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Clinicopathological Correlates in a *PRNP* P102L Mutation Carrier with Rapidly Progressing Parkinsonism-dystonia

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Abstract

Parkinsonism-dystonia is rare in carriers of PRNP P102L mutation. Severity and distribution of prion protein (PrP) deposition may influence the clinical presentation. We present such clinic-pathological correlation in a 56-year-old male with a PRNP P102L mutation associated with a phenotype characterized by rapidly progressing parkinsonism-dystonia. The patient was studied clinically (videotaped exams, brain MRIs); molecular genetically (gene sequence analysis); and neuropathologically (histology, immunohistochemistry) during his 7-month disease course. The patient had parkinsonism, apraxia, aphasia, and dystonia, which progressed rapidly. Molecular genetic analysis revealed PRNP P102L mutation carrier status. Brain MRIs revealed progressive global volume loss and T2/FLAIR hyperintensity in neocortex and basal ganglia. Postmortem

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examination showed neuronal loss, gliosis, spongiform changes, and PrP deposition in the striatum. PrP immunohistochemistry revealed widespread severe PrP deposition in the thalamus and cerebellar cortex. Based on the neuropathological and molecular-genetic analysis, the rapidly progressing parkinsonism-dystonia correlated with nigrostriatal, thalamic, and cerebellar pathology.

Keywords

Gerstmann-Sträussler-Scheinker disease; prion protein; parkinsonism; dystonia; P102L mutation

Introduction

Gerstmann-Sträussler-Scheinker disease (GSS) is a rare, adult onset, autosomal-dominant neurodegenerative prion disease. Genetically, GSS is associated with a variety of point mutations in the *Prion Protein* gene (*PRNP*).[1] The most common mutation identified among affected subjects is P102L in which the pathogenic *PRNP* has a proline-to-leucine substitution at codon 102 (P102L). [1, 2] The clinical phenotype of GSS associated with the P102L mutation shows a high degree of heterogeneity. However, it is predominantly characterized by progressive ataxia, pyramidal signs, and dementia over a course lasting several years. Pathologically, GSS is characterized by deposits of prion protein (PrP) in the form of diffuse and amyloid plaques in the central nervous system (CNS).[2-4] Prominent parkinsonism and dystonia are not typical in subjects carrying the P102L mutation. We herein present a *PRNP* P102L mutation carrier demonstrating a clinical presentation characterized by rapidly progressive parkinsonism-dystonia. We describe the clinicopathological features in this case and discuss the possible mechanism of this unique clinical presentation.

Methods

Clinical evaluations were carried out via detailed, videotaped, longitudinal movement disorder neurology examinations, EEG, and serial brain magnetic resonance imaging (MRI). Videotaping was performed with the patient's informed consent. Molecular genetic assessments were accomplished using gene sequence analysis and neuropathological examination was performed using standard histological and immunohistochemical techniques.

Results

A 56 year-old-man presented with initial symptoms of bradykinesia, right arm rigidity, intermittent resting tremor and gait imbalance. Two months after the onset of symptoms, he developed memory impairment and expressive dysphasia with decreased verbal fluency. He had rapid functional decline and required assistance with his daily living activities. He was evaluated at the Johns Hopkins Movement Disorder Clinic three months after the onset of symptoms. On motor exam, he had bradykinesia, moderate right arm rigidity with dystonic forearm flexor posturing, and dystonic right thumb flexion. His gait exam showed evidence

of decreased arm swing and postural instability (Video 1). Furthermore, he had dysphasia, dysarthria, memory impairment, and apraxia.

Further investigation revealed that he had several family members that had been previously diagnosed with Gerstmann-Sträussler-Scheinker disease (Figure 1). Molecular genetic analysis revealed that he was a *PRNP* P102L-129M mutation carrier and heterozygous for M/V polymorphism at codon 129. Sequential high resolution brain MRI showed progressive cerebral and cerebellar volume loss and T2/FLAIR hyperintensity in the neocortex and basal ganglia (Figure 2).[5]

Subsequently, he had a rapid decline with progressive aphasia, bradykinesia, rigidity and dystonia leading to a bed-bound state, and death within 7 months of the onset of symptoms.

