ELSEVIER

Journal of the Neurological Sciences 253 (2007) 69 – 72

Journal of the Neurological Sciences

www.elsevier.com/locate/jns

Short communication

Supranuclear vertical gaze abnormalities in sporadic Creutzfeldt–Jakob disease

Sashank Prasad *, Melissa W. Ko, Edward B. Lee, Nicholas K. Gonatas, Matthew B. Stern, Steven Galetta

Departments of Neurology and Pathology, Hospital of the University of Pennsylvania, United States

Received 20 September 2006; received in revised form 31 October 2006; accepted 7 November 2006
Available online 17 January 2007

Abstract

Supranuclear gaze palsies are an uncommon feature of Creutzfeldt–Jakob disease (CJD). Most reported cases of CJD with features of supranuclear gaze palsy are familial. We report 2 patients with supranuclear vertical gaze abnormalities associated with spongiform changes in the midbrain. Both patients were found to have sporadic CJD after genetic testing. Distinguishing familial from sporadic CJD in this setting has important genetic and epidemiological implications.

Keywords: Creutzfeldt–Jakob disease; Prion; Progressive supranuclear palsy; Ophthalmoplegia

1. Introduction

Supranuclear gaze palsies occasionally accompany neurodegenerative disorders, but are rarely reported in familial or sporadic Creutzfeldt–Jakob disease. More often, supranuclear vertical gaze palsy associated with slowly progressive dementia and gait unsteadiness suggests a diagnosis of progressive supranuclear palsy (PSP). We report two patients who presented with supranuclear ophthalmoparesis and gait unsteadiness as their initial manifestation of sporadic CJD.

2. Case 1

A 74 year-old salesman presented with 3 months of rapidly progressive discoordination, gait instability, and weakness. He initially noticed his deficits when his tennis game began to deteriorate. He soon required a walker for ambulation.

On examination he was alert and oriented. He correctly spelled WORLD backwards. He had good short-term memory. Language was normal. Corrected visual acuity was 20/20 bilaterally and fields were full. He had normal pupillary responses. He had a severe supranuclear upgaze palsy for saccades and pursuit. In downgaze there were slow saccades and impaired pursuit. Vertical eye movements were full for oculocephalic and Bell's maneuvers. In addition, he had a partial left horizontal gaze palsy with hypometric saccades, but otherwise full ocular rotations. There was a mild right abduction deficit which did not improve with oculocephalics. He had no nystagmus, normal facial strength and sensation, and midline tongue, uvula, and palate. Strength was 5/5 throughout, except 4+/5 right hip flexion and a slight left pronator drift. He had diffuse fasciculations, predominantly in the legs. He had diminished sensation of touch, temperature, pinprick, and vibration in the lower extremities, up to the knees bilaterally. He demonstrated slowed and dysmetric rapid alternating movements, and significant dysmetria and past-pointing on finger-to-nose testing. He was unable to perform tandem gait due to ataxia. Reflexes were ++ symmetrically in the upper extremities and 0 in the lower extremities. Plantar responses were flexor.

* Corresponding author. Department of Neurology, Hospital of the University of Pennsylvania, 3W Gates Bldg, 3600 Spruce St., Philadelphia, PA 19104, United States. Tel.: +1 215 662 2700; fax: +1 215 349 5579.
E-mail address: sashank.prasad@uphs.upenn.edu (S. Prasad).

0022-510X/$ - see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.jns.2006.11.010

Blood cell counts, serum electrolytes, and liver function tests were all normal, except a creatinine of 1.2 mg/dl. Erythrocyte sedimentation rate was 3.0 mm/h. Cerebrospinal fluid white blood cell count was 0 cells/μL, red blood cell count was 48 cells/μL, protein was 58 mg/dL, and glucose was 77 mg/dL. Gram stain and culture were negative. Cytology and flow cytometry showed no evidence of neoplasia. Paraneoplastic antibody studies were negative. CT of the chest revealed an 8 mm right lower lobe nodule and a 6 mm left lower lobe nodule, but PET scan did not show increased metabolic activity. CT of the abdomen and pelvis were normal. Nerve conduction studies and electromyography were essentially normal for age, but with fasciculation potentials in multiple leg muscles without associated denervation. Brain MRI revealed bilateral caudate nuclei and putaminal hyperintensities, which demonstrated restricted diffusion, but no significant gadolinium enhancement (Fig. 1). EEG showed decreased voltage, but no periodic epileptiform discharges. CSF 14-3-3 protein was positive.

