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Tremor and Other Hyperkinetic Movements

Reviews

Movement Disorders in Prionopathies: A Systematic Review

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Abstract

Background: Movement disorders are frequent features of prionopathies. However, their prevalence and onset remain poorly described.

Methods: We performed a systematic review of case reports and case series of pathologically- and genetically confirmed prionopathies. Timing of symptom and movement disorder onset were documented. Continuous variables were compared between two groups using the Wilcoxon rank sum test and between multiple groups using Kruskal–Wallis test. Categorical variables were compared using Fisher's exact test.

Results: A total of 324 cases were included in this analysis. Movement disorders were a common feature at the onset of symptoms in most prionopathies. Gait ataxia was present in more than half of cases in all types of prionopathies. The prevalence of limb ataxia (20%) and myoclonus (24%) was lower in Gerstmann–Sträussler–Scheinker disease compared to other prionopathies ($p \leq 0.004$). Myoclonus was common but often a later feature in sporadic Creutzfeldt–Jakob disease (2 months before death). Chorea was uncommon but disproportionately prevalent in variant Creutzfeldt–Jakob disease (30% of cases; $p < 0.001$). In genetic Creutzfeldt–Jakob disease, E200K *PRNP* carriers exhibited gait and limb ataxia more often when compared to other mutation carriers.

Discussion: Movement disorders are differentially present in the course of the various prionopathies. The movement phenomenology and appearance are associated with the type of prion disease and the *PRNP* genotype and likely reflect the underlying pattern of neurodegeneration. Reliance on myoclonus as a diagnostic feature of sporadic Creutzfeldt–Jakob disease may delay its recognition given its relatively late appearance in the disease course.

Keywords: Prion, Creutzfeldt–Jakob, Gerstmann–Sträussler–Scheinker, fatal familial insomnia, movement disorders, ataxia, myoclonus

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Introduction

Human prionopathies are rapidly progressive neurodegenerative disorders of the central nervous system characterized by accumulation of the pathogenic, misfolded isoform of the endogenous cell-surface prion-related protein (PrP), known as prions. Prionopathies can be classified by their mode of transmission: Sporadic prion diseases include sporadic Creutzfeldt–Jakob (sCJD) and variably protease-sensitive prionopathy (VPSPr); acquired prion diseases include variant Creutzfeldt–Jakob disease (vCJD) and iatrogenic Creutzfeldt–Jakob disease (iCJD); genetic prion disorders include genetic Creutzfeldt–Jakob disease (gCJD), Gerstmann–Sträussler–Scheinker disease (GSS), and fatal familial insomnia (FFI).

The neurologic signs and symptoms of prionopathies reflect the anatomical pattern of neurodegeneration caused by prions. Multiple factors influence the clinical presentation, including the type of prion disorder, the methionine–valine polymorphism in codon 129, and the presence of other pathogenic mutations in the prion protein gene (*PRNP*).

Although prionopathies are traditionally associated with rapidly progressive dementia, movement disorders are often present, sometimes representing the initial manifestation or the only symptom. However, the diagnostic and prognostic utility of movement phenomenology in suspected prionopathies remains undetermined. Given the rarity of prion diseases and the substantial heterogeneity of their presentation, we reviewed published case reports and case series to describe the phenotypic spectrum and evaluate whether differences in semiology and timing of appearance can serve as distinguishing features.

Methods

Search strategy and data extraction

We performed a systematic review of prionopathies published from January 1970 until February 2019. We searched articles on PubMed without language restriction using the following terms: *prion or Creutzfeldt–Jakob or Jakob–Creutzfeldt or CJD or protease-sensitive prionopathy or variant CJD or iatrogenic CJD or familial CJD or genetic CJD or fatal familial insomnia or Gerstmann–Sträussler–Scheinker.* This strategy yielded 23,044 results. The titles were reviewed for eligibility criteria, specifically case reports and case series. Abstracts were reviewed as needed. We included only articles that contained: (1) well-documented patients; (2) report of time between symptom onset and death; (3) sCJD, vCJD, iCJD, and VPSPr confirmed by autopsy, or gCJD, FFI, and GSS confirmed by either genetic or autopsy evaluation. We also excluded articles with incomplete or absent disease phenomenology (Supplementary Figure S1).

