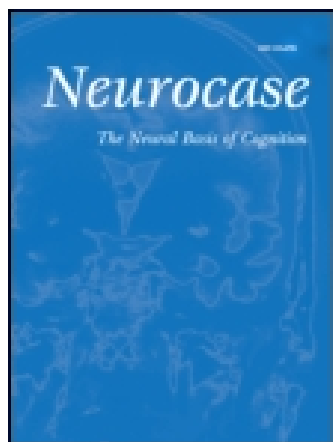


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Gerstmann–Sträussler–Scheinker syndrome with the P102L pathogenic mutation presenting as familial Creutzfeldt–Jakob disease: a case report and review of the literature

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Gerstmann–Sträussler–Scheinker syndrome is a rare autosomal dominant disease caused by a mutation in the prion gene, usually manifesting as progressive ataxia with late cognitive decline. A 44-year-old woman with a positive family history developed early personality and behavior changes, followed by paresthesias and ataxia, later associated with memory problems, pyramidal signs, anosognosia and very late myoclonus, spasticity, and severe dysexecutive impairment. Magnetic resonance showed caudate, mesio-frontal, and insular hyper-intensities, electroencephalography revealed generalized triphasic periodic complexes. A pathogenic P102L mutation in the prion gene was detected. Our case differed from classical Gerstmann–Sträussler–Scheinker syndrome by rapid progression, severe dementia, abnormal electroencephalography and magnetic resonance findings, which were highly suggestive of familial Creutzfeldt–Jakob disease.

Keywords: Gerstmann–Sträussler–Scheinker syndrome; Prion gene mutation; Prion; Dementia.

Gerstmann–Sträussler–Scheinker syndrome (GSS, MIM 137440) is a very rare, slowly progressive autosomal dominant inherited disease with onset in the late forties, and an average illness duration of 49–57 months (Kovács et al., 2005; Webb et al., 2008).

The ‘classical’ syndrome is comprised of prominent ataxia and gait disturbances followed, later on, by cognitive decline of varying severity. Hyporeflexia or absence of deep tendon reflexes; extrapyramidal signs and spasticity in the lower extremities (Arata et al., 2006; Kovács et al., 2002,

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2005) are often reported. Painful dysesthesias can also occur (Arata et al., 2006; Yamada et al., 1999), while visual disturbances, dystonia and myoclonus are uncommon in GSS (Chi, Lee, Lu, Wu, & Soong, 2010). Other manifestations are rare; associations with ataxia, dementia and peripheral involvement including fasciculations, fibrillations, and amyotrophy (Kretzschmar et al., 1992) and a phenotype similar to progressive supranuclear palsy (A133V mutation) (Rowe et al., 2007) have been described. Even a clinical course resembling that of sporadic Creutzfeldt–Jakob disease (sCJD, Majtényi, Brown, Cervenáková, Goldfarb, & Tateishi, 2000) has been reported.

Neuropathologically, GSS is characterized by spongiform encephalopathy in different brain regions and varying severity with prion protein (PrP) immunoreactive amyloid deposits mostly prominent in cerebral and cerebellar cortices and basal ganglia (Aguzzi & Calella, 2009; Bugiani et al., 2000; Liberski & Budka, 2004). GSS is caused by a pathogenic mutation in the prion protein gene (PRNP) located on chromosome 20. Several pathogenic variations, causing the GSS phenotype, have been described. The most common (more than 80% of cases) and first discovered mutation in PRNP was P102L (Hsiao et al., 1989), which has a relatively broad phenotypic spectrum (Neumann, 2009). The P102L mutation has also been found in the original GSS family (Kretzschmar et al., 1991). Other causal mutations in GSS include P105L, P105S, A117V, G131V, A133V, Y145X, H187R, F198S, D202N, Q212P, Q217R, M232T, and base pair insertions at positions 96, 192, or 216 (Aguzzi & Calella, 2009; OMIM Database, 2010).

Herein, we present a case of definite P102L GSS that is noteworthy by differing considerably from typical GSS presentations with regard to disease duration, symptomatology, neuroimaging, and laboratory findings. This is also the first genetically demonstrated case of GSS in the Czech Republic.