Over the course of 3 weeks his neurological condition deteriorated. In addition to developing progressive ataxia and startle myoclonus, he developed increasing lethargy, impaired memory, and periodic visual hallucinations. He died of an aspiration pneumonia.

Post-mortem histologic examination of select brain regions demonstrated varying degrees of spongiosus ranging from minimal to severe (Table 1 and Fig. 2). Severe spongiosus was found in the midbrain, the molecular layer of the cerebellum, thalamus, striatum, and globus pallidus. There were also milder changes involving the pons, medulla, dentate nucleus, inferior olive, hypothalamus, and focally the subiculum and hippocampus. In contrast, entorhinal and neocortical regions exhibited no to minimal spongiosus. While there was evidence of gliosis in affected regions, neuronal loss was minimal.

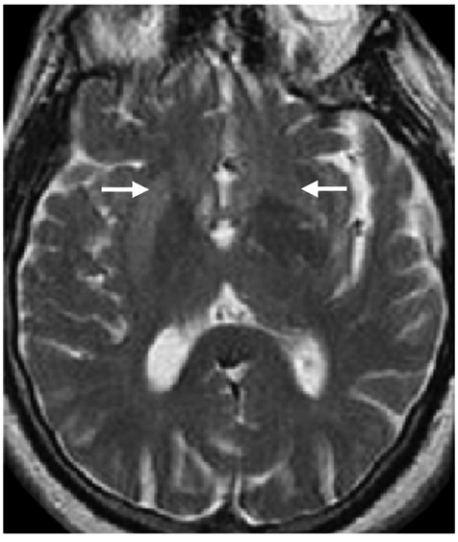

Fig. 1. T2-weighted brain MRI, patient 1. Bilateral hyperintensities of the caudate and putamen.

Table 1
Degree of spongiosus on pathologic examination, graded as none (−), minimal (+/−), mild (+), moderate (++), or severe (+++)

Area	Spongiosus		Remarks	
	Case 1	Case 2	Case 1	Case 2
Neocortex	+/−	−	Includes frontal, temporal, parietal and occipital, with focal + in parietal white matter	
Entorhinal ctx	+/−	++	Focal +++ in subiculum	+ in subiculum
Hippocampus	−	−	Focal + of the endplate/ dentate gyrus	Focal + of the endplate/dentate gyrus
Striatum	+++	+++		
Globus pallidus	+++			
Thalamus	+++			
Cerebellum	+++	+/−	+++ of molecular layer +of dentate	
Midbrain	+++	+	Diffuse involvement including the substantia nigra and periaqueductal grey	
Pons	+/++	+/−	Diffuse +, with focal ++ of locus ceruleus	
Medulla	+	−	Including inferior olive	

Several regions from Case 2 were not available for histologic analysis.

Immunohistochemical stains for prion protein using the monoclonal antibody 3F4 demonstrated the presence of granular deposits (Fig. 2, panel I). Immunoblots revealed abnormal, protease-resistant prion protein (PrP^{Sc}) (Fig. 2, panel J), commonly identified as PrP27-30, confirming the diagnosis of prion disease. Sequencing of the PrP gene excluded a pathogenic PrP gene mutation, confirming the diagnosis of sporadic CJD.

3. Case 2

A 61 year-old electric contractor presented with one year of progressively ataxic gait necessitating the use of a walker. He also had one month of binocular horizontal diplopia in all directions of gaze, and slurred speech. Medical history was significant for benign prostatic hypertrophy and mild diabetes.

On examination, he was alert and oriented. He had normal language and short-term memory. Visual acuity was 20/25 bilaterally, with normal color vision, and full visual fields. Pupillary responses were normal and discs were sharp on fundoscopy. Eyelids were retracted bilaterally. He had full ductions in both eyes, but had gaze-holding difficulties in upgaze. He had severely slowed vertical saccades, particularly for downgaze. Horizontal saccades were mildly hypometric. Rebound nystagmus and square wave jerks were present. He had impaired smooth pursuit in all directions. On Maddox rod testing he had a mild exophoria. He had mild facial masking, hypophonia, and slurred speech. Tongue, uvula, and palate were midline. Strength was 5/5 throughout, without a pronator drift. Sensation of vibration,