All subjects from articles that met inclusion criteria were included in a database. From these articles, we extracted demographic data (e.g., age, gender, and disease duration), chronology of symptom onset (e.g., cognitive or behavioral impairment, abnormal movements, sleep impairment, autonomic dysfunction, and others) and onset of movement disorders, measured in months before death, and the ratio of these values to total disease duration. The specific genetic mutations were documented for the genetic prionopathies gCJD, FFI, and GSS.

Statistical analysis

Each subject extracted was defined to be a unit for analysis, and no weight was assigned to any study. Continuous data were expressed by median with interquartile range (IQR), while categorical data were expressed by frequency and percentage. Due to unequal and varying group sizes, all statistical analyses were conducted using nonparametric tests. Continuous variables were compared between two groups using Wilcoxon rank sum test and between multiple groups using the Kruskal–Wallis test. Categorical variables were compared using Fisher's exact test. In the case of multiple groups with low cell frequencies, chi square was used. Symptom/total disease duration ratio was compared with one-way ANOVA and presented with mean and standard deviation. In addition, we performed multivariable logistic regression analyses to compare the prevalence of movement disorders by the presence of specific prion disease after accounting for differences in age at presentation and disease duration.

Post-hoc group comparisons were conducted by either Wilcoxon rank sum test or Fisher's exact test. The sub-group analysis of GSS and gCJD patients' prevalence gene type was performed using Kruskal–Wallis test or Fisher's exact test. In addition, we performed sensitivity analyses excluding either reports published in non-neurological journals, without documentation of cognitive changes or both. All statistical analyses were carried out using STATA 15 (StataCorp LLC, Texas, USA). P-values less than 5% were considered as statistically significant results.

Results

A total of 275 articles yielded 326 patients for analysis. As only two case reports of VPSPr fulfilled our criteria, their data were not included. The most frequent phenotype was sCJD (50.6% of total cases), followed by GSS (15.4%), gCJD (13.9%), FFI (9.3%), vCJD (7.1%), and iCJD (3.7%).

Disease onset and symptom course

The age of onset was different between groups. The median age of onset for sCJD and gCJD was about 60 years, while the median for the other prionopathies was below 50 years. Sporadic CJD had the highest median age of onset (62 years, $p < 0.001$) and vCJD has the lowest median age (36 years $p < 0.001$) (Table 1). The course of disease was longer in GSS (median, 58.5 months) compared to the other prionopathies ($p < 0.001$) and shorter in gCJD (5 months; $p < 0.001$) (Table 1).

The timing of symptom onset (i.e., cognitive/behavioral, movement disorders, dysautonomia, or sleep disturbances) differed between groups. Cognitive/behavioral symptoms were part of the initial presentation in more than half of all prionopathies except for FFI, in which it was present at onset in only one third of cases. Cognitive/behavioral symptoms were absent in 18.9% of cases of sCJD, a significant difference from other groups ($p < 0.001$) (Table 1).

Movement disorders were present at some point in almost all cases reviewed and were part of the initial presentation in more than half of sCJD, iCJD, and GSS cases. Dysautonomia and sleep impairment were

Table 1. **Clinical and Demographic Features of Human Prionopathies in the Published Literature**

