Acta Neuropathol (1999) 98 : 458–460

SHORT ORIGINAL COMMUNICATION

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Disease associated prion protein may deposit in the peripheral nervous system in human transmissible spongiform encephalopathies

Received: 5 May 1999 / Revised, accepted: 5 July 1999

Abstract There is increasing evidence indicating involvement of the peripheral nervous system (PNS) in the pathogenesis of transmissible spongiform encephalopathies (TSEs). Immunocytochemically detectable deposits of TSE-specific abnormal prion protein (PrP^{sc}) are considered as a surrogate marker for infectivity. We used anti-PrP immunocytochemistry to trace PrP^{sc} deposition in spinal and enteric ganglia, and peripheral nerve in Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker disease (GSS), and fatal familial insomnia. Discrete PrP^{sc} deposits were detectable only in a few posterior root nerve fibers in an adaxonal location in one of nine CJD and the one GSS patients examined. Follicular dendritic cells of the gut and enteric nervous system were not labeled. Thus, PrP^{sc} may spread to the PNS in different forms of human prion disease. In contrast to our observations in experimental scrapie (Groschup et al., Acta Neuropathol, this issue), the deposits were scant. Possible explanations for this discrepancy comprise strain difference, or centripetal (experimental scrapie) versus centrifugal (sporadic and genetic human prion diseases) spread of PrP^{sc}, resulting in different patterns and amounts of PrP^{sc} accumulation in the PNS.

Key words Creutzfeldt-Jakob disease · Gerstmann-Sträussler-Scheinker disease · Prion protein · Peripheral nervous system · Immunocytochemistry

Introduction

Recent bioassays have revealed presence of infectivity in the peripheral nervous system (PNS) in experimental bovine spongiform encephalopathy [6]. These observations led to public concern culminating in the British beef-on-the-bone ban. In an accompanying article on experimental scrapie [2], we identified by means of anti-prion protein (PrP) immunocytochemistry prominent pathological PrP (PrP^{sc}), which is a surrogate marker for infectivity, in peripheral ganglia. In nerve fibers adjacent to ganglia, scant PrP^{sc} deposits were detectable in an adaxonal location [2]. In Creutzfeldt-Jakob disease (CJD), PrP immunolabeling of satellite cells and neurons of trigeminal ganglia has been described [3]. We report here the results of anti-PrP immunostaining of spinal and enteric ganglia, and peripheral nerve in CJD, Gerstmann-Sträussler-Scheinker disease (GSS), fatal familial insomnia (FFI) and control patients (Table 1).

Materials and methods

For nine CJD and one GSS patients, nerve roots and ganglia with spinal cords were sampled from archived, formalin-immersed tissues, and routinely processed for histology. Other tissues included peripheral nerve and intestinal ganglia from CJD case no. 1, paraffin-embedded caecum or colon from two further CJD patients, and appendix from one FFI patient. Time of fixation in formalin ranged between 2 weeks and 26 years. Family history indicates a genetic prion disease in only one CJD patient (case 11 in Table 1), although *PRNP* genotyping on paraffin-embedded brain tissue of this patient has not been successful. Pathogenic *PRNP* mutations were excluded, however, in the patient's son. Immunocytochemistry for PrP^{sc} was performed on all tissue samples using the monoclonal antibodies 3F4, 6H4, and L42 [2].

Results and discussion

All three antibodies detected variable amounts of PrP^{sc} in the spinal cords of seven of nine CJD patients (Fig. 1), as previously described by others [1], and the GSS case. Spinal ganglia of our patients did not show the characteristic dot-like immunoreactivity of neuronal and satellite cells, as observed in experimental scrapie [2]. However, discrete PrP^{sc} deposits were detectable with the 3F4 and L42 antibodies in an adaxonal location in few nerve fibers of the posterior roots of one CJD and the GSS patients

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Table 1 Details of investigated patients and controls (*ALS* amyotrophic lateral sclerosis, *CJD* Creutzfeldt-Jakob disease, *GSS* Gerstmann-Sträussler-Scheinker disease, *FFI* fatal familial insomnia, *n.a.* not available, *n.d.* anti-PrP immunocytochemistry not done, *syn* synaptic, *pp* patchy-perivacuolar, *pl* plaque-type PrP^{sc} deposits, – no PrP^{sc}, + slight PrP^{sc} accumulation, ++ prominent PrP^{sc} accumulation)

Case no	Age (years)	Diagnosis	PrP^{sc} in:						
			Cerebrum	Cerebellum	Spinal cord	Spinal ganglia (no. examined)	Posterior roots	Anterior roots	Enteric ganglia
1	78	CJD, sporadic	syn	syn	syn, +[b]	– (1)	–	–	–
2	50	CJD, sporadic	syn	syn	syn, +[b]	– (10)	–	–	n.a.
3	77	CJD, sporadic	syn	syn	syn, +[b]	[d]	–	–	n.a.
4	63	CJD, sporadic	syn	syn	syn, +[b]	– (4)	–	–	n.a.
5	64	CJD, sporadic	syn	syn	syn, +[b]	– (2)	–	–	n.a.
6	62	CJD, sporadic	syn	syn	syn, +[b]	– (1)	–	–	n.a.
7	65	CJD, sporadic	syn	syn	–	– (1)	–	–	n.a.
8	60	CJD, sporadic	syn	syn	–	– (1)	–	–	n.a.
9	60	CJD, sporadic	syn	syn	n.a.	n.a.	n.a.	n.a.	–
10	44	CJD, sporadic	syn, pl	syn, pl	n.a.	n.a.	n.a.	n.a.	–
11	51	CJD, possibly familial	syn, pp, pl	syn, pl	syn, ++[a]	[d]	+	–	n.a.
12	40	GSS P102L	syn, pl	syn, pl	syn, +[c]	– (1)	+	–	n.a.
13	37	FFI	syn[e]	patchy[e]	n.a.	n.a.	n.a.	n.a.	–
14	68	ALS	n.d.	n.d.	–	n.a.	–	–	n.a.
15	59	ALS	n.d.	n.d.	–	n.a.	–	–	n.a.
16	77	ALS	n.d.	n.d.	–	n.a.	–	–	n.a.
17	59	ALS	n.d.	n.d.	–	n.a.	–	–	n.a.
18	77	ALS	n.d.	n.d.	–	– (1)	–	–	n.a.
19	69	Anti–Hu syndrome	n.d.	n.d.	–	– (4)	–	–	n.a.
20	34	Multiple sclerosis	n.d.	n.d.	–	n.a.	–	–	n.a.
21	62	Multiple sclerosis	n.d.	n.d.	–	n.a.	–	–	n.a.
22	46	M. Recklinghausen	n.d.	n.d.	–	– (2)	–	–	n.a.

