The VV2 subtype of Creutzfeldt-Jakob disease: A clinically recognizable form of subacute ataxia “plus”

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BACKGROUND. Sporadic Creutzfeldt-Jakob disease (sCJD), the most common human prion disease, comprises six major clinical-pathological disease subtypes that are largely determined by the genotype at the methionine/valine (M/V) polymorphic codon 129 of *PRPN* gene and the type (1 or 2) of pathologic prion protein accumulating in the brain (namely MM1, MM2, MV1, MV2, VV1 and VV2). Current diagnostic criteria consider sCJD as a single entity and include dementia as the main clinical feature, although the latter is not always a prominent and early sign. A better characterization of subtype-specific clinical features and results of diagnostic investigations, especially at early stages, may improve the clinical diagnosis of sCJD, which is often challenging, and provide the basis for improved and subtype-specific diagnostic criteria.

OBJECTIVE. To describe early clinical features and results of diagnostic tests in a large series of sporadic CJD of the VV2 subtype (sCJDVV2).

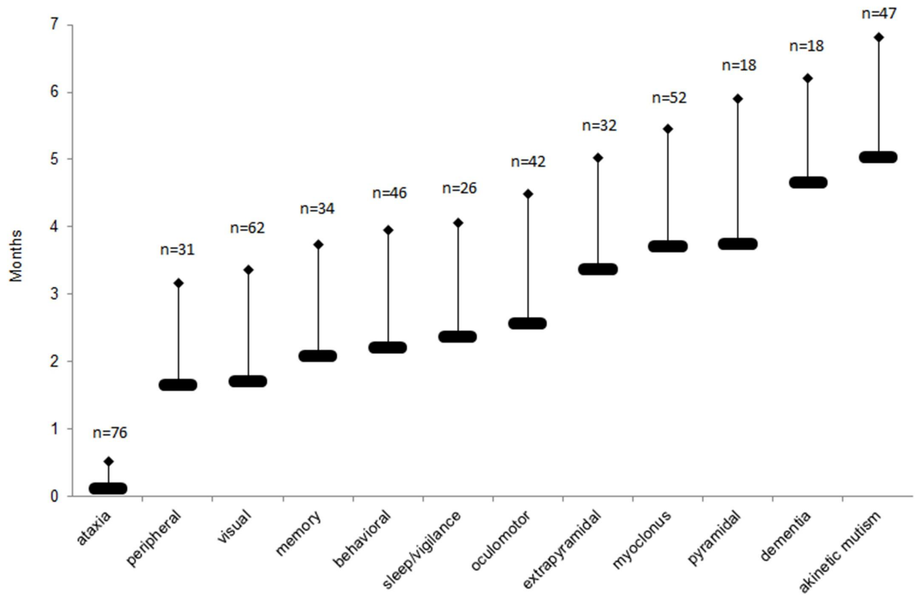
MATERIAL AND METHODS. We evaluated neurological symptoms and signs, and the results of cerebral MRI, EEG and CSF biomarker studies in 76 patients with a definite diagnosis of sCJDVV2.

RESULTS.
All patients presented with prominent cerebellar signs, particularly unsteadiness of gait, which were often associated with memory loss and/or oculomotor or visual signs. In contrast, dementia was invariably a late finding.

A positive 14-3-3 protein assay as well as total tau protein levels above 1300 pg/ml characterized all CSF VV2 samples that were tested.

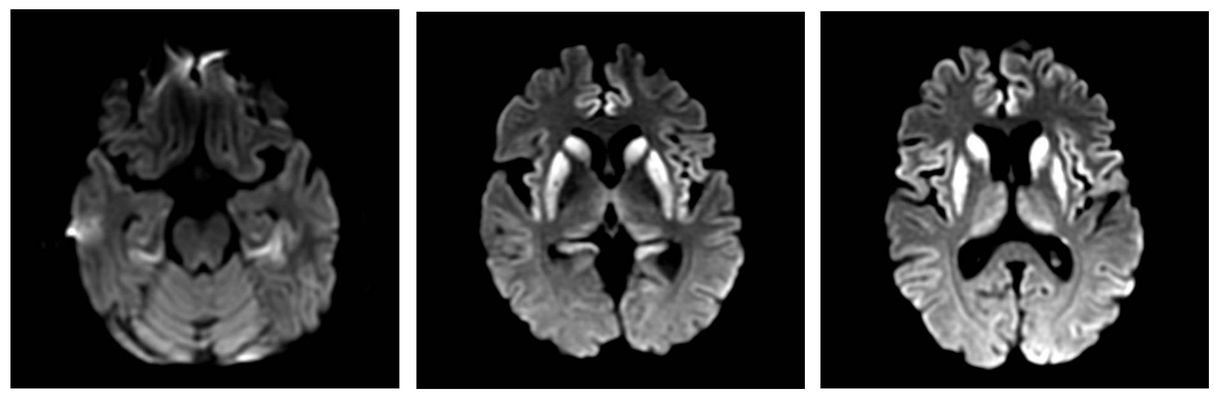
EEG revealed periodic sharp wave complexes in only 13.9% of cases at a relatively late disease stage.