N	sCJD	vCJD	iCJD	gCJD	FFI	GSS	p
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	
	164	23	12	45	30	50	
Age at onset (y), median (IQR)	62 (54, 69)	36 (26, 41)	45.5 (37, 52.5)	60 (46, 68)	45 (34, 53)	48 (37, 56)	<0.001
Disease duration (m), median (IQR)	7 (4, 15.5)	17 (10, 18)	9.5 (6.5, 12)	5 (4, 16)	11 (9, 13)	58.5 (30, 96)	<0.001
Cognitive/Behavioral							<0.001
Onset	95 (57.9%)	18 (78.3%)	8 (66.7%)	34 (75.6%)	10 (33.3%)	29 (58%)	
Later in course	38 (23.2%)	4 (17.4%)	4 (33.3%)	9 (20%)	18 (60%)	16 (32%)	
Not reported	31 (18.9%)	1 (4.3%)	0 (0%)	2 (4.4%)	2 (6.7%)	5 (10%)	
Movement Disorders							<0.001
Onset	89 (54.3%)	6 (26.1%)	8 (66.7%)	14 (31.1%)	10 (33.3%)	30 (60%)	
Later in course	73 (44.5%)	17 (73.9%)	4 (33.3%)	30 (66.7%)	20 (46.7%)	18 (36%)	
Not reported	2 (1.2%)	0 (0%)	0 (0%)	1 (2.2%)	0 (0%)	2 (4%)	
Dysautonomia							<0.001
Onset	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (16.7%)	0 (0%)	
Later in course	1 (0.6%)	0 (0%)	1 (8.3%)	7 (15.6%)	16 (53.3%)	0 (0%)	
Not reported	163 (99.4%)	23 (100%)	11 (91.7%)	38 (84.4%)	9 (30%)	50 (100%)	
Sleep disorder							<0.001
Onset	2 (1.2%)	0 (0%)	1 (8.3%)	7 (15.7%)	19 (63.3%)	0 (0%)	
Later in course	1 (0.6%)	0 (0%)	0 (0%)	5 (10%)	8 (26.6%)	0 (0%)	
Not reported	161 (98.2%)	23 (100%)	11 (91.7%)	33 (73.3%)	3 (10%)	50 (100%)	

Abbreviations: FFI, Fatal Familial Insomnia; gCJD, Genetic Creutzfeldt–Jakob Disease; GSS, Gerstmann–Sträussler–Scheinker Disease; iCJD, Iatrogenic Creutzfeldt–Jakob Disease; IQR, Interquartile Range; p-value, Wilcoxon rank sum test for continuous data and chi-square test for categorical data; sCJD, Sporadic Creutzfeldt–Jakob Disease; vCJD, Variant Creutzfeldt–Jakob Disease.

more common in FFI patients at onset and during the course of the disease ($p < 0.001$). No sleep impairments were reported in GSS cases (Table 1).

Prevalence of movement disorders

Gait ataxia was the most common movement disorder in all prionopathies combined. Indeed, it was the only manifestation reported in greater than half of all diseases, being most common in vCJD (91.3% of cases; $p = 0.01$). Gait ataxia was also the most common movement disorder in sCJD (62.8% of cases), iCJD (75% of cases), and GSS (74% of cases) (Table 2). Myoclonus was the most frequent movement disorder in gCJD and FFI, followed by gait ataxia (Table 2). Except for GSS patients, myoclonus was also present in more than half of the prionopathies (24% of GSS cases, $p < 0.001$) (Table 2).

Chorea was the least frequent movement disorder encountered in prionopathies, reported in only 15 cases, disproportionally clustering in vCJD (47% of cases; $p < 0.001$). Dystonia was also uncommon but, when present, more often associated with sCJD (75% of cases; $p = 0.036$).

Parkinsonism and isolated rigidity were least common in sCJD (7.3%, $p = 0.043$) and FFI (23.3%, $p = 0.034$) compared to other prionopathies, respectively. GSS had a lower prevalence of limb ataxia (20% of cases; $p = 0.004$) compared to other prionopathies. Gaze palsy was seen in just over 10% of sCJD (Table 2). The results reported in this section did not change after adjusting for age at onset and duration of disease neither after performing sensitivity analyses (Supplementary Tables 1–9)

Time from movement disorder onset until death

The time of movement disorder onset until death varied across diseases, being shorter in sCJD compared with other prionopathies for gait ataxia (5 months; $p = 0.014$), myoclonus (2 months; $p < 0.001$), parkinsonism (3 months; $p = 0.024$) and isolated rigidity (5.5 months; $p = 0.018$). The respective durations of gait ataxia (56 months; $p < 0.001$), limb ataxia (58.5 months; $p < 0.001$), parkinsonism (36 months; $p < 0.001$), and rigidity (42 months; $p < 0.001$) were longer in GSS compared with other prionopathies (Table 3). When compared to disease duration, gait and limb ataxia appeared as early features in the course of sCJD and GSS, whereas

