REVIEW

Creutzfeldt–Jakob disease and the eye. II. Ophthalmic and neuro-ophthalmic features

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In this article, we discuss the various ophthalmic and neuro-ophthalmic manifestations of transmissible spongiform encephalopathies (TSEs) as they affect man. Such symptoms and signs are common, a number of studies reporting them as the third most frequently presenting symptoms of Creutzfeldt-Jakob disease (CJD).[1,2] As a result, it is likely that some patients will present to an ophthalmologist. Recognition of these patients is important, not simply from the point of view of diagnosis, but also from the aspect of preventing possible transmission of the disease to other patients. The accompanying article[3] provides a summary of our current understanding of the molecular biology and general clinical features of the conditions.

For ease of classification, the various symptoms and signs have been described in three groups: those which affect vision, those which affect ocular motor function, and the remainder.

Visual symptoms/signs

At presentation, visual disturbance is evident in some 10–20% of cases of sporadic CJD,[2,4–12] but the incidence rises to 30–50% over the course of the disease.[1,2,4,9,11,13–17] In familial CJD, the figures quoted are 10% and 20%, respectively.[9] In iatrogenic CJD, the incidence of visual/oculomotor symptoms at presentation has been reported to vary from 15%[18] to 88%[19] in cases transmitted by human growth hormone (hGH). In cases transmitted by dura mater or corneal transplantation, some 50% have visual/oculomotor symptoms at presentation, rising to 64% during the course of the illness.[20] It is of interest that visual disturbance has also been described in animals with transmitted CJD, in particular squirrel monkeys[21] and chimpanzees.[14]

In 1928, Heidenhain[22] described three patients with spongiform encephalography, two of whom presented with disturbed vision, became blind, and rapidly developed dementia. In these cases, the spongiform changes were noted to be most marked in the occipital cortex. A similar case involving hemianopia was reported by Meyer *et al.*[23] in 1954, and they coined the term 'Heidenhain syndrome'. This term is now generally taken to describe any case of CJD in which visual symptoms predominate in the early stages. Many studies suggest that the pathology of these cases is most marked in the occipital lobes,[12,22–33] and electroencephalogram (EEG) abnormalities may also be more prominent over the occipital lobes.[34]

Many reports describe visual symptoms and signs in detail, and these will be dealt with below. In some cases, the description of the visual disturbance is too vague to allow further comment. Such descriptions include 'visual disturbance',[35–48] 'visual problems',[49] 'visual defects',[50] 'vague visual difficulties',[51] 'failing vision',[52] 'visual loss',[53,54] 'distorted vision',[25] 'visuospatial disturbance',[55] 'ocular symptoms',[56] 'some loss of vision',[57] 'central impairment of . . . visual function',[58] 'could only see large objects'[59] or that the eyes were 'not clear'.[60] It is of note that the visual disturbance can rarely be transient, and mimic amaurosis fugax.[32,55,61]

Blurred/dim vision

Many patients are unable to describe their visual disturbance more clearly than that it is 'blurred' or 'dim'. In some cases this has been referred to as 'reduced' or 'diminished' visual acuity,[34,62–65] but some authors have been able to document acuities of 20/50,[66–69] 20/400[68] or even perception of light only.[70]

As a symptom, blurred or dim vision has been reported to occur in sporadic CJD,[2,14,23,71–75] with a frequency of some 9% at presentation.[8] In one case, the onset of dim vision was sudden.[68] It is also described in 'panencephalopathic' CJD,[54,76,77] familial CJD,[78] and iatrogenic CJD due to hGH,[19] human pituitary gonadotrophin (hPG)[79] and cadaveric

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dura mater grafts.[80–84] It has also been reported in Gerstmann–Sträussler–Scheinker disease (GSS),[58,85] though this is uncommon.