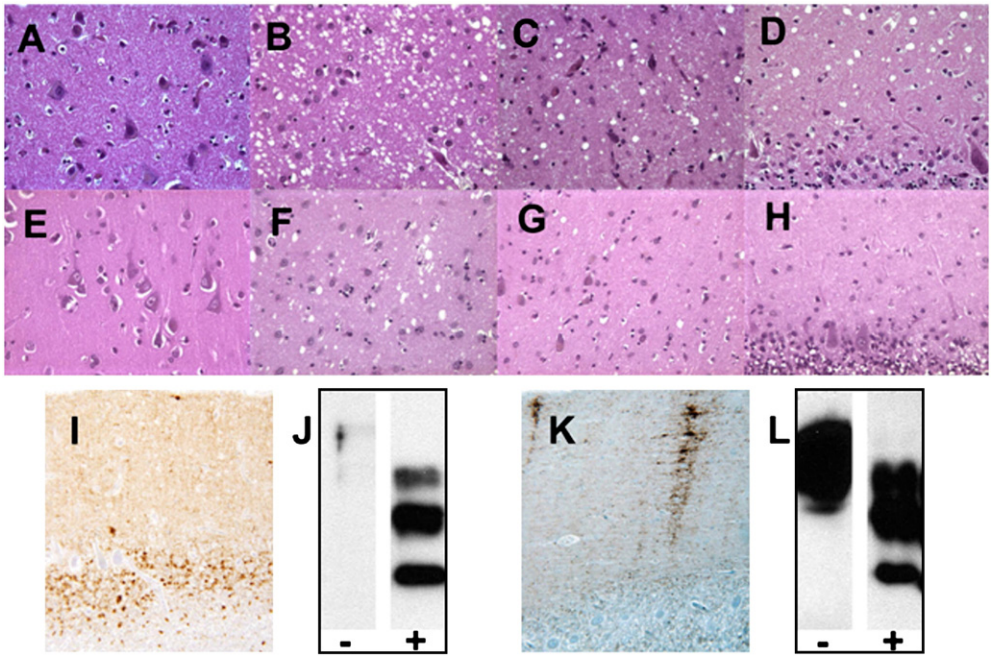

Fig. 2. Regional distribution of spongiosus. Representative images of H&E sections from case 1 (A through D) and case 2 (E though H) are shown corresponding to the neocortex (A and E), striatum (B and F), midbrain (C and G) and cerebellum (D and H). Immunohistochemical stains for prion protein deposits from the cerebellum are shown for Case 1 (I) and Case 2 (K). Biochemical analysis with (+) and without (−) proteinase K treatment of brain lysates demonstrate the presence of protease-resistant prion protein, for Case 1 (J) and Case 2 (L).

temperature, joint position, and light touch was intact throughout. On finger to nose testing he had mild slowing on the right, and normal rapid alternating movements. Reflexes were ++ symmetrically. His gait was initially characterized by marked postural instability with a slightly wide base and upright posture. After several months, his gait became more wide-based and ataxic. Plantar responses were flexor bilaterally.

CSF wbc count was 1 cell/μL, rbc count was 27 cells/μL, protein was 46 mg/dL, and glucose was 117 mg/dL. Cytology and flow cytometry revealed no atypical cells. Screen for paraneoplastic antibodies was negative, and CT scan of the chest, abdomen, and pelvis revealed no malignancy. CSF *Tropheryma whippelii* PCR was negative. Serum TSH, ANA, RF, ANCA, SSA/SSB, SPEP, vitamin E, ESR, lyme, and RPR were normal. Anti-gliadin and GQ1b autoantibodies were negative. Immunoassay for CSF 14-3-3 was weakly reactive, interpreted as an ambiguous result. MRI of the brain was normal.

His cognitive function progressively declined and he became unable to communicate. He became progressively contracted in the arms and legs. He died three months later.

Post-mortem histologic examination of select brain regions demonstrated varying degrees of spongiosus (Table 1 and Fig. 2), with severe changes in the striatum (caudate and putamen), and milder changes in the midbrain, and entorhinal cortex. Focal spongiosus was also noted in the hippocampus. The molecular layer of the cerebellum exhibited no spongiosus, although involvement of the dentate and the cerebellar white matter could not be excluded. Neocortical regions, the pons, and the medulla exhibited minimal to no spongiosus. Immunohistochemical stains for prion protein demonstrated the presence of granular deposits and immunoblots revealed PrP27-30, confirming the diagnosis of prion disease (Fig. 2, panels K and L). Sequencing of the PrP gene confirmed the diagnosis of sporadic CJD.

4. Discussion

Supranuclear vertical gaze deficits are not uncommon in neurodegenerative diseases, and can be a cardinal feature of conditions such as PSP [1]. In contrast, supranuclear vertical ophthalmoparesis is less recognized as a manifestation of prion diseases [2]. Familial Creutzfeldt–Jakob disease (CJD), due to mutations at codons 129 and 200 of the prion protein gene on chromosome 20, has been associated with a progressive supranuclear vertical gaze deficit [3,4]. However, the phenotype of PSP as a presentation of sporadic CJD appears to be rare [5,6]. A study of eye movements in one case of sporadic CJD revealed sluggish horizontal saccades, with normal pursuit and oculocephalic movements, although vertical eye movements were not specifically described [7]. We report two cases of autopsy-proven sporadic CJD which included prominent supranuclear vertical gaze abnormalities, and were felt to have phenotypic PSP early in their presentation.