Table 2. **Prevalence of Movement Disorders in Human Prionopathies**

N	sCJD	vCJD	iCJD	gCJD	FFI	GSS	p-value
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	
	164	23	12	45	30	50	
Gait ataxia	103 (62.8%)	21 (91.3%)	9 (75%)	30 (66.7%)	17 (56.7%)	37 (74%)	0.051
Limb ataxia	66 (40.2%)	9 (39.1%)	7 (58.3%)	24 (53.3%)	8 (26.7%)	10 (20%)	0.012
Myoclonus	96 (58.5%)	13 (56.5%)	8 (66.7%)	32 (71.1%)	20 (66.7%)	12 (24%)	<0.001
Tremor	8 (4.9%)	2 (8.7%)	1 (8.3%)	3 (6.7%)	4 (13.3%)	4 (8%)	0.47
Parkinsonism	12 (7.3%)	2 (8.7%)	1 (8.3%)	7 (15.6%)	4 (13.3%)	9 (18%)	0.24
Rigidity	72 (43.9%)	7 (30.4%)	3 (25%)	26 (57.8%)	7 (23.3%)	20 (40%)	0.037
Chorea	6 (3.7%)	7 (30.4%)	0 (0%)	0 (0%)	0 (0%)	2 (4%)	<0.001
Dystonia	15 (9.1%)	2 (8.7%)	0 (0%)	1 (2.2%)	0 (0%)	2 (4%)	0.28
Gaze palsy	18 (11%)	3 (13%)	1 (8.3%)	1 (2.2%)	0 (0%)	0 (0%)	0.011

Abbreviations: FFI, Fatal Familial Insomnia; gCJD, Genetic Creutzfeldt–Jakob Disease; GSS, Gerstmann–Sträussler–Scheinker Disease; iCJD, Iatrogenic Creutzfeldt–Jakob Disease; p-value, Fisher's exact test; sCJD, Sporadic Creutzfeldt–Jakob Disease; vCJD, Variant Creutzfeldt–Jakob Disease.

Table 3. **Time (Months) from Movement Disorder Onset until Death**

	sCJD	vCJD	iCJD	gCJD	FFI	GSS	p-value
Gait ataxia, median (IQR)	5 (2, 12)	8 (6, 18)	7 (6, 8)	4.5 (4, 10)	9 (5, 12)	56 (13, 84)	<0.001
Limb ataxia, median (IQR)	4 (2, 12)	7 (6, 18)	6 (4, 13)	5 (3, 9.5)	5.5 (3.5, 18.5)	58.5 (48, 72)	0.017
Myoclonus, median (IQR)	2 (2, 4.5)	6 (3, 12)	4.5 (2, 9)	4 (2, 10)	5 (3, 8)	5.5 (2.5, 71)	0.025
Tremor, median (IQR)	3 (1.5, 7)	23.5 (12, 35)	10 (10, 10)	4 (4, 60)	9.5 (5, 13)	31.5 (2, 84)	0.57
Parkinsonism, median (IQR)	3 (3, 13.5)	4.5 (1, 8)	10 (10, 10)	18 (16, 90)	8.5 (5.5, 18)	36 (24, 65)	0.100
Rigidity, median (IQR)	5.5 (2, 12.5)	17 (7, 18)	13 (8, 13)	5 (4, 16)	9 (5, 17)	42 (9.5, 102)	0.002
Chorea, median (IQR)	14 (4, 27)	3 (2, 8)	-	-	-	2. (2, 3)	0.12
Dystonia, median (IQR)	2 (2, 6)	14.5 (11, 18)	-	3 (3, 3)	-	60.5 (1, 120)	0.48
Gaze palsy, median (IQR)	8.5 (2, 14)	8 (7, 14)	13 (13, 13)	16 (16, 16)	-	-	0.71

Abbreviations: FFI, Fatal Familial Insomnia; gCJD, Genetic Creutzfeldt–Jakob Disease; GSS, Gerstmann–Sträussler–Scheinker Disease; iCJD, Iatrogenic Creutzfeldt–Jakob Disease; IQR, Interquartile Range; p-value, Wilcoxon rank sum test; sCJD, Sporadic CJD; vCJD, Variant Creutzfeldt–Jakob Disease.

myoclonus appeared in the middle stages of these diseases, a feature observed in sCJD and other prionopathies (Supplementary Table 1).

