Takao et al. Acta Neuropathologica Communications (2018) 6:78
https://doi.org/10.1186/s40478-018-0582-5

Acta Neuropathologica Communications

LETTER TO THE EDITOR Open Access

PrP^{res} deposition in the retina is a common finding of sporadic, familial and iatrogenic Creutzfeldt-Jakob diseases (CJD)

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Keywords: Prion, Creutzfeldt-Jakob disease, Retina, Immunohistochemistry

Text

Creutzfeldt-Jakob disease (CJD) is clinically characterized by progressive dementia and neuropathologically characterized by deposits of a protease-resistant isoform of the prion protein (PrP^{res}) in the central nervous system. PrP^{res} deposits in the neural retina were identified in the outer and inner plexiform layers (OPL and IPL) in a limited number of sporadic Creutzfeldt-Jakob diseases (sCJD) and two variant CJDs [1, 2]. However, the presence of PrP^{res} in the neural retina remains unknown in other types of CJDs. Therefore, we analyzed 16 prion cases from our brain bank, including sporadic, familial, and iatrogenic CJDs by using retinal sections [3].

At the time of autopsy, full permission was obtained from each patient's next-of-kin. The posterior portion of the eye ball was removed with a scalpel, leaving the cornea and lens for funereal purposes. The following cases were available: nine cases of sCJD (MM1), two cases of sCJD (MM1 + 2, MM1 > 2), one case of sCJD (MM2), three cases of familial CJD (fCJD) (two of V180I and one of M232R), and one case of iatrogenic CJD (cadaveric dura mater graft, dCJD). We classified sCJDs based on the Parchi's methodology [4, 5]. We also used four autopsy-confirmed neurological cases as controls (Table 1). For immunohistochemical studies to detect PrP^{res}, formalin-fixed and formic acid-treated sections of the retina were immunolabeled with monoclonal antibodies specific to prion proteins 3F4 (109–112) (1:200, Biolegend, USA) and 12F10 (142–160) (1200, Bertin Bioreagent, France). The retinal sections were processed by using a Ventana Discovery automated immunostainer. Evaluations of 3F4 and 12F10-immunoreactive deposits (PrP^{res}-irs) of the outer and inner plexiform layers were performed by using both antibodies in a semi-quantitative manner: 0 = none, 1 = positive and scattered, 2 = positive (Table 1). PrP^{res}-irs staining was weak or focal in the outer and inner nuclear layers (ONL and INL), as well as in the ganglion cell and nerve fiber layers (GCL and NFL); thus, we calculated the frequency of cases with PrP^{res}-irs staining, separated on the basis of each anatomical region of the neural retina.

In all CJD cases, 3F4 and 12F10-irs were consistently and clearly observed in the OPL and IPL of the neural retina (Fig. 1a). In our series, 12F10-irs staining was stronger than 3F4-irs. PrP^{res}-irs staining exhibited granular and fine synaptic patterns in the OPL and IPL, respectively. Although PrP^{res}-irs staining was always present in both OPL and IPL, PrP^{res}-irs staining was stronger in sCJD (MM2), fCJD, and dCJD cases than in sCJD (MM1) cases (Fig. 1a).

In some instances, fine-dot PrP^{res}-irs staining was observed in the INL, ONL, GCL and NFL. More consistent findings were observed in sCJD (MM2), fCJD, and dCJD cases (Fig. 1b). No PrP^{res}-irs staining was present in the photoreceptor cell layer. In addition, there was no amyloid-beta (4G8), p-tau (AT8), p-synuclein, or TDP-43-irs staining in the retina. No PrP^{res}-irs staining was observed in retinas from control cases. There was no clear PrP^{res}-irs staining in the optic nerves.

Clinical characteristics, such as age at onset, duration, gender, and initial presentation were not associated with the presence or absence of PrP^{res}-irs in the retina. Our methodology analyzing the posterior portion of the eye

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Table 1 PrP immunoreactivity of the retina in 16 cases of Creutzfeldt- Jakob disease (CJD)

Case number	AAD (y)	Duration (months)	Sex	Initial symptom	Diagnosis	Codon 129	Western blot analysis of PrP^{res}	OPL		IPL	
								3F4-irs	12F10-irs	3F4-irs	12F10-irs
Case 1	72	18	F	visual acuity, color agnosia	sCJD	MM	Type 1	1	2	2	2
Case 2	67	51	F	amnesia	sCJD	MM	Type 1	1	2	1	2
Case 3	75	17	F	palilalia	sCJD	MM	Type 1	2	1	2	1
Case 4	74	6	M	metamorphopsia	sCJD	MM	Type 1	1	1	0	1
Case 5	73	2	M	amnesia	sCJD	MM	Type 1	2	2	2	2
Case 6	82	5	F	sensory disturbance	sCJD	MM	Type 1	1	2	1	2
Case 7	62	42	M	loss of motivation	sCJD	MM	Type 1	1	2	1	2
Case 8	68	8	M	visuospatial disturbance	sCJD	MM	Type 1	2	2	2	2
Case 9	85	7	F	communication disturbance	sCJD	MM	Type 1	2	2	2	2
Case 10	67	30	M	amnesia	sCJD	MM	Type 2	1	2	1	2
Case 11	62	10	F	dizziness, ataxia	sCJD	MM	Type 1 + 2	2	2	2	2
Case 12	72	21	F	visual hallucination	sCJD	MM	Type 1 > 2	2	2	2	2
Case 13	94	90	F	hearing disturbance	V180I	MV	Type 2 equivalence	2	2	2	2
Case 14	93	46	F	communication disturbance	V180I	MM	Type 2 equivalence	2	2	2	2
Case 15	70	19	M	dementia	M232R	MM	Type 1 equivalence	2	2	2	2
Case 16	74	7	M	dementia	dCJD	MM	Type 1 equivalence	2	2	2	2
Control 1	95		F		AD+DLB			0	0	0	0
Control 2	69		M		ALS			0	0	0	0
Control 3	53		F		ALS			0	0	0	0
Control 4	61		M		MSA			0	0	0	0