Neuropathological evaluation revealed moderate nigral neuronal loss and severe neuronal loss, gliosis, spongiform changes, and PrP deposition in the dentate and striatum (Figure 2). In the cerebral cortex, neuronal loss, gliosis, spongiform changes and PrP deposition involved more severely the parietal than the frontal cortex. PrP immunohistochemistry revealed widespread severe PrP deposition in the thalamus and cerebellar cortex. Alpha-synuclein and tau immunostaining of the substantia nigra were carried out to rule out incidental synucleinopathy or tauopathy contributing to the Parkinsonism. Both alpha-synuclein and tau immunostaining were negative (data not shown). Western blot characterization of the protease-resistant prion protein (PrP^{res}) showed three major bands of 21, 27 and 30 kDa together with an 8 kDa fragment, typically present in GSS-P102L (Figure 3).

Discussion

To expand upon the clinicopathological phenotype observed in GSS associated with *PRNP* P102L mutation, we describe a case with a rapid clinical progression and a severe movement disorder. In fact, the severe PrP deposition and spongiform changes in the substantia nigra, striatum, thalamus, and cerebellum may well correlate with this patient's clinical presentation characterized by impairment of motor control, parkinsonism, and dystonia.

Clinical and pathological heterogeneity is known to occur in GSS. Even in subjects with P102L mutations, phenotypic variations can be seen. *PRNP* P102L mutation carriers may present with cerebellar ataxia, dementia, pyramidal signs and rarely parkinsonism.[6] In P102L carriers, disease duration ranges from 1 to 10 years with the age of onset variable from the 40s to the 70s.[6] In a recent report of atypical parkinsonism in GSS, clinical heterogeneity in a family pedigree with the same Y218N mutation in the PRNP gene was described, suggesting that there are a variety of factors influencing the clinical phenotype.[7] While the authors describe a GSS case with a Y218N mutation in the PRNP gene with atypical parkinsonism mimicking progressive supranuclear palsy,[7] our case showed a more rapidly progressing parkinsonism-dystonia in a *PRNP* P102L mutation carrier. In GSS, PrP deposits resulting from degradation products found in the cerebral/cerebellar cortices and in the basal ganglia are characteristic pathological findings, however, spongiform changes and neuronal loss are also frequently seen.[3, 6] The severity and extent of pathological changes

may not easily explain the rapid clinical course, which in turn might be better explained by distribution and toxicity of the PrP^{Sc}.

The basis for the variable clinicopathological phenotypes observed in GSS is not fully understood, but several mechanisms have been postulated. Polymorphisms in PrP, including either methionine or valine at residue 129, are proposed to influence the clinical and pathological phenotype.[3] Additionally, variations in the anatomical distribution of pathologic PrP may account for the phenotypic differences seen among individuals carrying the same mutation.[8] Finally, in GSS P102L, the presence of proteinase-K resistant PrP isoforms of molecular weight 21-30 kDa have been associated with pathologic phenotypes characterized by significant spongiform degeneration.[9]

In the initial evaluation of patients with suspected GSS, a broad differential diagnosis should be considered including corticobasal syndrome (CBS) which can present with similar clinical signs. Features of CBS include parkinsonian rigidity, dystonia, apraxia and cognitive impairment,[10, 11] similar to the presenting features of our case. Further investigations including brain MRI and genetic testing can aid in narrowing the diagnosis between these neurodegenerative conditions.