CASE REPORT

Our patient was a 44-year-old woman with a positive family history involving her mother, who died at age 49, of a progressive disease (lasting 2 years), which manifested with ataxia and cognitive impairment. An autopsy was not done on the patient's mother.

In 1999, at the age of 34, the patient had a stroke in the right cerebellar hemisphere. The clinical presentation was acute-onset dysarthria with right-sided ataxia and nystagmus. The etiology remained unclear; the only risk factor was the use of oral contraception. There were no arguments for a thromboembolic origin (negative carotid ultrasonography and echocardiography), and we did not detect changes in genes known to be related to thrombophilia (FV Leiden, FII, MTHFR). The symptomatology regressed considerably, 5 years later a routine neurological examination showed only mild ataxia with minimal hypermetria involving the right upper limb.

The first non-specific manifestations occurred insidiously, during the summer of 2008, mainly taking the form of personality changes (decreased spontaneity, loss of empathy, indifference) and gait instability. The patient also noted painful nocturnal limb paresthesias in September 2008 and complained about headache and anxiety. All symptoms worsened markedly in June 2009 following orthopedic surgery involving ankle osteosynthesis. The surgery was indicated after a fall, which likely resulted from gait instability. During the post-surgical period, the patient and her relatives reported slurred speech, significant gait ataxia, and reduced coordination involving the right hand.

As the clinical state continued to worsen, the patient was admitted to a local hospital. On admittance, in September 2009, memory problems, ataxia, and pyramidal signs were reported. MRI showed a residual post-stroke lesion within the right cerebellar hemisphere and a FLAIR and DWI hyper-intense signal in the caudate, and the mesio-frontal and insular cortical regions bilaterally (Figure 1). Cerebrospinal fluid analysis showed normal cell count, protein, and glucose levels.

She was examined in our department 1 month later (October 2009). At this time, she had severe anosognosia, confabulations, stereotypical behavior, right-side prevalent ataxia, spasticity in all limbs, but more prevalent in the lower extremities, with hyperreflexia, bilaterally positive pyramidal signs and severe gait apraxia. Verbal fluency was considerably reduced. A few weeks later, axial rigidity developed and sporadic startle myoclonus appeared. Cerebrospinal fluid remained normal in cell count, protein, and glucose levels. We found no oligoclonal bands, onconeuronal antibodies (anti-Yo, anti-Hu) and protein 14-3-3 were negative; beta-amyloid was slightly elevated (522 ng/L; $N=100-450$), phospho-tau was normal

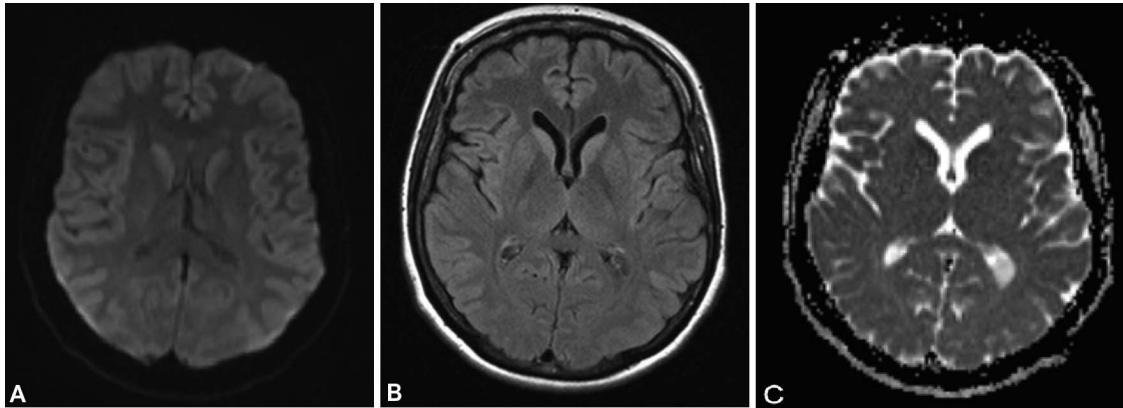


Figure 1. Magnetic resonance shows hyper-intense signal in diffusion-weighted (A) and FLAIR (B) images in caudatum and cortical ribboning (involving frontal, temporal-parietal, retrosplenial posterior cingulate regions, while sparing the occipital cortex (A) and right-sided prevalent anterior cingulate, insula and bilateral lateral temporal lobe cortical ribboning (B)). Apparent diffusion coefficient (ADC) imaging (C) shows discrete corresponding caudate and cortical hypointensities.