Visual distortion/dyschromatopsia/visual agnosia/micropsia/dyslexia

Many different symptoms of cortical visual dysfunction have been reported, including visual distortion,[8,9,25] micropsia,[12,14,86–88] macropsia,[10] metamorphopsia,[12,26,53,60,69,88–92] dyschromatopsia,[1,2,12,14,60,68,93] difficulty with depth,[10] agnosia (numbers, shapes, images, faces, letters or colours),[26,63,71,91,93–101] dyslexia,[14,71,88,92,95,100,102,103] optic ataxia,[32,104,105] or simply that things 'look funny'.[10,106] It is not uncommon for such patients to present to ophthalmologists or opticians in such circumstances.[30,88]

Homonymous hemianopias/hemifield neglect/field loss

Hemianopia is a common visual field disturbance in CJD,[107] occurring in at least 7% of sporadic cases,[7] though it may go undetected since patients may not be able to cooperate with perimetry, or even confrontation fields.

In sporadic CJD, the defect may be patchy or incomplete at presentation,[34,60,70,95] may be complete[14,23,65,68,93,105,108–111] or may be evident as visual inattention or neglect,[1,5,10,14,26,112,113] or reduced blink response to menace.[114] Alternatively, the field disturbance may develop during the course of the illness.[2,13,32,66,94,115–118] Other types of visual field disturbance are rare, and include bilateral central scotomata,[7] right homonymous central scotoma,[92] 'scotomata'[119] and homonymous quadrantanopia.[31,116,120]

Hemifield disturbances have occasionally been reported in dura-mater-transmitted CJD,[88,121] and as a late feature of ataxic CJD[86] and familial CJD.[42,89,122]

While other clinical features of CJD are often present in association with visual field disturbance, this is not necessarily the case. It has been suggested that the finding of a normal magnetic resonance imaging (MRI) scan in a patient who develops a homonymous hemianopia should prompt consideration of CJD.[68]

Cortical blindness

As stated above, cortical blindness as a dominant early feature of spongiform encephalopathy was first reported by Heidenhain in 1928,[22] and there have been many subsequent reports.[5,10,12,14,24,26–30,34,55,97,107,108,118,123–126]

Early studies found that the overall incidence of cortical blindness in CJD was about 13%,[7,8] but more recent studies suggest that it develops at some stage in the illness in 25–50% of cases.[2,127,128] Possible reasons for this discrepancy are that patients may deny they are blind (Anton's syndrome),[12,34,60,65,126] or may be too inconsistent to permit accurate assessment of visual fields.[68] About 9% of patients are blind at presentation.[128]

Cortical blindness has been reported as a late feature of classic sporadic CJD,[25,32,55,71,75,95,98,113,129,130] ataxic CJD,[86] 'panencephalopathic' CJD,[96] familial CJD,[104] transmitted CJD[87] and variant CJD (vCJD).[131] Interestingly, there is one report of recurrent transient cortical blindness in the early stages of the disease.[4]

Palinopsia (visual perseveration)

To our knowledge, in only one case has palinopsia been reported as a presenting complaint of CJD,[66] but illusory motion and palinopsia have previously been reported to occur occasionally in the course of the illness.[1]

Visual hallucinations

Visual illusions, hallucinations, misperceptions and delusions are well reported in the early literature,[107] and have been reported to occur in 10–50% of cases of sporadic CJD at some point in the illness.[7,13,32,50,64,127,128,132] They may occur in the early stages,[27,30,33,34,74,75,105,126,133–142] in one case up to 18 months before the rest of the illness developed,[7] but the incidence of hallucinations at presentation is generally reported to be low, of the order of 1%.[8,128] They occur more frequently during the course of the disease, and are not specific to the Heidenhain variant.[2,5,10,12,43,55,65,71,98,113,143–149] They are also common in vCJD, occurring in 57% of cases,[150,151] and have been reported in other types of sporadic CJD, including ataxic[86] and 'panencephalopathic'[76] types.

Hallucinations have been reported in CJD transmitted by dura mater[81,88,152–154] and hGH.[155] They occur occasionally as a late feature in families with CJD[102,104,156,157] and GSS.[10,158] Complex hallucinations and enacted dreams are reported in the more advanced stages of fatal familial insomnia (FFI),[159–161] sporadic fatal insomnia (SFI)[157] and familial CJD with insomnia.[162]

The hallucinations themselves are variable, but frequently involve people or animals who are often disfigured, diseased or deformed. They are often frightening, but this is not always the case. The precise pathogenesis of the hallucinations is currently unknown.

Symptom elaboration (functional visual loss)

One case report specifically suggested symptom elaboration,[68] but this is difficult to interpret in the light of a concurrent dementing process.

