EXTENDED REPORT

Isolated visual symptoms at onset in sporadic Creutzfeldt-Jakob disease: the clinical phenotype of the ''Heidenhain variant''

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Background: The Heidenhain variant of sporadic Creutzfeldt-Jakob disease (sCJD) is commonly understood to represent cases with early, prominent visual complaints. The term is clarified to represent those who present with isolated visual symptoms. This group may pose diagnostic difficulties and often present to ophthalmologists where they may undergo needless invasive procedures.

Method: A retrospective review of 594 pathologically proved sCJD cases referred to the UK National CJD Surveillance Unit over a 15 year period to identify Heidenhain cases.

Results: 22 cases had isolated visual symptoms at onset with a mean illness duration of 4 months. The mean age at disease onset was 67 years. Most displayed myoclonus, pyramidal signs, and a delay in the onset of dementia for some weeks. 17 (77%) were referred initially to ophthalmology. Two underwent cataract extraction before diagnosis. All tested cases were homozygous for methionine at codon 129 of the prion protein gene.

Conclusions: This rare, but clinically distinct, group of patients with sCJD may cause diagnostic difficulties. Because ocular intervention carries with it the risk of onward transmission awareness of this condition among ophthalmologists is important.

Sporadic Creutzfeldt-Jakob disease (sCJD) is a rare and uniformly fatal prion disease classically presenting as a rapidly progressive dementia resulting in death usually within 6 months.[1 2]

A subgroup of cases of sCJD present with isolated visual symptoms. These can persist in the absence of cognitive decline for some weeks.[3] Historically, these are termed the ''Heidenhain variant'' of sCJD after work by Heidenhain in 1929.[4] He described three cases of spongiform encephalopathy, two of which had prominent, early visual symptoms. The third presented with sensory complaints and athetosis. Meyer *et al* described, in 1954, the case of a 38 year old man who ''became forgetful, experienced difficulty in concentrating…suffered from headaches and his vision began to fail.'' A right homonymous hemianopia was detected and death occurred 6 months after the onset of symptoms.[5]

Subsequently, the term has been used rather imprecisely in all cases where visual symptoms occur along with otherwise characteristic early features. Visual symptoms are common in sCJD and, in the early stages of the disease, have been described in 20%.[6] This study seeks to clarify Heidenhain cases as a clinically distinct group where visual symptoms occur initially in isolation. These cases may cause diagnostic difficulty and raise particular public health concerns. They are likely to present to ophthalmologists and may be subject to needless ocular intervention, with risks of onward transmission.

MATERIALS AND METHODS

A retrospective case file review was performed on all pathologically proved cases of sCJD referred to the UK National CJD Surveillance Unit (NCJDSU) between January 1990 and March 2005 inclusive. Case files comprised clinical and epidemiological information collected by NCJDSU staff and copies of hospital and general practitioner records. A clinical assessment and interview with patients' relatives was conducted by a surveillance neurologist whenever possible and usually while the patient was alive. Electroencephalogram (EEG) recordings and magnetic resonance brain imaging (MRI) were reviewed at the NCJDSU.

Cases were identified whose first symptom was visual and who exhibited no other cognitive, behavioural, or physical symptoms for at least 2 weeks. The presence or absence of cognitive decline was assessed by a review of case files, including a detailed discussion with relatives and a questionnaire completed by the NCJDSU neurologist. Patients were excluded if there were any memory difficulties, behavioural changes, episodes of confusion or disorientation, speech problems, or other neurological symptoms or signs within 2 weeks of the first symptom. Cases were identified on a clinical basis without awareness of PRNP codon 129 genotype data. Genetic analysis was performed with informed consent of the patient or the next of kin.

RESULTS

Twenty two patients out of 594 (3.7%) with pathologically proved sCJD had clearly documented purely visual symptoms for at least the first 2 weeks of the illness. The nature of these initial symptoms is summarised in table 1.

Fourteen (64%) cases were women. Mean age at onset was 67 years (median 66 years, range 50–88 years). Mean duration of illness was 4 months (median 3 months, range 1–17 months). Seventeen patients (77%) lived for 3 months or less.

