Early Cortical and Late Striatal Diffusion Restriction on 3T MRI in a Long-Lived Sporadic Creutzfeldt–Jakob Disease Case

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To the Editor:

Sporadic Creutzfeldt–Jakob Disease (sCJD) is a potentially transmissible, fatal, neurodegenerative disorder, caused by an abnormal isoform of prion protein (PrPSc). Classic presentation is of a rapidly progressive dementia with ataxia and myoclonus, median survival of about 5 months from obvious symptom onset, an electroencephalogram (EEG) showing about 1 Hz periodic sharp wave complexes (PSWCs), and cerebrospinal fluid (CSF) with very elevated tau values. However, some patients are characterized by a much longer clinical course, and the characteristic EEG patterns and CSF profile are often negative.[1] In such cases, brain magnetic resonance imaging (MRI), which has been included in the diagnostic criteria for sCJD,[2] is even more crucial for diagnosis in early phases. Cross-sectional studies showed that cortical ribboning and striatal hyperintensity with diffusion restriction is the more common MRI presentation, even if 30% of cases can have

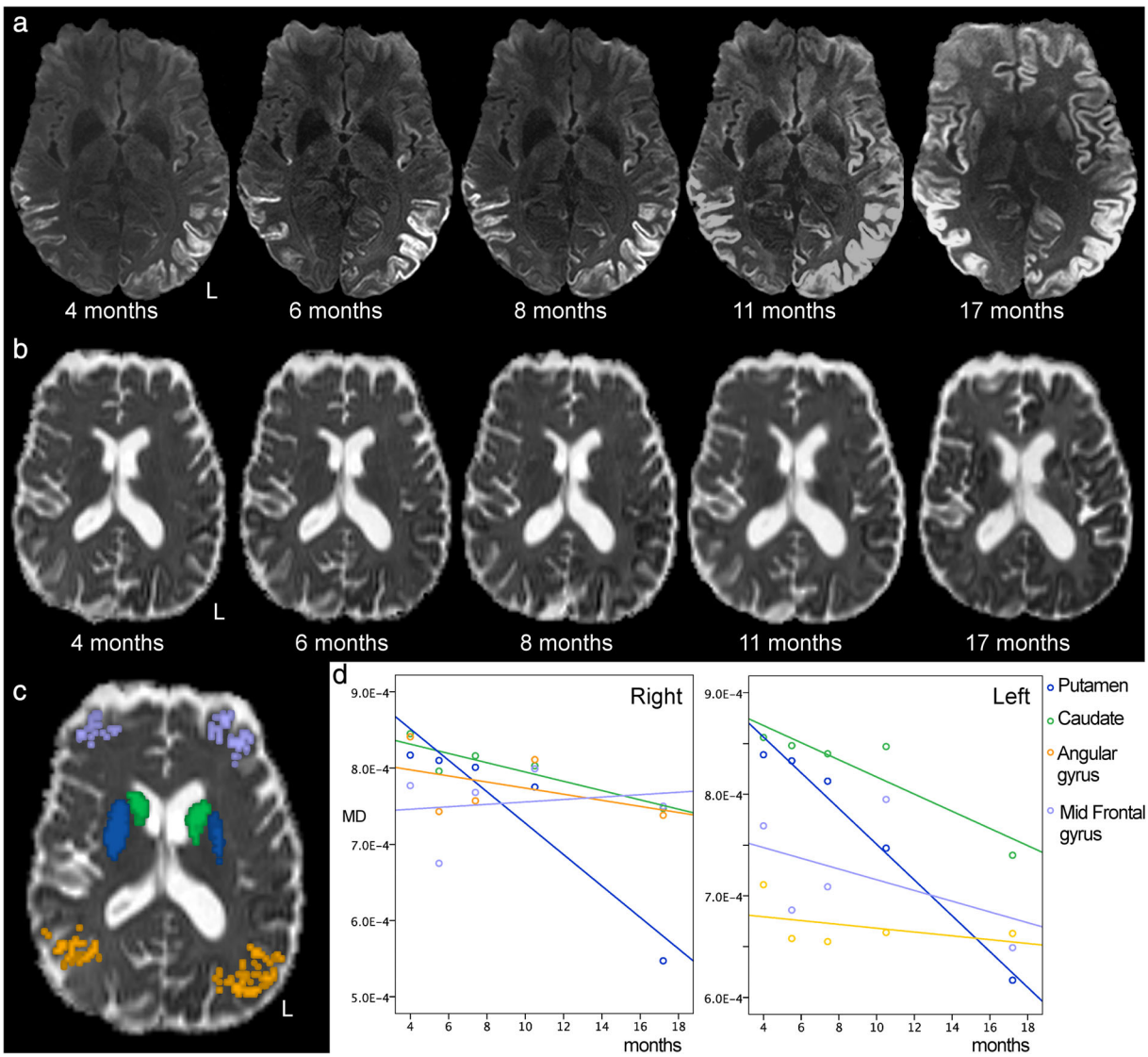