at 61 ng/L ($N=25-80$), but total tau was considerably increased >1200 ng/L ($N=200-450$).

EEG revealed a slowed background frequency with the presence of generalized triphasic complexes (Figure 2).

The neuropsychological assessment was incomplete and difficult to realize because of significant motor impairment and ataxia. Overall comprehension was reduced, and marked

concentration difficulties were noted, and instructions had to be repeated. Speech was dysarthric and slurred and verbal fluency was diminished. Additionally, episodes of echolalia developed. We observed stereotypic thinking, important perseverative behavior and impulsivity with disinhibition.

The administered tests disclosed severe global cognitive impairment and are summarized in



Figure 2. Electroencephalography shows generalized triphasic complexes.

TABLE 1
Summary of neuropsychological findings in our patient

<i>MMSE</i>	13/30
RPM	under 5th percentile
WMS-R	MQ = 55
CDT	1/10 (Sunderland)

MMSE, Mini-Mental State Examination; RPM, Raven Progressive Matrices; WMS-R, Wechsler Memory Scale – Revised; MQ, mnesic quotient; CDT, Clock Drawing Test; Sunderland, CDT scoring scale (Sunderland et al., 1989).

Table 1. The Mini-Mental State Examination (MMSE) score was 13/30. Significant mnesic difficulties, more pronounced in visual reproduction, were found using the Wechsler Memory Scale – revised form (WMS-R). Both early and delayed retrieval were severely affected and frequent intrusions developed. Verbal encoding was profoundly impaired. Logical memory was less impaired than other memory subtypes. In the story recall (Logical Memory subtest) only the last two items were reproduced and many intrusions occurred. In the digit span subtest, only 4 items were recalled forwards and none backwards. The patient was able to count backwards from 20 to 1, but failed in letter sequences. Further testing was not possible, in the verbal pair association subtest because the patient did not understand the instructions and due to severe agraphia, visual reproduction was impossible to assess.

Non-verbal performance was reduced. Raven's Coloured Progressive Matrices showed position stereotypies, absence of image analysis, and marked impulsivity in problem solving. The Clock Drawing Test was considerably impaired, only lines were drawn without numbers even though the patient was able to spell some of the numbers.

With respect to the clinical presentation, familial history and based on WHO diagnostic criteria, we concluded the patient probably had a genetic form of Creutzfeldt–Jakob disease (CJD, WHO Manual, 2003). The patient died of bronchopneumonia in November 2009, about 15 months after the first non-specific behavioral and personality changes and 6 months after the onset of focal signs on the neurologic examination.

During the autopsy, spongiform dystrophy, of varying severity, was observed in cortical and subcortical areas (Figure 3a, b). Neuropathological hallmarks of GSS were found with prominent amyloid plaques in the cerebellar and cerebral

cortex as well as in subcortical gray matter structures, which were positive in immunohistochemical reactions with anti-PrP antibodies (Figure 3c, e–g). Amyloid plaques revealed the histochemical property of amyloid, as demonstrated by their reaction with Congo red (Figure 3d). The presence of pathological prion protein deposits were verified using Western blot analysis of cerebral tissues (Figure 4). Genetic investigation of the *PRNP* gene revealed methionine homozygosity at codon 129, glutamate homozygosity at codon 219, and the pathogenic variant P102L, specific for GSS, was also detected (Figure 5). The case was closed as definite GSS. Additionally, an ancient post-ischemic lesion was found in the right cerebellar hemisphere (Figure 3 h).