Clinical features of gCJD due to E200K mutation

While gCJD is most often due to E200K mutations in the *PRNP* gene, other genetic PRNP mutations have been identified as causative. Compared to other nine mutations associated with gCJD, carriers of the E200K mutation had a shorter disease course (4 months) compared to carriers of other mutations (12 months) ($p < 0.001$). In addition, E200K *PRNP* carriers presented more often with autonomic ($p = 0.015$) and sleep changes ($p = 0.019$). Gait and limb ataxia were more common in E200K compared to other mutation carriers ($p < 0.001$). Parkinsonism was not reported in E200K carriers, whereas it was present in almost a third of non-E200K mutations ($p = 0.016$) (Table 4).

Clinical features of GSS due to P102L mutation

Multiple mutations to the PRNP gene have been associated with GSS, with P102L being the most common. Movement disorders were more often seen as the initial presentation in subjects with P102L mutations compared to those with the other nine mutations associated with GSS ($p = 0.047$). Except for parkinsonism being more common in non-P102L carriers compared to P102L carrier (41% of cases vs. 6%, p-value = 0.004), there were no significant differences in the presentation or duration of symptoms (Table 5).

Table 4. **Difference in Clinical Features in gCJD with and without E200K Mutation**

	gCJD E200K+(n = 19)	gCJD E200K-(n = 26)	p-value
Age at presentation (years), median (IQR)	54 (46, 64)	60.5 (47, 73)	0.32
Total disease duration (months), median (IQR)	4 (2, 5)	12 (4, 22)	<0.001
Cognitive/Behavioral			0.15
Initial presentation, N (%)	12 (63%)	22 (85%)	
Later in course, N (%)	6 (32%)	3 (11%)	
Not reported, N (%)	1 (5%)	1 (4%)	
Movement Disorders			0.35
Initial presentation, N (%)	8 (42%)	6 (23%)	
Later in course, N (%)	11 (58%)	19 (73%)	
Not reported, N (%)	0 (0%)	1 (4%)	
Dysautonomia			0.015
Initial presentation, N (%)	0 (0%)	0 (0%)	
Later in course, N (%)	4 (21%)	2 (8%)	
Not reported, N (%)	15 (79%)	24 (92%)	
Sleep disorder			0.019
Initial presentation, N (%)	6 (32%)	1 (4%)	
Later in course, N (%)	0 (0%)	3 (11%)	
Not reported, N (%)	13 (68%)	22 (85%)	
Presence of movement disorders			
Gait ataxia, N (%)	18 (95%)	12 (46%)	<0.001
Limb ataxia, N (%)	16 (84%)	8 (31%)	<0.001
Myoclonus, N (%)	14 (74%)	18 (69%)	1.00
Tremor, N (%)	0 (0%)	3 (11%)	0.25
Parkinsonism, N (%)	0 (0%)	7 (27%)	0.016
Rigidity, N (%)	13 (68%)	13 (50%)	0.24
Chorea, N (%)	0 (0%)	0 (0%)	
Dystonia, N (%)	1 (5%)	0 (0%)	0.42
Gaze palsy, N (%)	0 (0%)	1 (4%)	1.00

Abbreviations: gCJD, Genetic Creutzfeldt–Jakob Disease; IQR, Interquartile Range; p-value, Wilcoxon rank sum test for continuous data and Fisher's exact test for categorical data.
E200K- group included the following mutations to the PRNP gene, E196K; D178N/129V; G114K; M232R; P105T; R208H; T183A; T188R and V180I.