FIGURE 1: (a) DWI at 4th, 6th, 8th, 11th, and 17th months after symptom onset. Progressive striatal and frontal lobe involvement is shown. (b) MD maps from DTI acquisitions at 4th, 6th, 7th, 11th, and 17th months after symptom onset. Progressive diffusion restriction in striatum is more evident. (c) ROIs placed on putamen, pallidum, middle frontal, and parietal cortex (angular gyrus) of both hemispheres. MD time course in these ROIs confirms the dominant diffusion decrease in striatum. (d) Scatterplots of MD values across time for both left and right side ROIs.

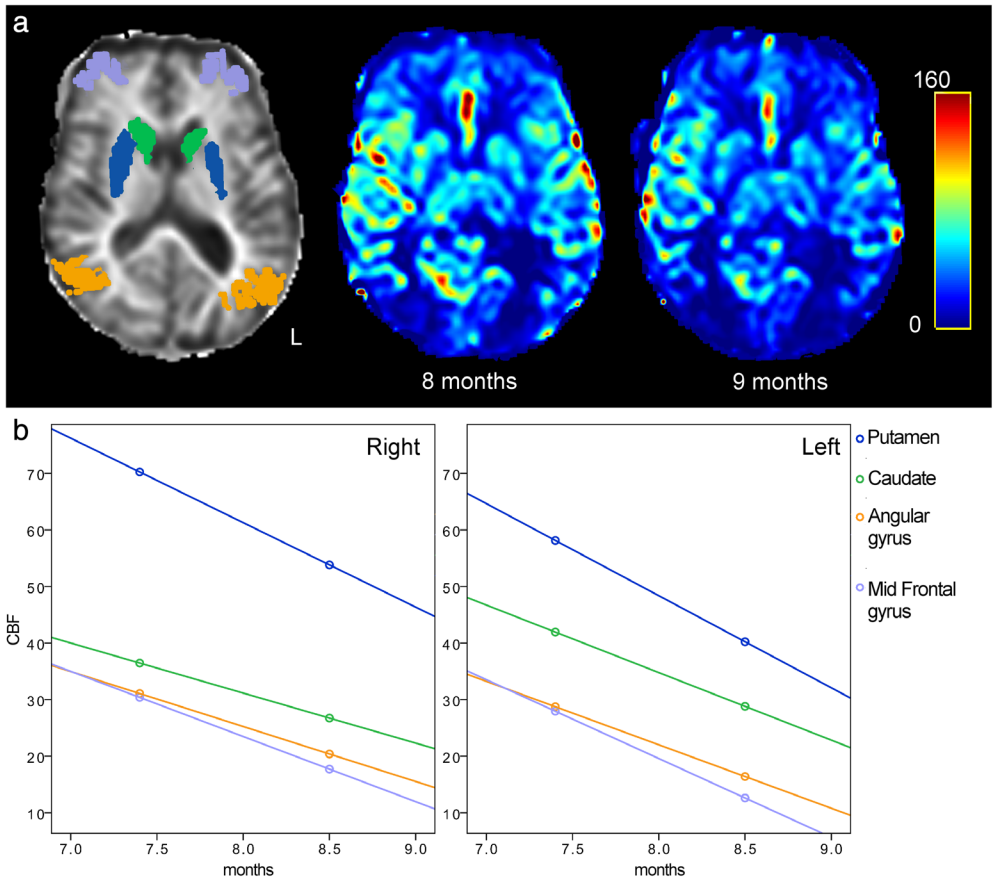

FIGURE 2: (a) ROIs placed on pseudo-T_1 map calculated in the same space of CBF map. CBF maps from ASL acquisitions at the 8th and 9th months after symptom onset. Progressive striatal and frontal lobe involvement. (b) Scatterplots of CBF values across time for both left and right side ROIs.

exclusive cortical involvement, with deep nuclei preservation.[3,4] Due to the usual rapid progressive course, a few longitudinal studies have analyzed the pattern of MRI changes in sCJD, with only two studies analyzing quantitative diffusion changes.[5,6] Here we present a unique long-lived sCJD case longitudinally studied with seven 3T MRI scans, including quantitative assessment by diffusion tensor imaging (DTI) and arterial spin labeling (ASL).