DISCUSSION

This case represents the first genetically established case of GSS in the Czech Republic, although in the 1980s one case of GSS was discovered (Jirásek et al., 1988). The present case is interesting because it was atypical in several aspects that made the final clinical diagnosis difficult due to similarities with CJD symptomatology.

First, the time course of GSS is usually slow, being 3 or more years from the first symptoms to death (Kovács et al., 2002; Webb et al., 2008). The duration in our case, however, was very short. Death occurred only 6 months after the first verified neurological signs and 15 months after the occurrence of first non-specific behavioral changes, which was similar to a previously described family, where the duration from onset to death was about 2.5 months (Majtényi et al., 2000).

Second, although the GSS phenotype heterogeneity is considerable, mainly in the most frequent P102L mutation (De Michele et al., 2003; Neumann, 2009; Tanaka et al., 1997), ataxia is usually one of the first significant symptoms (Young et al., 1995; Webb et al., 2008). The main clinical, imaging, and laboratory findings of P102L mutations described in the literature are summarized in Table 2. Cognitive decline is typically present, but is usually mild and occurs later in the evolution of the disease (Cagnoli et al., 2008; Kovács et al., 2002; Park et al., 2010; Takazawa et al., 2010; Young, Clark, Piccardo, Dlouhy, & Ghetti, 1997); although, GSS P120L cases with cognitive decline, as one of the prominent symptoms, have been reported (Barbanti et al., 1996; Chi et al., 2010;