Clinical features

Throughout the illness myoclonus was observed in 21 (95%), pyramidal signs in 19 (86%), cerebellar signs in 12 (55%), psychiatric symptoms in seven (32%), other involuntary movements in six (27%), sensory symptoms in four (18%),

Abbreviations: EEG, electroencephalogram; MRI, magnetic resonance imaging; NCJDSU, National CJD Surveillance Unit; sCJD, sporadic Creutzfeldt-Jakob disease

Table 1 Visual symptoms at onset (n = 22)

Visual symptom	Number of patients (n = 22)*
Decreased visual acuity	8
Blurred vision	6
Peripheral visual field defect	2
Visual distortions	3
Impaired colour vision	2
Palinopsia	1
Tunnel vision	1

*One patient experienced both impaired colour vision and visual distortions at onset.

and extrapyramidal signs in one (5%). None had documented seizures. A rapidly progressive dementia was observed in all after the initial period of cognitive preservation which lasted from 2–6 weeks.

Case 1

A 73 year old man complained of difficulty reading, with blank spaces appearing in words. He also complained of colours appearing abnormally enhanced. He was assessed by an ophthalmologist when there was normal visual acuity but dense scotomata lying to the right of fixation bilaterally. A provisional diagnosis of an occipital infarct was made. Six weeks after onset he developed myoclonus, followed by ataxia and ultimately dementia. His vision deteriorated with oculomotor apraxia and cortical blindness. He died 3 months after disease onset.

Case 2

A 62 year old woman presented with deteriorating visual acuity. She felt that her vision was ''fogging up'' and complained of tunnel vision. She attended an optician but no abnormality was identified. A week later she complained that everything appeared green. An MRI brain scan was ordered following referral to the ophthalmology department but no diagnosis made. Over the next month her gait became unsteady and she was increasingly forgetful. By the time she developed myoclonus she could only perceive light. She died in an akinetic and mute state 4 months after onset.

Investigation results

Twenty patients had at least one EEG. These were considered typical for sCJD[1] after review at the NCJDSU in seven cases (35%). CSF 14-3-3 was analysed in five patients (positive in all). Cerebral MRI was available for review in only six cases, showing high signal in the basal ganglia in two (33%) and being normal in four. Sixteen cases (73%) had PRNP gene codon 129 genotype data. All of these were homozygous for methionine. In nine the glycotype was known and was type 1 in all.[1]

Seventeen patients (77%) were initially referred to the ophthalmology department. Two underwent cataract extraction after the onset of symptoms and before a diagnosis of sCJD. Thirteen (59%) were referred to the NCJDSU within 2 months of onset. Three cases were referred after death, one of these after a necropsy revealed sCJD.

DISCUSSION

Although visual symptoms in sCJD are not uncommon they often occur in the context of symptoms indicative of a more widespread cortical involvement. These cases are distinct because of the isolated visual symptoms at onset and the striking early preservation of cognitive function. Aside from the onset the cases are remarkably ''typical'' for sCJD. The majority display an extremely rapid decline with associated myoclonus once dementia has supervened. Nearly 60% of these patients were referred to the NCJDSU within 2 months of onset and only one case was referred as a result of diagnosis at necropsy (compared to 19% of total cases of sCJD referred in this way[7]). Two cases underwent cataract extraction before the diagnosis of sCJD was considered. Previous work has highlighted the incidence of ocular surgery in sCJD cases with visual symptoms[8]. Although there have not been any reports of CJD transmission following cataract surgery, it has been reported after corneal grafting. Abnormal prion protein has been isolated from ocular tissue.[9] It is important that ophthalmologists are aware of the condition despite its rarity as onward transmission through ocular surgical intervention remains a concern.

All tested cases were homozygous for methionine at codon 129 of the PRNP gene. This genotype is associated with a clinically typical disease course[10] rather than isolated visual symptoms themselves. The methodology in this study differs from that previously employed as unselected, consecutive cases from surveillance in one country were obtained by applying a careful definition of a ''Heidenhain'' case. We have shown that 22 cases have been identified over 15 years out of a population of approximately 58 million in the United Kingdom. The more defined inclusion criteria for visual onset cases used here compared to those employed in the past[6] may have identified a distinct subgroup of cases as reflected in the genotype findings.

Defining a group of cases with isolated visual symptoms at onset may aid future recognition of similar cases. By clarifying the definition of Heidenhain cases we have identified a group who generally exhibit short illness duration, myoclonus, and a PRNP codon 129 MM genotype. As well as aiding diagnosis these findings may contribute to the understanding of the how abnormal prion protein causes disease within the central nervous system.

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