible to relate homozygosity at the naturally occurring polymorphic position 129 (methionine or valine) to both disease susceptibility and clinical symptoms. Methionine or valine homozygosity at codon 129 of the PRNP correlates with different forms of PrP deposition of the scrapie-like isoform of PrP (PrPSc) in brain tissue, which typically can be related to dementia or ataxia as a clinical leading sign.[18,19] According to these objective criteria of PRNP genotype and PrPSc typing, Parchi et al[18] established a novel classification of sporadic CJD.

A disease course described by Heidenhain in 1929[20] including the leading symptoms of a visual disorder and rapid progression, has been referred to as the “Heidenhain variant” of CJD since 1954.[19] The visual disorder can manifest in different ways: disturbed perception of colors or structures, optical hallucinations, cortical blindness, and optical anosognosia (Anton syndrome) may occur.[21] At disease onset, patients apparently not fully demented typically give up reading or watching television, even though ophthalmologic examination does not show any conspicuous findings, or new spectacles do not improve their vision. The clinical symptoms can be classified as typical of Heidenhain variant if visual disorders occur as a leading symptom and if these disorders predominantly persist in the course of the disease.[21,22] Cortical blindness as an extreme manifestation of a visual disorder is observed in some of the cases; however, at least in our patient group, it is no longer verifiable later in the course of the disease because of increasingly occurring neurologic symptoms and dementia. At disease onset, visual disorders may be present without any further neurologic signs and dementia. It has been reported that the Heidenhain variant, in accordance with the clinical
symptoms, shows the most pronounced neuropsychological changes in the occipital lobe.14,21,22,23,26 It is the aim of this study to characterize the CJD cases with the clinical appearance of a Heidenhain variant with respect to the disease course, neuropathological pattern of damage, and paraclinical findings. To demonstrate the difference in the neuropathological distribution pattern, a group of patients with Heidenhain variant with typical clinical signs was compared with a group of patients with definite CJD with ataxia as the most prominent sign.

RESULTS

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In the period between June 15, 1993, and October 31, 1997, the diagnosis of sporadic CJD was confirmed neuropathologically by the Reference Centre for Spongiform Encephalopathies in 169 neurologically examined and prospectively classified patients. In 34 cases the clinical symptoms of a Heidenhain variant were observed (20.1% of the total number of 169 cases), but in 9 medical records of these 34 patients, details of clinical examinations were missing. Twenty-five cases definitely fulfilled the criteria for evaluation. The median age of these 25 patients with Heidenhain variant was 65.7 years (range, 51.6-76.4 years), similar to the median age of 65.7 years (range, 31.1-87.5 years) in 144 definite sporadic cases. The mean disease duration in the Heidenhain group was significantly shorter (5.7 months; range, 2.3-14.1 months) than in 144 definite sporadic cases (7.5 months; range, 1.3-32.4 months) (P = .02; t test).

Fourteen patients with the Heidenhain variant were investigated neuropathologically and compared with 14
patients with CJD who showed ataxia as the leading sign. The clinical findings in the Heidenhain group (n = 14) at disease onset were deterioration of vision, visual field restriction, and blurred vision. Five patients suffered from headache; 3 of them experienced mainly occipital headache. Seven patients reported optical hallucinations, and 10 patients suffered from disturbed perception of structures and colors (metamorphopsia, micropsia, and dyschromatopsia). Six patients became blind during the course of the disease; in 2 of them the diagnosis of optical anosognosia (Anton syndrome) was established. All patients developed additional neurologic symptoms in the course of the disease that, based on the classification criteria, allowed the diagnosis of probable CJD (11 cases) and possible CJD (3 cases).

NEUROPATHOLOGICAL EXAMINATIONS, GENETIC ANALYSIS, AND PRION PROTEIN TYPING

The neuropathological examinations showed typical features such as spongiform changes, gliosis, and nerve cell loss. In all Heidenhain cases, gliosis and nerve cell loss were particularly severe in the occipital lobe. When a "lesion pattern" (Figure 1) was created by means of semiquantitative evaluation of spongiform changes, gliosis, and nerve cell loss, pathological changes were shown to be more pronounced in the occipital region than other brain regions. Gliosis and nerve cell loss in the occipital region were more prominent than spongiform changes. In comparison with a group of 14 patients with CJD who had ataxia as the predominant clinical sign, the pathological changes were more pronounced in the occipital region. In the region of the cingulate gyrus and basal ganglia, lesions were less pronounced than in control cases. Clinical signs of an involvement of the limbic system, such as aggressiveness (4 of 14 cases), and of basal ganglia damage, such as generalized rigidity, tremor, athetosis, and limb hypertonicity (8 of 14 cases), were found less often in patients with Heidenhain variant than in controls with CJD (affected limbic system in 6 of 14 controls, signs of basal ganglia damage in 10 of 14). In all Heidenhain cases, a PrP deposition pattern of the synaptic type according to Kitamoto et al was observed. Twelve patients with the Heidenhain variant were analyzed for the polymorphism at codon 129; 11 of them were homozygous for methionine and 1 was heterozygous. In 6 of 14 Heidenhain cases, typing of PrP<sup>CJD</sup> was possible with the Western blot technique. In all cases investigated, PrP<sup>CJD</sup> type 1 was found.