Ocular motor symptoms/signs

'Oculomotor disturbances' have been reported to occur at some point in 20–30% of patients with sporadic CJD,[17,50,128] 36% with familial CJD[128] and 56% with iatrogenic CJD.[128] As with visual disturbance, many reports use terms which do not allow further comment, such as 'difficulty with conjugate eye movements',[124] 'erratic eye movements',[163] 'fluttering ocular movements',[63] or 'ophthalmoplegia'.[164]

Diplopia

Diplopia is a commonly reported symptom in CJD,[2,14,26,51,55,67,71,107,165] often seen as an early feature.[1,10,60,133,166–168] The diplopia is usually horizontal, but can be vertical, and may be intermittent[68,77,169–171] or of abrupt onset.[62] It is particularly common in cases transmitted by hGH[19,164,172–176] and hPG,[171] occurring in up to 53% of hGH cases,[19,173] but it can also occur in sporadic CJD,[33,64,137] familial CJD,[177] ataxic CJD,[86,169] panencephalopathic CJD[76,77] and CJD due to cadaveric dura mater graft[81] and, in one case, following liver transplantation.[178] It is reported to occur in GSS[57] and FFI[179] and as an early feature of kuru.[180]

Oscillopsia

Oscillopsia is reported extremely rarely and, to our knowledge, only three case reports refer to it.[67,82,171]

Supranuclear palsies

Disturbance of vertical gaze appears to be the commonest ocular motor abnormality described in sporadic CJD, occurring in some 3–5% of cases,[2,64,181] though it was not mentioned in several early series.[4,14,15,29,76,107,182,183] This can take the form of limitation of upgaze,[1,60,94,109,117,134,135,146,165,168,170,184–187] a clear supranuclear gaze palsy,[95,188] a skew deviation[189] or total limitation of vertical gaze.[67]

Loss of upward gaze has been described in CJD transmitted by hGH[174,190,191] and cadaveric dura mater graft,[81,192] but one of the latter cases had previously had an Arnold–Chiari malformation, and possibly also suffered a brainstem infarct.[81] Fifty per cent of patients with (new) vCJD develop upgaze paresis at some point in their illness,[131] and vertical eye movement paralysis has been described in the panencephalopathic type at presentation.[77] A prominent supranuclear gaze palsy has also been described in some families with CJD,[156,186,193] but this has not been reported in many others.[194,195]

Loss of upward gaze occurs as a late feature in GSS[10,57,85,196–198] and may progress to complete vertical gaze palsy.[199]

Horizontal eye movements can be affected in a number of different ways, ranging from 'poor conjugate gaze',[21,81] slowing of eye movements,[188] through oculomotor apraxia,[100,105,188] periodic alternation of gaze[67,156,189] to tonic eye (and head) deviations[43,60,74,110,130,200,201] and complete ophthalmoparesis.[176,188]

Histological studies have suggested that saccadic involvement may be due to involvement of burst neurons in the paramedian pontine reticular formation,[67] and the cases of skew deviation[189] showed pathology in the pretectal region, an area previously reported to be involved in patients with alternating skew deviation.[202] Otherwise, little is known about the precise pathogenesis of these disorders.

Infranuclear/internuclear palsies

Despite the fact that diplopia is a frequent symptom of CJD (see above), ocular motor nerve palsies are rarely reported.[94,156] In some cases, the diplopia may be of central origin, as has been suggested for other diseases affecting visual cortex.[203] Third,[2] fourth[67] and sixth[1,10,115,134,174,204] nerve palsies are occasionally reported, but some of these may have other explanations, such as Wernicke's encephalopathy.[134]

Internuclear ophthalmoplegia is present in as many as 68% of cases of hGH-transmitted CJD.[19] A 'convergent strabismus' is common in kuru, particularly in the late stages.[10,205,206]

Nystagmus

Both horizontal and vertical gaze-evoked nystagmus occur commonly in those patients with the ataxic form of CJD,[86,170,207,208] and there may be a torsional component in addition.[24,169] Consequently, it is not surprising that nystagmus is commonly reported in iatrogenic CJD, particularly those cases due to hGH (up to 50% cases)[19,79,128,172,190,209–215] and hPG[171,216] and, in one case, following liver transplantation.[178] There are two reports in cases involving dura mater,[81,217] but one of these had had a previous Arnold–Chiari malformation with nystagmus and possibly an ischaemic brainstem lesion as well.[81]