Brain DW-MRI showed basal ganglia and thalamic hyperintensities in 92% and 56% of cases respectively, whereas cortical hyperintensities were present in only 16% of them.



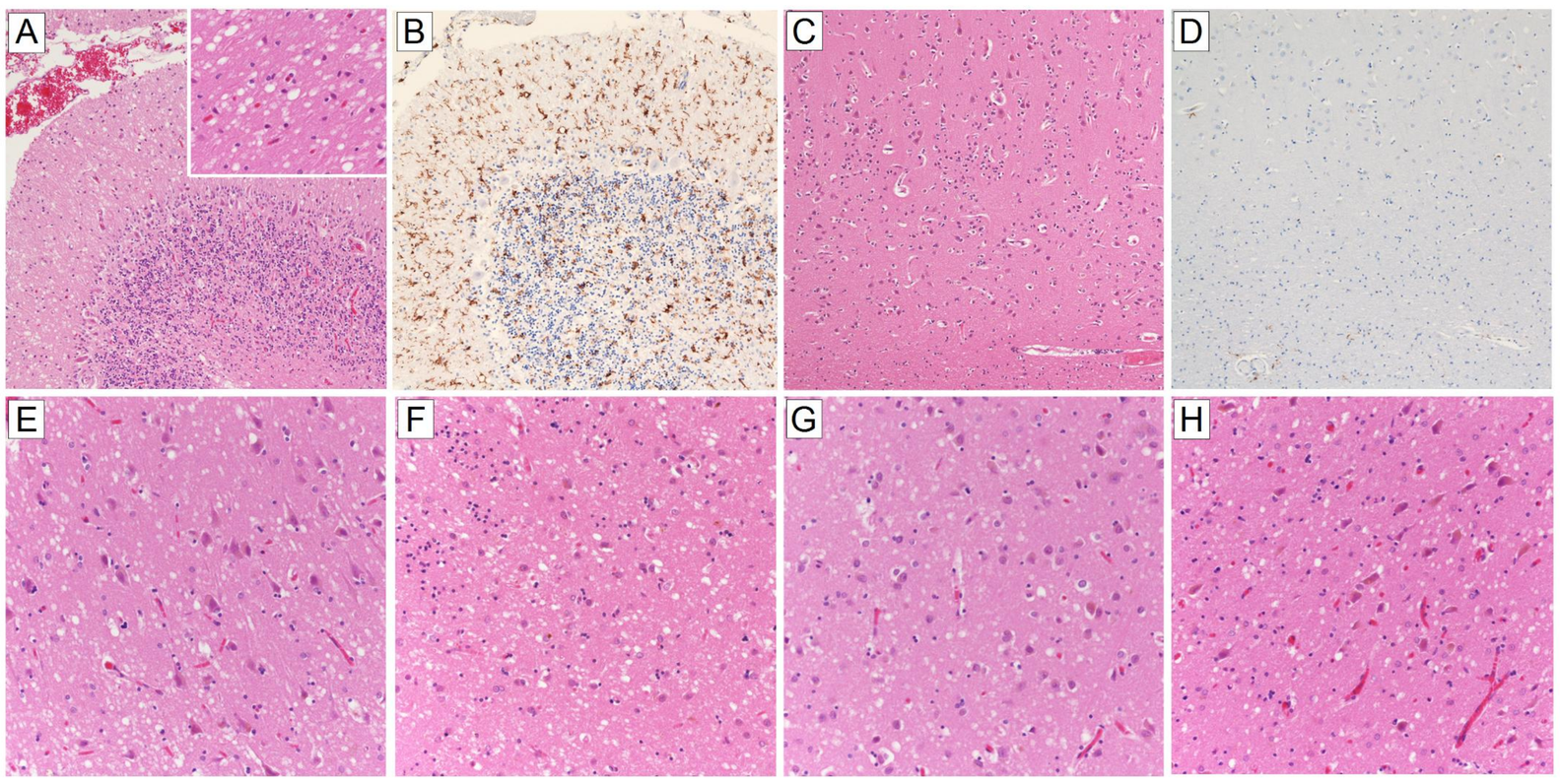
Clinical course. The mean time of appearence (in months) from disease onset is indicated for each group of symptoms/signs