Discussion

In this systematic review, we evaluated the prevalence of movement disorders in prionopathies and their timing of presentation. To our knowledge, this is the first systematic assessment of movement disorders in all human prionopathies. The age of onset was older (over 60) in sCJD and gCJD compared with other prionopathies (under 50). Gait ataxia was the most common movement disorder, noted in more than half of all prionopathies; limb ataxia was, however, uncommon in GSS and FFI (20 and 25%) compared to other prionopathies. Myoclonus was common but appeared later in all prionopathies; chorea was uncommon but disproportionately prevalent in vCJD. In terms of gCJD, E200K *PRNP* carriers had a shorter disease course, more sleep disturbances, and dysautonomia at onset compared to other gCJD mutation carriers. Not surprisingly, sleep disorders were the most common presentation in FFI.

As previously reported, patients with GSS had a significantly longer median disease duration (58.5 months) compared to those with other prionopathies.[1] Thus, GSS should be considered a chronic, rather than a subacute, progressive disorder. Previous studies suggested that cognitive and behavioral symptoms were more common in sCJD, whereas

Table 5. **Difference in Clinical Features in GSS with and without P102L Mutation**

	GSS P102L+(n = 33)	GSS P102L-(n = 17)	p-value
Age at presentation (y), mean (IQR)	50 (38, 56)	47 (37, 60)	0.67
Total disease duration (s), mean (IQR)	56 (30, 84)	72 (30, 120)	0.47
Cognitive/Behavioral			0.059
Initial presentation, N (%)	16 (49%)	13 (76%)	
Later in course, N (%)	13 (39%)	3 (18%)	
Not reported, N (%)	4 (12%)	1 (6%)	
Movement Disorders			0.047
Initial presentation, N (%)	23 (70%)	7 (41%)	
Later in course, N (%)	8 (24%)	10 (59%)	
Not reported, N (%)	2 (6%)	0 (0%)	
Dysautonomia			
Not reported N (%)	33 (100%)	17 (100%)	
Sleep disorder			
Not Reported N (%)	33 (100%)	17 (100%)	
Movement disorders			
Gait ataxia, N (%)	26 (79%)	11 (65%)	0.32
Limb ataxia, N (%)	6 (18%)	4 (24%)	0.72
Myoclonus, N (%)	5 (15%)	7 (41%)	0.077
Tremor, N (%)	2 (6%)	2 (12%)	0.60
Parkinsonism, N (%)	2 (6%)	7 (41%)	0.004
Rigidity, N (%)	11 (33%)	9 (53%)	0.23
Chorea, N (%)	1 (3%)	1 (6%)	1.00
Dystonia, N (%)	0 (0%)	2 (12%)	0.11
Gaze palsy, N (%)	0 (0%)	0 (0%)	

Abbreviations: GSS, Gerstmann–Sträussler–Scheinker Disease; IQR, Interquartile Range; p-value, Wilcoxon rank sum test for continuous data and Fisher's exact test for categorical data.
P102L-group included the following mutations to the PRNP gene: A117V, D202N, G131V, H187R, P84S, Q212P, Q217R, 6 and 7 octapeptide repeat insertions.

movement disorders, specifically gait ataxia, were most common as initial features in GSS.[1,2] However, in this systematic review, cognitive/behavioral symptoms and movement disorders were similar in frequency at the onset of sCJD, iCJD, and GSS. Cognitive and behavioral changes were markedly more common at onset in vCJD and gCJD compared to other prionopathies. Indeed, the initial manifestation with behavioral abnormalities is a well-known feature of vCJD.[3]

Cerebellar degeneration is typically considered the neuroanatomical substrate of gait and limb ataxia in the prionopathies. However, ataxia may also be exceptionally contributed to by myelopathy, peripheral neuropathy, or frontal lobe impairment.[4,5] Gait ataxia has been reported as common in sCJD and GSS.[1,6] Isolated gait ataxia presenting years to decades before the onset of cognitive symptoms has been described as a characteristic feature of the VV2 (ataxic) subtype of sCJD, and in missense mutations causing GSS.[7,8] However, while gait ataxia was common in GSS, our results showed limb ataxia was less common compared to other prionopathies. The nature of this discrepancy can be attributed to the degeneration of the spinocerebellar tracts and the posterior horn of the spinal cord as the main driver of symptoms of GSS rather than cerebellar degeneration.[9,10] In addition, the presence of gait and limb ataxia early in the disease course may be suggestive of gCJD due to an E200K mutation.[11,12] Although not common at presentation, almost all vCJD patients manifest gait ataxia at some point during the disease.[3,13]