Typing of prion protein was performed on the basis of biochemical analysis of the frontal cortex. Diagnosis was performed on the basis of neuropathology and molecular biology analyses

Semi-quantification: 0 = none, 1 = positive and scattered staining, 2 = positive and consistent staining in both outer and inner plexiform layers

Abbreviations: AAD age at death, *M* male, *F* female, *sCJD* sporadic CJD, *dCJD* cadaveric dura matter graft CJD, *AD* Alzheimer's disease, *DLB* dementia with Lewy body disease, *ALS* amyotrophic lateral sclerosis, *MSA* multiple system atrophy, *MM* methionine/ methionine, *VV* valine/valine, *–irs* -immunoreactive deposits

ball accurately reflected the pathologic condition of the neural retina in prion diseases. Indeed, a previous study showed that PrP^{res}-irs were not prominent in the anterior portion of the neural retina [2].

Our study is the first to describe PrP^{res}-irs within the retina in a series of cases of sCJD (MM1), sCJD (MM2, MM1 + 2), fCJD, and dCJD. Although we did not quantitatively evaluate the amount of PrP^{res} in each case, PrP^{res}-irs in the OPL and IPL may be more prominent in fCJD and dCJD cases. In addition, PrP^{res}-irs were occasionally observed within layers of neural retina other than the OPL and IPL.

Protease-sensitive normal cellular PrP was identified in the neural retina of healthy controls [1]. Because no 3F4-irs and 12F10-irs were present in control cases, we suspect that 3F4-irs and 12F10-irs in the retina of the present cases reflect PrP^{res} accumulation. Head et al. performed a detailed analysis of PrP^{res} in the neural retina [1, 2]; they found that PrP^{res}-irs were present in the OPL (granular pattern) and IPL (synaptic pattern) in one case of sCJD (MM1) and two cases of variant CJD. PrP^{res} was reported as less detectable in the neural retina of sCJD (MM1) [2]. Another study reported the presence of PrP^{res} in the neural retina in vCJD, but not in sCJD, by Western blotting analysis [6]. In Gerstmann–Sträussler–Scheinker disease (F198S), PrP deposits were found in the inner portion of the OPL [7]. We suspect that the type of prion disease is associated with the pattern and severity of PrP^{res}-irs in the neural retina. There was no clear association between the clinical duration and PrP^{res}-irs in the neural retina.

The present study has some limitations. The sample sizes were small, except for cases of sCJD (MM1). This study was able to describe PrP^{res} staining in the OPL and IPL; thus, PrP^{res} must be analyzed in other layers of the retina with another methodology, such as laser micro-dissection or biochemical analysis, because PrP^{res}-irs staining in other layers was very weak. In the future, specific eye examinations may become a potential biomarker for the clinical diagnosis of prion diseases, similar to potential clinical diagnosis of AD by detection of amyloid-beta deposits in the retina [8]. In terms of infection protection, we need to understand PrP^{res} accumulation in the neural retina is common findings even in atypical clinical form of sCJD (MM2, MM1 + 2) as well as fCJD and dCJD.