Case Report

A 79 year-old right-handed woman presented with 3 months of mild right limb ataxia, postural instability, and impairment of executive functions and memory. Over the following 9 months, she developed behavioral disturbances with rapidly progressive cognitive decline, including aphasia, apraxia, visuospatial impairment, and severe amnesia. Nine months after onset, motor impairment became severe, with unsteady gait and bradykinesia prevailing on the right side, suggestive of a corticobasal syndrome. Twelve months after onset, the patient was bedridden, with severe rigidity of limbs and trunk, myoclonus, and akinetic mutism. She died 18 months after the first symptoms, with neuropathology showing sCJD MV2K + MV2C (M = methionine, V = valine, 1 or 2 = abnormal isoforms of PrP, C = cortical form, K = form with kuru plaques). In the first two lumbar puncture assessments (performed 4 and 9 months after onset), routine CSF analysis was unremarkable, including negative 14-3-3 protein, and normal total tau; EEG showed only transient delta activity in the left hemisphere. Only 17 months after symptom onset, the 14-3-3 protein result was positive and EEG showed typical PSWCs on the right hemisphere.

Seven 3T MRI scans were acquired at 4, 6, 8, 9, 11, 13 (with sedation), and 17 (with sedation) months with a 3T Siemens Skyra scanner (Erlangen, Germany). A high-resolution 3D T_1-weighted scan (repetition time / echo time / inversion time [TR/TE/TI] = 2300/2.95/900 msec, flip angle = 9°, 176 sagittal slices, matrix = 256 × 256, voxel = 1.05 × 1.05 × 1.2 mm), a DTI spin-echo echo planar imaging (SE-EPI) sequence (TR/TE = 10,000/97 msec, 70 axial slices, matrix = 122 × 122, 2 mm isotropic voxel; 64 diffusion directions with b = 1200 s/mm^2 and 10 volumes with b_0 = 0 s/mm^2) and a 3D pulsed ASL gradient- and spin-echo (GRASE) sequence (TR/TE/TI = 3500/21.1/2020 msec, 20 axial slices, matrix = 128 × 128, voxel = 1.9 × 1.9 × 5.3 mm) were acquired. Visual assessment of diffusion weighted imaging (DWI) (Fig. 1a) revealed diffuse cortical ribboning on the first scan, with posterior and left hemispheric prominence. This pattern was stable up to 11 months, when a subtle hyperintensity of the left external putamen was observed. Typical bilateral involvement of anterior striatum[3] appeared only at 13 months, involving the whole striatum at the 17th month. This last scan showed involvement of posteromesial thalami, diffuse cortical ribboning including the precentral gyri, and severe atrophy. To confirm the visually assessed changes in diffusion, quantitative assessment of DTI was performed in five of the seven MRIs; DTI images were corrected for distortions (BrainSuite, http://brainsuite.org/), and for motion (eddy, FSL, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki). Diffusion tensor and mean diffusivity (MD) maps (Fig. 1b) were obtained with FDT (FSL). Segmentation of cortical and subcortical