The presence of myoclonus in the context of cognitive impairment is often associated with sCJD, justifying its inclusion in most diagnostic criteria.[14–16] In sCJD, spontaneous myoclonus presents as distal and symmetric in the hands, becoming generalized later in the disease. However, asymmetric stimulus-sensitive myoclonus has also been described.[17] The latter is reminiscent of a startle response but can be distinguished from

it by the presence of habituation.[18] Although myoclonus is a common feature in sCJD, it appears in the mid-to-late stages in this and other prionopathies. Myoclonus is rare in GSS.

Other movement disorders were less frequently observed but their presence may help inform the differential diagnosis. Although chorea was rarely reported, almost half of the cases with chorea were associated with vCJD, and thus, this diagnosis should be considered in the differential diagnosis of Huntington disease.[3,19] The presence of movement disorders in vCJD has been associated with the degeneration of cholinergic neurons in the caudate and putamen.[20] In the sporadic form, although less frequent, the duration of chorea was longer (14 months) than the median duration of the disease (7 months), which may suggest a longer survival in those who present with chorea. Patients with GSS had the longest disease duration overall, but the median duration of chorea was only 2.5 months, suggesting that when present, chorea may represent a late feature.

Finally, gaze palsy is rarely reported but likely to be under-recognized. We found the presence of gaze palsy to be more often associated with sCJD. However, limitations in upgaze and slowness of saccades are often present in vCJD and have been reported as early findings in iCJD.[21,22] These abnormalities usually progress to further affect eye movements, leading to ophthalmoparesis.[23] Gaze limitations are also described in gCJD and GSS as a later manifestation.[23,24] Other oculomotor abnormalities include impaired pursuit and nystagmus.[23]

The classification of prionopathies is based on the morphology of the PrP and amyloid deposition.[25] PrP deposition is often associated with a pattern of neurodegeneration in which certain structures are more predisposed to damage or selectively vulnerable depending on the PrP conformation.[26] PrP predominantly affects cerebral cortical structures in sCJD; the anterior and medial nuclei of the thalamus in FFI; the medial and posterior thalamus as well as the striatum, neocortex, and cerebellum in vCJD; and the cerebellum and spinal cord and, to a lesser extent, the neocortex in GSS.[8,13,27,28] This selectivity decreases as PrP spreads to other areas toward later phases. These correlations are not precise and there are multiple factors affecting the spread of the prion pathology, which could explain the varied presentation. The most prominent example is sCJD, in which the different phenotypes (e.g., cortical, cerebellar, and thalamic variants) depended on the areas of predominant degeneration.[29] The differences in the patterns of neurodegeneration and associated clinical presentations are modulated by the combination of the variability of methionine/valine polymorphism at codon 129 in the PRNP (MV, MM, VV) and the electrophoretic pattern of PrP after exposure of prion protein to proteinase K digestion (classified as 1 or 2) (Table 6).[30] While MM1 and MV1 variants are more likely to exhibit rapidly progressive dementia with multisystem neurological disorder, the VV2 (cerebellar) variant accounts for the second most common subtype and it is almost invariably associated with a cerebellar syndrome at the onset, without preceding cognitive changes.[5,7] Further understanding of anatomical underpinnings of movement disorders in prionopathies and the factors affecting the selective vulnerability will have an impact on diagnosis, prognosis, and potential treatment.