[a] PrP^{sc} deposits all over the central gray matter, most prominent in Clarke's column
[b] PrP^{sc} restricted to substantia gelatinosa
[c] Coarse granular PrP^{sc} deposits in posterior horn, in addition to fine granular synaptic-type PrP^{sc} deposits
[d] Presence of one single neuron without PrP^{sc} positivity
[e] Restricted to one small focus

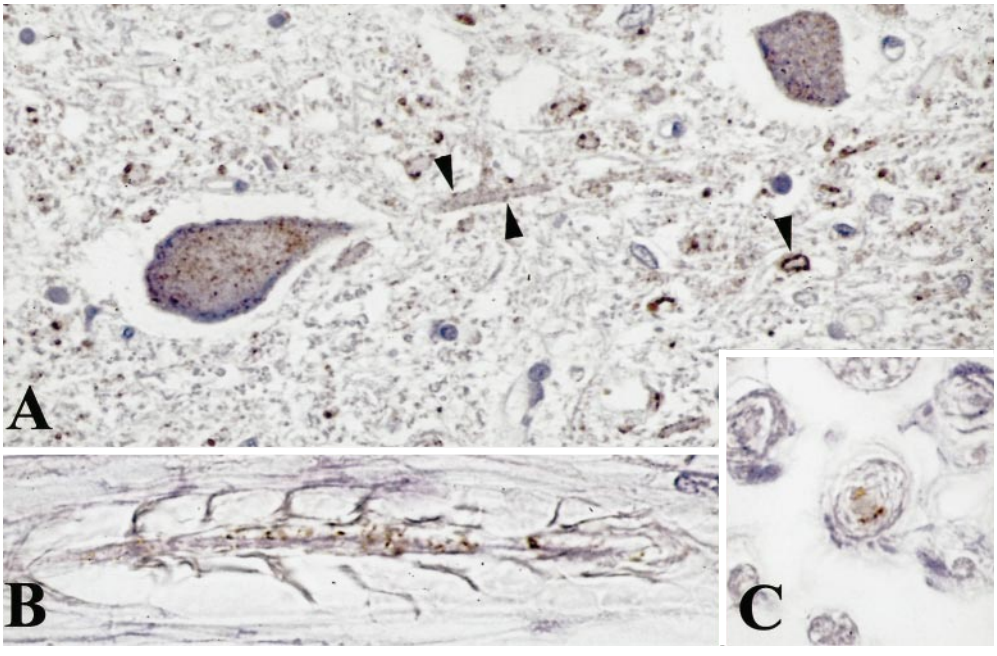

Fig. 1 Immunocytochemistry for PrP in spinal cord (**A**, Clarke's column; patient 11) and peripheral nerve fibers in Creutzfeldt Jakob disease (**B**, patient 11), and Gerstmann-Sträussler-Scheinker disease (**C**, patient 12). In Clarke's column, PrP^{sc} *(brown reaction product)* is present on neuronal and axonal surfaces (*arrowheads*, **A**). In nerve fibers of posterior roots, PrP^{sc} is detectable in an adaxonal location (**B**, **C**) (*PrP* prion protein). **A** × 570; **B**, **C** × 900

(Fig. 1). An identical deposition pattern was consistently seen in experimental scrapie [2]. None of the controls (Table 1) showed comparable deposits. In contrast to recent findings in new variant CJD [4], but in agreement with those in sporadic and familial transmissible spongiform encephalopathies [5], PrP^{sc} was not detectable in our cases in the follicular dendritic cells of the gut; in addition, the enteric nervous system was not labeled (Table 1).

We thus demonstrate that in different forms of human prion disease, PrP^{sc} may spread to the PNS. In contrast to experimental scrapie, the deposits were scant and were observed only in one of nine CJD patients and the one GSS patient in whom PrP^{sc} accumulation in the spinal cord was more prominent and widespread than in the others. A possible explanation for the discrepancy in our findings between experimental and human prion disease is strain difference or centripetal (experimental scrapie) versus centrifugal (sporadic and genetic human prion diseases) spread of PrP^{sc}, resulting in different patterns and amounts of PrP^{sc} accumulation in the PNS. In that respect, investigation of PrP^{sc} deposition in the PNS of new variant CJD could give interesting pathogenetic clues.

Acknowledgements The authors thank Ms. Elisabeth Dirnberger and Judith Ludwig for excellent technical assistance. This work was done within an EU Concerted Action of Human TSEs (Project Leader: H. Budka).

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