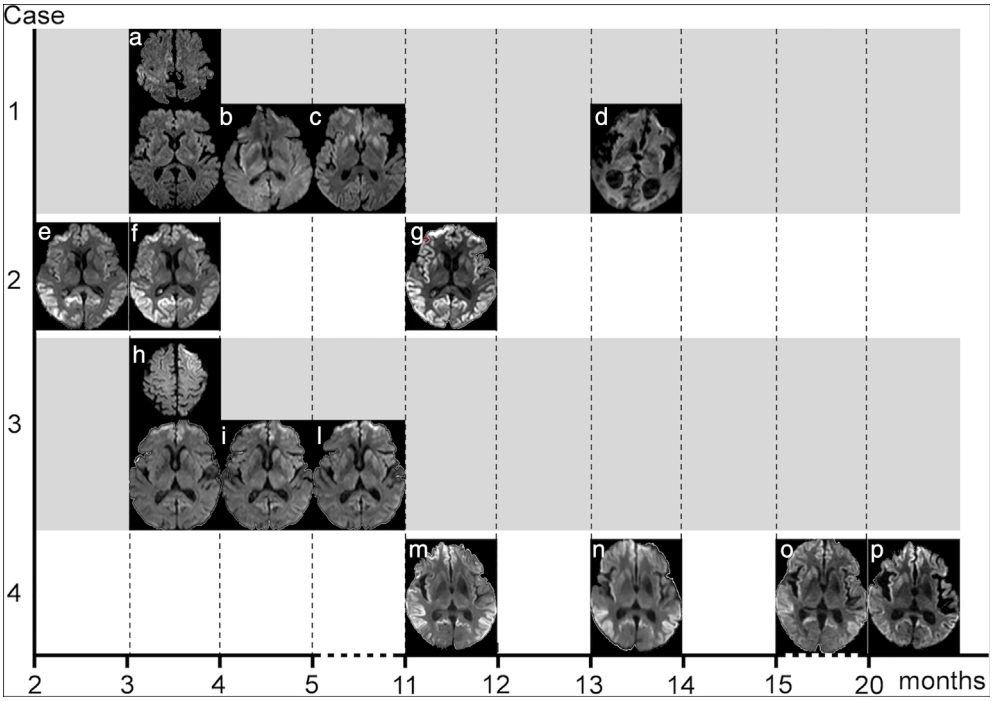

FIGURE 3: The other four long-lasting CJD cases previously studied[9] with longitudinal 1.5 T MRIs (DWI). Case 1: At onset: memory impairment; after 3 months (a) mini mental state examination (MMSE) = 24; after 4 months (b,c) progressively worsening dystonia, myoclonus, dysphagia, mutism; after 13 months (d) vegetative state Glasgow Coma Scale (GCS) = 5; after 14 months: exitus. PrPSc type 1, PRNP gene 129 codon methionine-methionine (MM) Case 2: At onset: apraxia, memory impairment, obsessive behavior; after 2 months (e) mini mental state examination (MMSE) = 18, mild extrapyramidal signs and ataxia, after 3 months (f) dysphagia, myoclonus, anarthria, after 11 months (g) Glasgow Coma Scale (GCS) = 9, after 16 months: exitus. PrPSc type 2, PRNP gene 129 codon MV Case 3: At onset: depression; after 2 months: disorientation, memory impairment; after 3 months (h) gait impairment; after 4 months (i,l) myoclonus and severe dysphagia, after 9 months: exitus. PrPSc type 1, PRNP gene 129 codon methionine-methionine (MM) Case 4: At onset: decreased verbal output, after 13 months: global aphasia, after 15 months: global cognitive deterioration, after 20 months: extrapyramidal signs, myclonus, mutism, after 22 months: exitus.

gray matter regions was performed using GIF (http://cmictig.cs.ucl.ac.uk/niftyweb/) and FIRST (FSL), respectively, on a 3D T_1-w scan, subsequently registered to the DTI data. Mean MDs were measured in the middle frontal gyrus, angular gyrus, caudate, and putamen of both hemispheres at each timepoint. MD measures confirmed the DWI changes by visual assessment: relative stability in the cortex and progressive decrease in the striatum (Fig. 1c).

The tardive involvement of left striatum, observed in DWI only at 11 months, was already depicted using ASL at 8 and 9 months. ASL images were processed using FSL and ANTS (http://stnava.github.io/ANTs/) according to the Buxton model to provide quantitative cerebral blood flow (CBF) maps (Fig. 2a), which mean values were calculated in the same regions of interest (ROIs) as for MD. CBF values confirmed the visually assessed asymmetry by detecting hypoperfusion of left putamen with respect to the right one.

Discussion

In our long-lived and slowly progressive case, DWI hyperintensities and reduced MD were present earlier in the cortex, whereas DWI and MD involved the striatum only in the advanced stages of the disease. This finding is consistent with data from a Chinese cross-sectional study[7] suggesting that lower striatal apparent diffusion coefficient (ADC) values correlate with shorter duration of disease and shorter time to akinetic mutism. A recent Korean study[8] classified 36 sCJD patients in four clinical stages based on the radiological involvement: five out of six poorly symptomatic cases showed an exclusive involvement of the cerebral cortex. Due to the usual short disease duration, longitudinal changes in quantitative MRI parameters have been reported as minimal.[5,6] In our case, both qualitative DWI and quantitative MD measurements showed progression from cortex to striatum. Moreover, late involvement of the striatum was shown, with ASL perfusion slightly before the diffusion images. Extrapyramidal motor signs and global disease worsening correlate with progressively decreasing diffusion in the striatum. These findings are consistent with our previous longitudinal observations[9] in other long-lasting cases that early cortical and late striatal DWI involvement usually correlates with early cognitive and late extrapyramidal motor impairment (Fig. 3).

Therefore, the early and exclusive cortical involvement revealed in MRI is a possible diagnostic finding in the initial stages of sCJD, when neurological signs are still confounding and laboratory tests are often negative. Moreover, quantitative diffusion changes on serial MRI scans can track the cortico-subcortical spreading of the prion disease, and seem to correlate with the clinical progression towards the final disease stage. Although further confirmation is required, this cortico-subcortical spreading could be employed as a radiological index of clinical progression in long-lasting cases and, thus, to better define the prognosis, which remains largely unpredictable.

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Disclosures

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