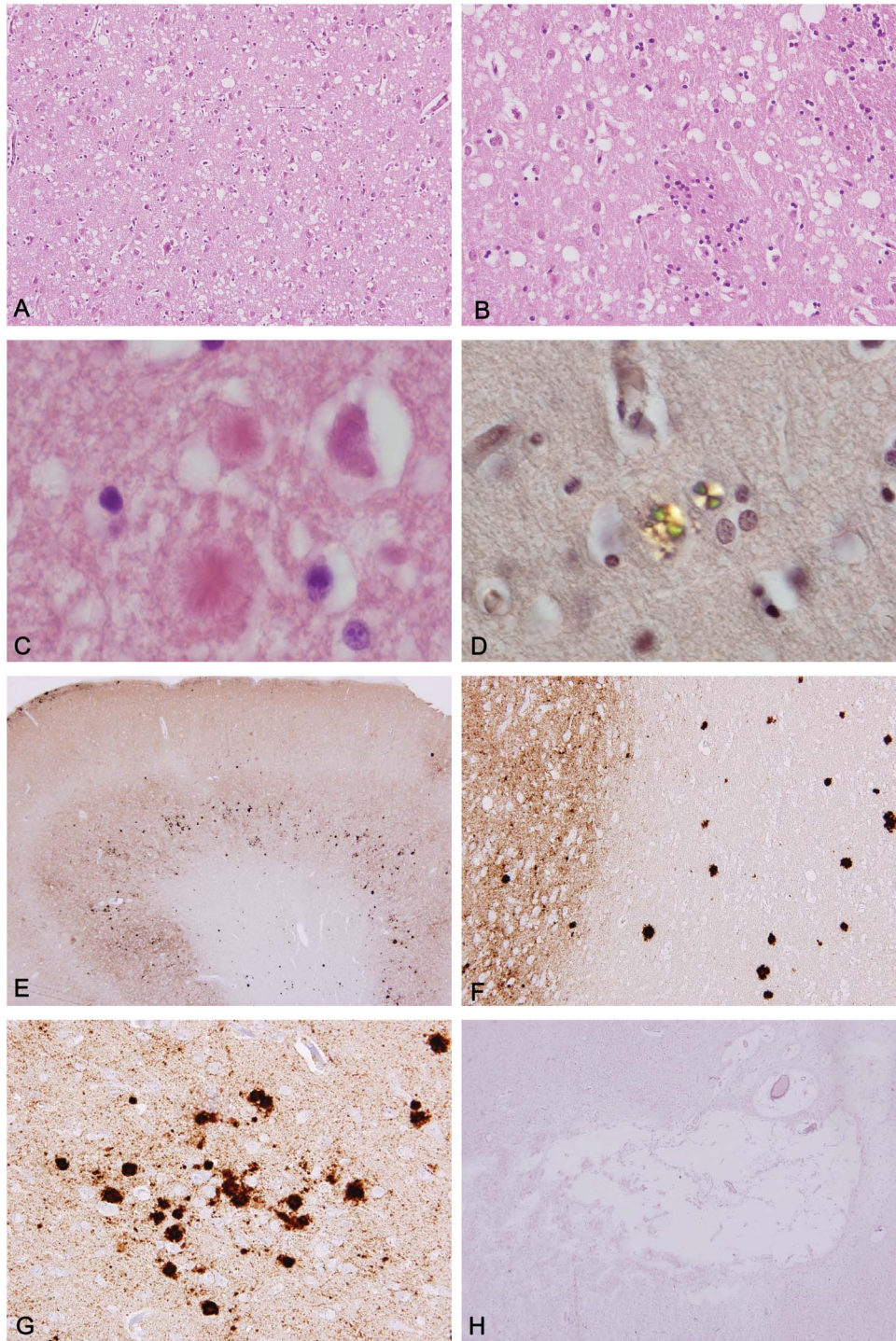


Figure 3. Neuropathological changes in the brain show severe spongiform dystrophy in the cerebral cortex (A) striatum (B), and amyloid deposits of pathological prion protein in the form of plaques (C); all in standard H&E staining. Histochemical properties of amyloid plaques are shown under polarized light in reaction with Congo red (D). Immunohistochemically; diffuse synaptic/perivacuolar positivity in the cerebrum (E), positivity of plaques in subcortical white matter (F), and in multi-centric amyloid plaques in the cortex (G); using monoclonal antibody raised against prion protein (clone 12F10). In the right cerebellar hemisphere, a post-ischemic lacune (H) was found using standard H&E staining. Original magnifications 50× (E), 100× (F, H), 200× (A), and 400× (B, C, D, G). [To view this figure in color, please visit the online version of this Journal.]

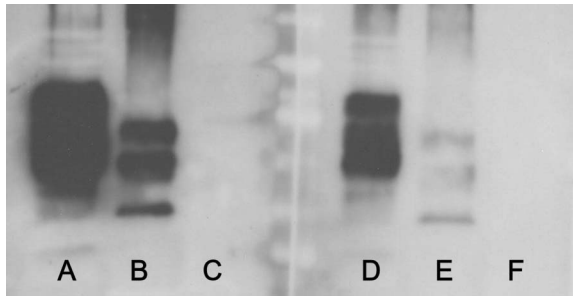


Figure 4. Confirmation of the presence of pathological prion protein in the brain tissue using western blot analysis and monoclonal antibodies against prion protein clone 6H4 (left panel) and clone 3F4 (right panel). Brain homogenates of the patient are shown in the lines B and E, positive controls A and D, and negative controls in C and F.

Giovagnoli et al., 2008; Majtényi et al., 2000; Park et al., 2010; Webb et al., 2008). Cognitive decline, if present, often develops late in the course of the disease, seldom manifests as prominent dementia and is usually not accompanied by behavioral and psychiatric symptoms such as paranoia, delusions, and severe anosognosia. Our patient did not develop psychiatric symptoms; however, early behavioral changes were the initial symptoms in this case.

Third, our case differed from usual GSS presentations in the association of positive EEG and MRI signs suggestive of sCJD. MRI scans, in GSS cases, usually show marked cerebral and cerebellar atrophy, basal ganglia abnormality –

decreased signal on T2-weighted images, and no restricted diffusion (Collins, Lawson, & Masters, 2004). A large review of GSS P102L cases reported cerebral and sometimes cerebellar-predominant atrophy; four cases had multiple white matter lesions, but none had abnormalities seen in other prion diseases such as cortical, pulvinar, or basal ganglia hyper-signals (Webb et al., 2008).