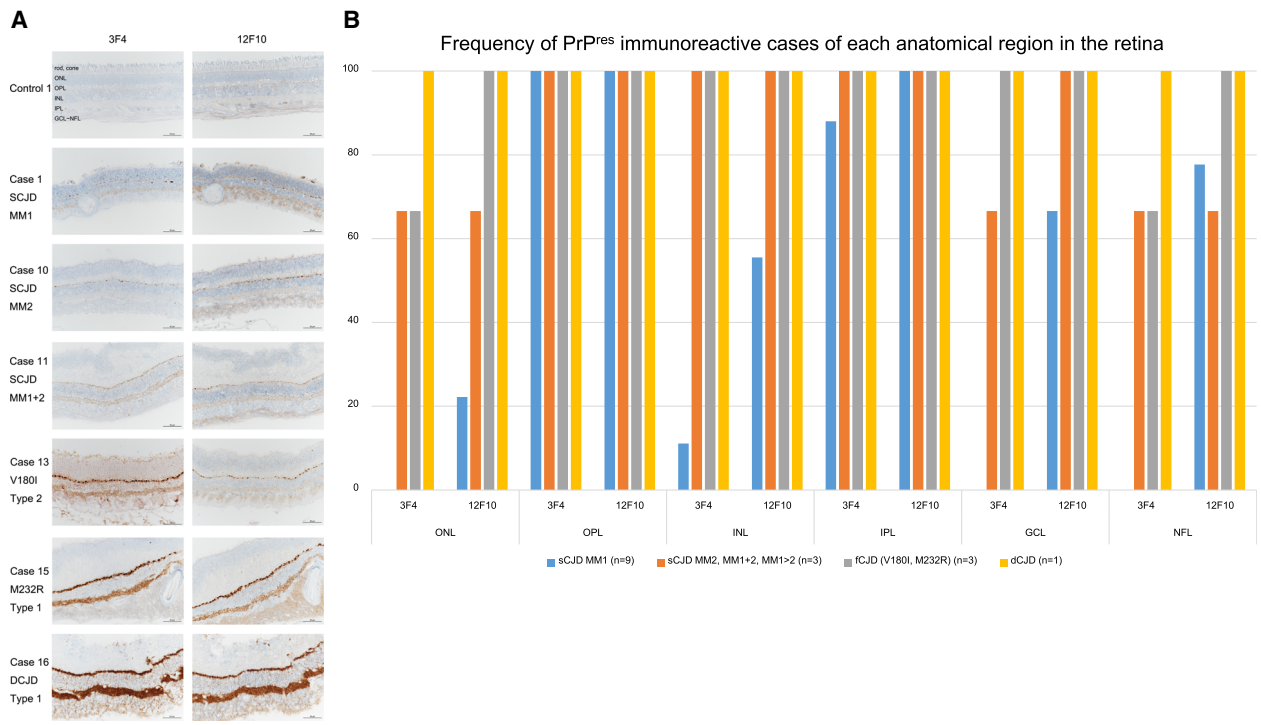

Fig. 1 a. Representative images of PrP immunohistochemistry of retinas in Creutzfeldt-Jakob disease. 3F4 and 12F10 immunoreactive deposits are present in the OPL and IPL. 12F10 immunoreactive deposits stain more strongly than those of 3F4. In particular, cases of MM2, MM1 + 2, V180I, M232R, and dCJD show 3F4 and 12F10 immunoreactive fine deposits in the INL, ONL, GCL, and NFL. B. 3F4 and 12F10 immunoreactive deposits are consistently observed in the OPL and IPL. ONL: outer nuclear layers, OPL: outer plexiform layer, INL: inner nuclear layer, IPL: inner plexiform layer, GCL: ganglion cell layer, NFL: nerve fiber layer. **b**. Frequency of PrP immunoreactivity of each anatomical region in the retina. Fine-dot PrPres-irs staining was occasionally observed in the INL, ONL, and NFL. Staining was more consistent in cases of MM2, fCJD, and dCJD

Abbreviations

CJD: Creutzfeldt-Jakob disease; dCJD: Cadaveric dura matter graft Creutzfeldt-Jakob disease; fCJD: Familial Creutzfeldt-Jakob disease; GCL: Ganglion cell layer; INL: Inner nuclear layer; IPL: Inner plexiform layer; -irs: -Immunoreactive deposits; NFL: Nerve fiber layer; ONL: Outer nuclear layer; OPL: Outer plexiform layer; PrP: Prion protein; PrP^{res}: Protease-resistant isoform of the prion protein; sCJD: Sporadic Creutzfeldt-Jakob disease

Acknowledgements

We are deeply grateful to all the study individuals and their relatives. We thank Mitsutoshi Tano and Shoken Aizawa for technical support. We thank Ryan Chastain-Gross, Ph.D., from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript. This study was supported in part by JSPS KAKENHI Grant Number 18 K06506, 16H06277, and Research Committee of Prion Disease and Slow Virus Infection, Research on Policy Planning and Evaluation for Rare and Intractable Diseases, Health and Labour Sciences Research Grants, The Ministry of Health, Labour and Welfare, Japan.

Funding

This study was supported in part by JSPS KAKENHI Grant Number 18 K06506, 16H06277, and Research Committee of Prion Disease and Slow Virus Infection, Research on Policy Planning and Evaluation for Rare and Intractable Diseases, Health and Labour Sciences Research Grants, The Ministry of Health, Labour and Welfare, Japan.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

MT: conceptualization, methodology, autopsy, investigation (neuropathological analysis), and writing of the manuscript; HK and BM: conceptualization of clinical study; TK: Genetic and biochemical analysis. All authors read and approved the final maniscript.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the intuitional review board of Mihara Memorial Hospital (084–02). We obtained written informed consent from the deceased relatives for autopsy and further neuropathological analysis, and all subjects were registered with our brain bank for future research. The brain bank was approved by the Ethics Committee of Mihara Memorial Hospital for neuropathological analysis (072–01, 078–01, 085–01).

Consent for publication

We obtained written informed consent from the deceased relatives for publication.

Competing interests

The authors declare that they have no competing interests.

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Received: 4 August 2018 Accepted: 5 August 2018
Published online: 10 August 2018

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