We present a GSS phenotype characterized by a rapid progression on the disease and by a movement disorder with symptoms of parkinsonism-dystonia. Based on clinical, imaging, and neuropathologic data obtained from the study of this patient, we hypothesize that the clinical manifestations, dominated by rapid progression and prominent movement disorder, may result from an early seeding and spread of a very toxic form of PrP^{Sc} within basal ganglia, substantia nigra, and cerebellum.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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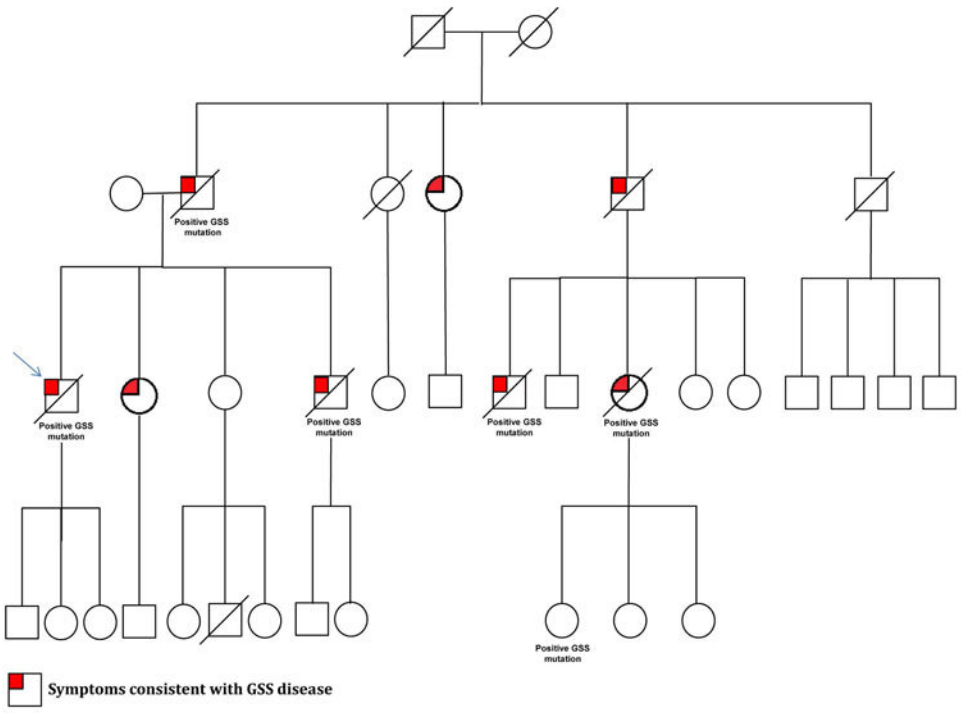

Figure 1.

Family pedigree. Case is indicated by the arrow. There were seven family members with symptoms consistent with GSS disease. Five family members were positive for the GSS mutation. One family member with a positive GSS mutation had no symptoms at time of testing (age 23). Mean age at symptom onset was 45. Clinical phenotypes of affected family members included ataxia, cognitive impairment, and dysarthria.

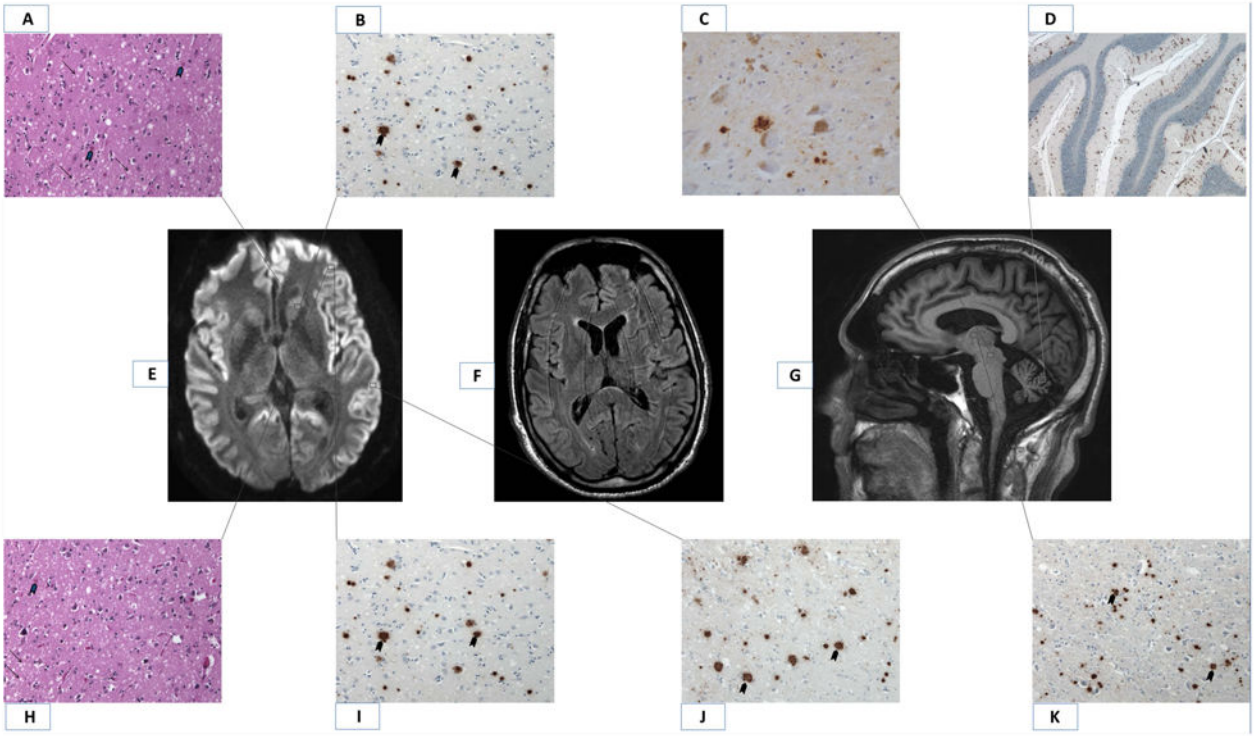

Figure 2.