These conclusions have to be tempered by a number of limitations when considering their applicability to clinical practice. First, the

Table 6. **Subtypes of Sporadic Creutzfeldt–Jakob Disease**

Subtype* (frequency)	Age of onset Years (range)	Duration Months (range)	Presentation	Movement disorders	Regions predominantly affected
MM1/MV1(65%)	68 (31–86)	5 (1–24)	Cognitive/ behavioral, visual changes	Ataxia Myoclonus	Neocortex (particularly occipital lobe), subcortical nuclei and cerebellum
VV2(20%)	64 (40–83)	6.5 (3–18)	Cerebellar dysfunction. Later, cognitive/behavioral changes	Gait and limb ataxia Oculomotor abnormalities	Cerebellum and subcortical nuclei
MV2(10%)	65 (36–83)	17 (4–48)	Cognitive/ behavioral or motor	Ataxia Parkinsonism Myoclonus	Cerebellum and subcortical nuclei. Less cortical involvement
MM2 (Thalamic)(<5%)	52 (26–71)	16 (8–36)	Insomnia, cognitive	Ataxia Myoclonus	Thalamus and inferior olive
MM2 (Cortical)(<5%)	64 (49–77)	16 (9–36)	Cognitive, apraxia, aphasia	Myoclonus	Neocortex
VV1(1%)	44 (19–55)	21 (17–42)	Cognitive/ behavioral	Ataxia Parkinsonism	Cortex and striatum

*Subtypes are based on the combination of methionine/valine polymorphism at codon 129 in the PRNP (MV, MM, VV) and the electrophoresis pattern of PrP after the exposure of prion protein to proteinase K digestion (classified as 1 or 2).
Frequency, age of onset, and duration values for this table were obtained from literature review.

selection of cases with genetic or pathological confirmation aimed for a more conservative selection but rendered many reports, mainly of sCJD, ineligible for analysis. This point should be considered when applying our findings to clinical practice, where patients are more often diagnosed based on clinical, imaging, and CSF findings, and only a minority have had an autopsy or genetic testing. Second, the reliance on reported cases invariably leads to a selection bias, as cases reported often need to justify their publication with an element of novelty, raising the concern that the sample is not representative of the whole of prionopathies. The presence of movement disorders is a common reason to publish a case report, which can lead to their overrepresentation, with potential under-representation of iCJD or vCJD. Reassuringly, the age at onset and the duration of the disease in this study are similar to those in prior reports. Third, the nature of case reports publication requires a succinct case presentation highlighting the features of interest for the report, sometimes leaving out details not considered of interest to the publication. This limits the identification of all the elements in the case presentation and may in part explain the absence of documented cognitive or behavioral changes in up to 20% of sCJD reports. However, our sensitivity analyses performed by excluding reports without the mention of cognitive changes or those not published in neurology journals did not affect our results. It should also be noted that most of these case reports were not accompanied by video material, and thus, the phenomenology, which may have been described by non-movement disorders specialists, cannot be confirmed. In addition, we did not include abnormalities not currently classified as movement disorders, such as spasticity and alien hand syndrome, which have also been reported in prionopathies.[31] Finally, our study aimed to report the onset of symptoms relative to the time to death. While this measure can help understand the progression of the disease, it may be misleading as the sole marker of disease duration. It should also be noted that this analysis was limited to the onset of symptoms but did not take into account whether the movement disorders remained present until death. In addition, while the analysis of the symptom/disease duration ratio can be helpful to understand the progression of the individual prionopathy, the total duration of each disease needs to be accounted for when translating it to the differential diagnosis of prionopathies. One solution to the limitations of our review, due to the heterogeneity of the reported clinical characteristics, could be a prospective study, with a standardized form to document clinical features as the disease progressed, which could be implemented in any case where the diagnosis is suspected. Despite these limitations, this is the first comprehensive systematic review to evaluate the prevalence and duration of movement disorders in prionopathies, and the results reported can help guide the evaluation of suspected prionopathies.

Conclusion

In conclusion, movement disorders are common in prionopathies, with differential appearance of specific movements in the various disorders. The differences in phenomenology and duration may result from selective neuronal and network vulnerability. A prospective epidemiologic study would be desirable to further refine the clinical variables that may affect the frequency, type, onset, and duration of movement disorders in prionopathies.

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