Supranuclear control of vertical eye movements is subserved by diffuse cortical projections from the frontal and supplementary eye fields reaching the rostral interstitial nuclei of the medial longitudinal fasciculus (riMLF) and the

interstitial nuclei of Cajal (inC) at the level of the midbrain pretectum [8]. The riMLF contains burst neurons involved in generating vertical saccades. The inC integrates signals from the riMLF burst neurons with signals from descending pursuit and vestibular inputs. Although vertical vestibular-ocular responses are abolished by a lesion of the inC, they are spared by a lesion of the riMLF or its inputs [8]. The pathologic basis of supranuclear vertical gaze deficits in PSP is felt to be neural degeneration preferentially in the riMLF [9].

Autopsy specimens in the two cases presented demonstrated spongiotic changes in the dorsal midbrain, among other brain regions. Early involvement of the midbrain vertical gaze centers may have been responsible for the initial neuro-ophthalmalogical findings typical of PSP. Patient 2 had a prominent downgaze palsy for saccades similar to that classically observed in PSP. Patient 1 had a severe supranuclear palsy for upgaze more than downgaze, but a previous review suggests that this pattern is also a fairly consistent presentation of PSP [1]. In addition, patient 1 had a mild abduction deficit which was likely due to spongiform involvement of 6th nerve fascicle in the pons. Hyperconvergence or a thalamic esotropia were considered less likely explanations for this abduction deficit because of the lack of improvement with oculocephalic testing.

Our second patient had lid retraction in addition to ophthalmoparesis, which is also characteristic of PSP. Pretectal eyelid retraction, or Collier's sign, may be related to disruption of the nucleus or fibers of the posterior commissure [10]. A lesion here causes decreased inhibition of the levator muscles, innervated by the central caudal nucleus [8].

These cases illustrate that the differential diagnosis for supranuclear vertical gaze abnormalities in an early dementing illness should include prion disease, which has a much less favorable prognosis than PSP.

Acknowledgment

We thank the National Prion Disease Pathology Surveillance Center (Case Western Reserve University, Cleveland, Ohio) for their generous assistance.

References

[1] Friedman DI, Jankovic J, McCrary JA. Neuro-ophthalmic findings in progressive supranuclear palsy. J Clin Neuro ophthalmol 1992;12:104–9.
[2] Kirschbaum WR. Jakob–Creutzfeldt disease. New York: Elsevier; 1968.
[3] Grant MP, Cohen M, Petersen RB, Halmagyi GM, McDougall A, Tusa RJ, et al. Abnormal eye movements in Creutzfeldt–Jakob disease. Ann Neurol 1993;34(2):192–7.
[4] Bertoni JM, Brown P, Goldfarb LG, Rubenstein R, Gajdusek DC. Familial Creutzfeldt–Jakob disease (codon 200 mutation) with supranuclear palsy. JAMA 1992;268(17):2413–5.
[5] Josephs KA, Tsuboi Y, Dickson DW. Creutzfeldt–Jakob disease presenting as progressive supranuclear palsy. Eur J Neurol 2004;11:343–6.
[6] Shimamura M, Uyama E, Hirano T, Murakami T, Mita S, Kitamoto T, et al. A unique case of sporadic Creutzfeldt–Jacob disease presenting as progressive supranuclear palsy. Intern Med 2003;42(2):195–8.
[7] Zarei M, Nouraei SAR, Caine D, Hodges JR, Carpenter RHS. Neuropsychological and quantitative oculometric study of a case of sporadic Creutzfeldt–Jakob disease at predementia stage. J Neurol Neurosurg Psychiatry 2002;73:56–8.
[8] Bhidayasiri R, Plant GT, Leigh RJ. A hypothetical scheme for the brainstem control of vertical gaze. Neurology 2000;54(10):1985–93.
[9] Daniel SE, de Bruin VMS, Lees AJ. The clinical and pathological spectrum of Steele–Richardon–Olszewski syndrome (progressive supranuclear palsy): a reappraisal. Brain 1995;118:759–70.
[10] Collier J. Nuclear ophthalmoplegia with especial reference to retraction of the lids and ptosis and to lesions of the posterior commissure. Brain 1927;50:488–98.