Brain MRI shows increased signal in multiple cortical and basal ganglia regions on diffusion (E) and T2 FLAIR (F) sequences. Cerebral (E-F) and cerebellar (G) atrophy is also present. Severe spongiform changes shown on H&E stain in the caudate (A) and frontal cortex (H), indicated by vacuoles in the neuropil (arrows). Note eosinophilic amyloid cores (blue arrowheads). Widespread PrP deposits are shown in the caudate (B), thalamus (K), frontal (I)/parietal (J) cortices (3F4 antibodies), substantia nigra (C, 3F4 antibodies), as well as the cerebellum (D, 12F10 antibodies)

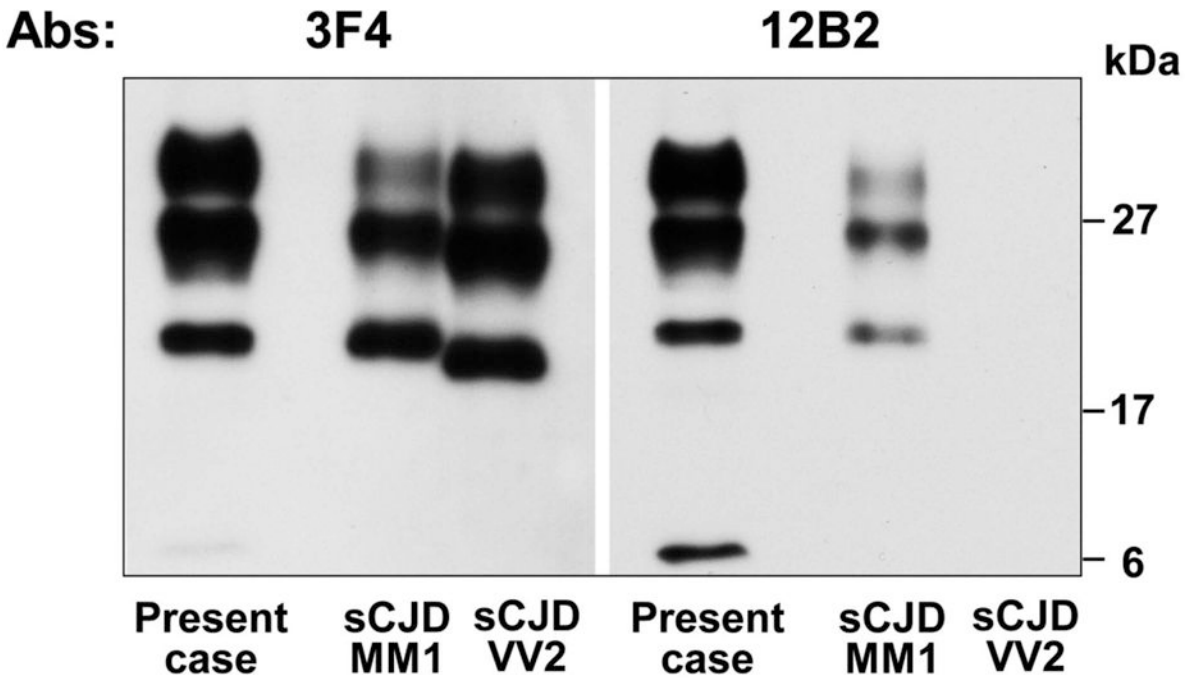

Figure 3.

Detection and characterization of protease-resistant prion protein (PrP^{res}): Immunoblot of total homogenates (TH), treated with proteinase K, obtained from the frontal cortex of the present case and of the most common sCJD subtypes, sCJD-MM1 and sCJD-VV2 (representing PrP^{res} types 1 and 2, respectively). Membranes were probed with monoclonal antibodies (mAbs) 3F4 (amino acids 109-112) and 12B2 (amino acids 89-93). PrPres of the present case includes an 8 kDa fragment, typically present in GSS-P102L. This fragment is much more visible when probed with 12B2, a type 1-specific antibody.