Gaze-evoked nystagmus (both horizontal and vertical) is a common feature of GSS[10,57,85,196–199,218,219] and familial CJD[119,156] but, curiously, is an unusual and inconspicuous feature of kuru.[205,206] It is frequently reported in sporadic CJD.[14,21,24,25,33,46,55,60,64,71,72,107,116,123,124,134,135,141,148,165,166,168,184,201,204,220–222] One study suggests that it can be seen in 20% of patients with sporadic disease at some time during the course of their illness.[128]

Unusual types of nystagmus have occasionally been reported in association with CJD, in particular gaze-holding deficits and shifts of the null region manifesting as periodic alternating nystagmus,[67] rebound nystagmus[67] (also noted in GSS[198]) or centripetal nystagmus[223] (though this case was not biopsy-proven). In line with this, there are also rare reports of periodic alternation of head posture.[67,189] Other unusual types of nystagmus include 'rotary' nystagmus[224] and 'aural adaptation nystagmus'.[115]

Ocular dipping

One case of CJD demonstrated ocular dipping.[225] To our knowledge, this has not been reported elsewhere.

Saccadic abnormalities

As stated above, internuclear ophthalmoplegia has been described in 68% of cases with hGH-associated CJD.[19] Apart from this, reports of specific saccadic abnormalities in CJD are rare. Saccadic dysmetria[67,100,226]

and slowing[67,189] are occasionally described, and poor initiation of saccades has been described in one case of hGH-transmitted CJD.[191] It is of interest that there was no evidence of damage to any of the brainstem structures known to be involved in generating saccades in the one case in which this was specifically sought.[189] An increase in square wave jerks (consistent with cerebellar disease) has been described in GSS,[198,199] along with hypometric voluntary saccades.[198]

'Rapid conjugate eye movements', presumably intrusive saccades, have also been noted to occur synchronously with myoclonic jerks.[14,54] and ocular flutter has been clearly described in one patient with CJD.[227]

Impaired smooth pursuit

Impairment of smooth pursuit occurs as a feature of GSS[95,199,228] and kuru.[180] Reports in CJD are rare, and variously described as 'cogwheel eye movements',[70] 'jerky pursuit movements',[119] 'impairment of smooth pursuit',[67,229] 'slowing of pursuit' (vCJD)[163] and 'saccadic pursuit'.[165,230]

Impaired optokinetic nystagmus (OKN)

OKN has been reported to be diminished or absent bilaterally in most patients with kuru, even at an early stage,[180] but there is little mention of it in case reports of CJD. Grant *et al.*[67] describe one case with impaired OKN, and impairment appears to occur as a late manifestation of GSS.[10,198,199,228]

Failure of convergence

Impaired convergence has been reported as an infrequent occurrence in two families with CJD[119,156] and it is also described in GSS.[57,196] Neetens & Martin[181] mention that it occurs, but give no further details.

Abnormal vestibulo-ocular reflex (VOR)

Very few studies mention VOR. Silberman *et al.*[24] and Khurana and Garcia[135] describe patients with tonic deviation of eyes in response to cold caloric stimulation, and Yokota *et al.*[189] state that three patients had 'abnormal calorics', though only one case was autopsy-proven. Grant *et al.*[67] describe a hyperactive VOR in one biopsy-proven case, and Schwaninger *et al.*[231] describe a patient in whom fixation did not suppress the oculocephalic reflex.