ELECTROENCEPHALOGRAPHY

On average, 4 EEG examinations (range, 2-7) were performed in the patients during the course of the disease. Eleven (79%) of 14 patients showed periodic sharp-wave complexes during the course; 5 of them showed bilateral occipital periodic sharp-wave complexes, and in 6 cases periodic activity was generalized; no regional or lateralized activity was found.

LABORATORY ANALYSIS

In 9 cases CSF could be obtained for analysis. The 14-3-3 protein was detectable in all of these CSF samples. In 7 (78%) of 9 cases, an elevation of neuron-specific enolase level in CSF with a concentration above 35 ng/mL was measured (range, 13-150 ng/mL; median, 55 ng/mL).

BRAIN IMAGING

Seven (64%) of 11 MR images showed increased signal intensity in the basal ganglia. In 4 of 11 cases the T<sub>2</sub>- and proton density–weighted images showed a pronounced signal increase confined to the gray matter of the occipital and visual cortex. Isolated atrophy of the visual cortex was noticeable in 2 of 11 cases. In 1 of these cases the changes were concurrent with a loss of vision. These changes are demonstrated in Figure 2, Figure 3, and Figure 4.

COMMENT

The Heidenhain variant is a clinical form of CJD. We found a short disease duration, typical EEG changes, a high percentage of cases homozygous for methionine at codon 129 of PRNP, and PrP<sup>CJD</sup> type 1 in these cases. The pathological pattern of damage reflects the clinical symptoms, which are characterized by a predominant vision impairment at onset with visual field restriction, blurred vision, vision loss, or even blindness. Neuropsychological disturbances, such as metamorphopsia, visual hallucinations, or visual neglect, were further symptoms. These findings are in accordance with previously published case reports. Marked neuropathological changes were found mainly in the occipital cortex. In single cases other authors described similar lesion patterns. In addition to the reported focus of the occipital brain region in the Heidenhain variant, we found lesser damage of the limbic system and the basal ganglia in the Heidenhain variant than in controls with CJD characterized by ataxia. This observation was made clinically and neuropathologically. Methionine homozygosity at
Figure 3. Images from a 66-year-old patient diagnosed as having Creutzfeldt-Jakob disease 1 month after visual loss, followed by blindness. Left, Axial $T_2$-weighted image demonstrates isolated atrophy of the visual cortex. Right, Axial proton-weighted magnetic resonance image shows bilateral signal intensity in the putamen and caudate, and to a lesser extent in both medial thalami, as well as localized signal intensity in the occipital lobes.

Figure 2. Images obtained in a 68-year-old woman 4 months after onset of visual symptoms consisting of metamorphopsia, dysmorphopsia, and later visual agnosia, followed by other neurologic symptoms. Left, Axial $T_1$-weighted image shows isolated atrophy of the visual cortex with slight widening of the sulci. Right, Axial fluid-attenuated inversion recovery image (echo time, 2000 milliseconds; repetition time, 6000 milliseconds; inversion time, 150 milliseconds) shows atrophy of the occipital lobes with localized signal intensity increase of the cortical gray matter.
occur at a later or at the terminal stage of the disease,\textsuperscript{40} the fact that the clinical signs required for classification might be encouraged in the early course of the disease. Heidenhain variant, further diagnostic procedures might be included in the diagnostic considerations or rejected by the analysis of CSF.\textsuperscript{36,37,41,42} The EEG provided a high sensitivity of 79% that underlines the diagnostic value of this easily obtainable method in CJD and the satisfying accuracy of the objective periodic sharp-wave complex criteria our group proposed earlier.\textsuperscript{35} When the Heidenhain variant of CJD is considered as a diagnosis in a patient, MR imaging (and, if possible, proton-weighted imaging, fluid-attenuated inversion recovery,\textsuperscript{45} or diffusion-weighted imaging) is the first-line imaging method to further confirm this diagnosis. Other imaging techniques, such as single photon emission computed tomography or positron emission tomography,\textsuperscript{44,45} may disclose damage of the visual cortex in single cases before the occurrence of neurologic symptoms other than visual symptoms or EEG findings typical of CJD.\textsuperscript{46} By means of MR imaging, space-occupying lesions or ischemic processes might be excluded and changes described as characteristic for CJD\textsuperscript{77,80} can be shown, further substantiating the diagnosis of CJD.

Changes in signal intensity in basal ganglia in the Heidenhain variant could only be detected in a limited number of cases. A correlation of MR imaging findings and pathological changes was not obtainable. In a single case in the literature\textsuperscript{80} these changes were no longer detectable in the course of the disease. This might also apply to some of our cases, in particular since MR images were often performed at a later stage of the disease when computed tomographic scans did not demonstrate any abnormalities, but progressive clinical symptoms with severe extrapyramidal signs such as generalized rigidity or limb hypertonicity were observed. Apart from the mentioned changes in the basal ganglia, a morphologic correlate of the visual disorders, as shown in Figures 2 through 4, can possibly be detected by MR imaging. In patients with visual disorders of unclear origin and signs of dementia, the differential diagnosis of a Heidenhain variant of CJD must be taken into consideration. An EEG, analysis of CSF for surrogate markers, and MR imaging can provide further information on the presence of possible spongiform encephalopathy in these patients.

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