	Brain MRI early (n=13)		Brain MRI late (n=12)	
	T2-FLAIR	*DWI*	*T2-FLAIR*	*DWI*
CORTICAL	-	-	4 (33%)	4 (33%)
- **Frontal**	-	-	3 (25%)	3 (25%)
- **Parietal**	-	-	1 (8%)	1 (8%)
- **Temporal**	-	-	-	-
- **Occipital**	-	-	-	-
LIMBIC AREAS	2 (15%)	3 (23%)	4 (33%)	4 (33%)
- **Hippocampus**	2 (15%)	3 (23%)	3 (25%)	3 (25%)
- **Insula**	-	-	1 (8%)	1 (8%)
STRIATUM	8 (62%)	11 (85%)	10 (83%)	12 (100%)
THALAMUS	3 (23%)	8 (62%)	5 (42%)	6 (50%)
CEREBELLUM	-	-	-	-

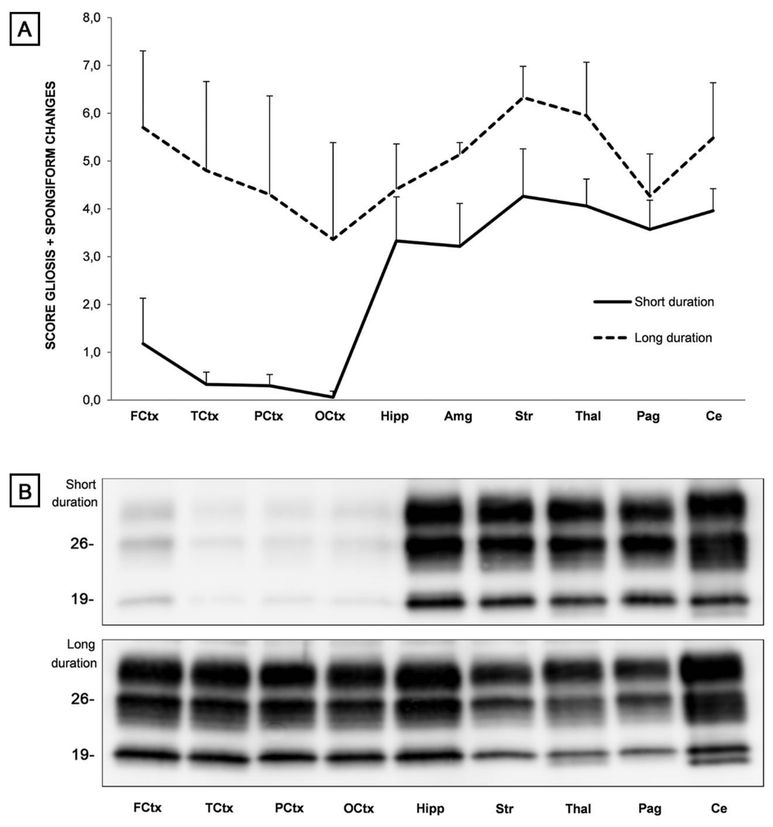


Brain MRI findings in a long duration case.
The figure shows a bilateral hyperintensity of striatum, thalamus, insula, hippocampus and a left frontal cortex hyperintensity on DWI sequence.

Neuropathological examination of cases with the shortest clinical course revealed a widespread involvement of cerebellum and other sub-cortical structures (hippocampus, amygdala, striatum, thalamus, and midbrain), with an almost complete sparing of the cerebral cortex.



Histopathological findings in sCJDVV2 of short duration (cerebellum vermis A,B; occipital cortex C,D; hippoocampal subiculum E; anterior striatum F; lateral amygdal G; medial thalamus H; B and D immunohistochemistry with primary Ab C3/43, all the others H&E stain)



Lesion profile (A) and **regional distribution of PrP^{Sc}** (B) in sCJDVV2.

CONCLUSIONS

sCJDVV2 should be considered in any patient presenting with a **rapidly progressive ataxia**, especially when **associated with memory loss, oculomotor and/or visual symptoms**, even if other neurological deficits considered as typical CJD features, such as dementia or myoclonus, are absent. **CSF protein assays (14-3-3 and t-tau) and brain DWI-MRI currently represent the most sensitive diagnostic tests supporting the clinical diagnosis**. Taken together these data indicate that sCJDVV2 can be clinically diagnosed early and with very high accuracy based on clinical data, results of CSF biomarker assays, brain MR-DWI studies and codon 129 genotyping.