Other neuro-ophthalmic features

Fundus abnormalities

If they are mentioned, optic fundi are usually reported as normal,[22,23,27,29,59,68,72,123,134,167,194,224,227,232–235] though most studies do not comment (presumably because they were thought to be normal). However, a number of abnormalities have very occasionally been described. Of these, the most common is optic disc pallor,[35,57,81,82,119,191] though in some cases there is a possible alternative explanation such as previous removal of a cerebellar astrocytoma[82] or craniopharyngioma.[191] One case report was entitled 'Creutzfeldt–Jakob disease and optic atrophy',[70] but, in fact, the optic atrophy was only detectable histologically. No optic disc pallor was detected clinically. Papilloedema has occasionally been described[207,236] but, again, there is often an alternative explanation such as a recently-removed meningioma.[236] One case report describes a macular star, but the cause of this is obscure.[190]

Histological studies on the retina in CJD have sometimes shown spongiform changes in the nerve fibre layer, with loss of ganglion and bipolar cells, but few changes in the photoreceptors.[40,70,98,235] Other reports do not show any abnormality.[167] Reports in the animal literature describe retinal abnormalities, including some abnormalities of the photoreceptors.[237–242] In man, both histologically normal[134] and abnormal[40,70,167,243] optic nerves have occasionally been reported.

The fundi in kuru have been reported to be normal.[206] In general, therefore, ocular signs are not detectable in human TSEs.

Eyelid abnormalities

Various abnormalities of eyelid function have occasionally been mentioned in CJD, including ptosis,[1,14,165,181,244] blepharospasm, blepharoclonus and resistance to eyelid opening,[7,162,165,187] lid retraction[30,156] and apraxia of eyelid closure[188] (also reported in GSS[228]). Reduced blink rate has been reported in CJD[156] and GSS,[198,199] but one report found increased blink rate.[226] Slight ptosis has been reported in kuru.[206] Our clinical impression is that lid retraction is quite common, and is often quite striking, giving patients a very frightened appearance whether they are actually frightened or not.

Pupillary abnormalities

There are no consistent pupillary abnormalities in CJD. Some studies report anisocoria,[107,226] others report slowly reacting pupils[35,119,156,189,221] (in two cases with Horner's syndrome[135,226]), mydriasis[1,119,181] or even unreactive pupils.[65,98] However, other studies report normal pupils,[22,28–30,59,98,109,123,133,167,224,227,234] including patients whose acuities are down to perception of light only, presumably due to cortical blindness.[24,70,78]

In patients with FFI (in whom autonomic disturbance is a major feature), pupils may be small and unreactive at presentation, and in these patients there is evidence of parasympathetic hyperactivity rather than sympathetic underactivity.[179] Pupils have been reported as normal as kuru.[206]

Miscellaneous

Decreased lacrimination was noted in two patients[135] but we are not aware of other reports.

In view of the fact that the disease can be transmitted by corneal transplantation (see above), the cornea has been looked at histologically in one case, and found to show marked epithelial changes (thinning with cellular disorganisation), but these probably related to the terminal state of the patient; there were no other changes in the cornea.[134] Nevertheless, it is important to point out that normal histology does not exclude the presence of abnormal prion protein. In future, histochemical techniques may be useful clinically to determine its presence or absence, but this technology is not yet available.

Conclusions

Ophthalmic and neuro-ophthalmic features are common in human TSEs. Some 10% of patients with CJD may present with prominent visual disturbance (the Heidenhain variant), but at least 50% are troubled by disturbed vision, or hallucinations, at some point during their illness. Many different ocular motor features have been described, but most of these occur only rarely. The common manifestations are supranuclear gaze disturbance (particularly upgaze palsy) and nystagmus.

It is well reported that patients with CJD may present initially to an ophthalmologist or an optician. Though the condition is rare, it is important to be familiar with it because of the potential risks of transmitting it inadvertently, particularly by means of ophthalmic surgery. Though by no means certain, it is possible that there may be many more cases of the recently described vCJD which will compound this problem. Greater awareness of the issues involved could be extremely important in preventing spread of this disease, and it is hoped that this article and its companion[3] go some way to explaining the issues involved.

Appendix. List of abbreviations used

CJD	Creutzfeldt-Jakob disease
EEG	Electroencephalogram/electroencephalography
FFI	Fatal familial insomnia
GSS	Gerstmann-Sträussler-Scheinker disease
hGH	Human growth hormone
hPG	Human pituitary gonadotrophin
MRI	Magnetic resonance imaging
OKN	Optokinetic nystagmus
SFI	Sporadic fatal insomnia
TSE	Transmissible spongiform encephalopathy
vCJD	(new) Variant Creutzfeldt-Jakob disease
VOR	Vestibulo-ocular response

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