MRI signal abnormalities probably depend on the stage of the disease and a specific preponderance of histopathological changes to certain brain structures (Mittal, Farmer, Kalina, Kingsley, & Halperin, 2002; Shiga et al., 2004). In GSS, initial MRIs are usually normal. Later in the course, at 4 months (Irisawa, Amanuma, Kozawa, Kimura, & Araki, 2007) and 3 years (Arata et al., 2006) after disease onset, DWI, FLAIR, or T2 images can present increased signals in the thalamic, caudate, frontal, occipital, or insular regions, similar to sCJD cases. Finally, in late stages of prion disease, when there is significant atrophy, the DWI abnormalities typically decrease.

In a well-documented case report (Irisawa et al., 2007), early, strong, bilateral thalami, and caudate nuclei DWI hyperintensities decreased 10 months after initial examination; whereas the intensities of the cerebral and insular cortices on DWI gradually increased for a period of 12 months after initial examination and then decreased. This situation could explain negative MRIs in the majority of cases with slow progression (Barbanti et al., 1996;

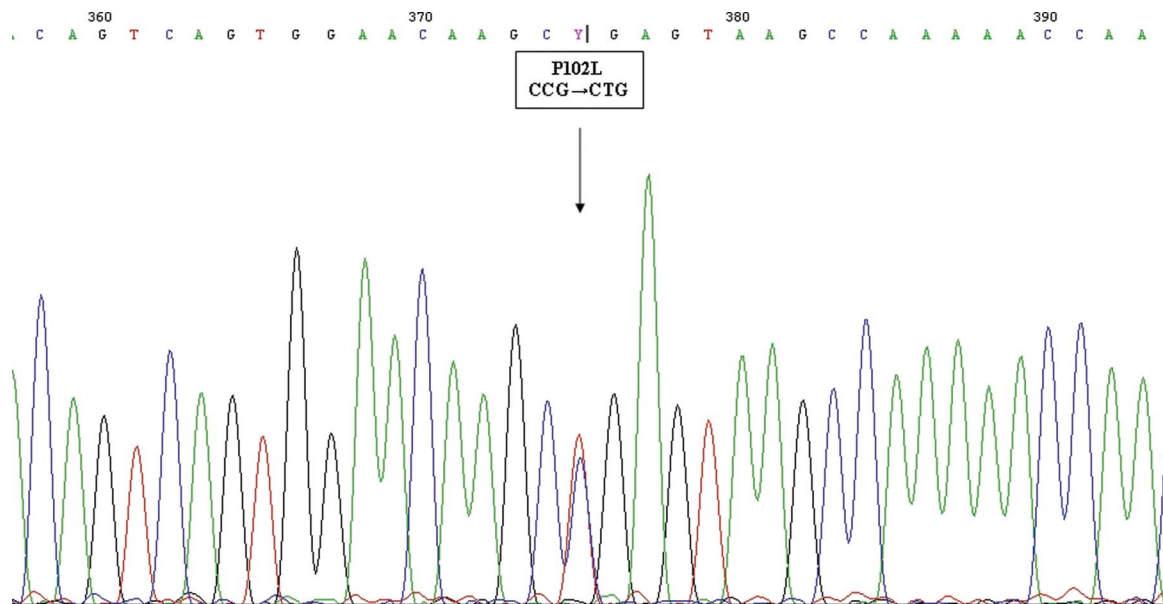


Figure 5. The P102L pathogenic mutation in PRNP. The arrow shows the precise position of the pathogenic variation on the sequencing curve.

TABLE 2
Comparison of basic features of GSS cases with P102L mutation in the literature

Articles	Age at onset, gender	Clinical presentation	Duration of illness	Mutation	EEG	14-3-3	MRI	Neuropathology
Arata et al. (2006)	11 cases 38–70 years (nine families)	Gait disturbance, dysesthesia and hypo-reflexia of the lower legs, truncal ataxia; proximal leg muscle weakness. Late dementia and mutism	3–8 years	P102L–M129	Normal or no specific abnormality	Moderately positive in two patients	High-intensity cerebral cortex lesions in occipital lobes on DWI in one patient 3 years after onset. In other cases atrophy after 4–5 years from onset.	Not performed
Barbanti et al. (1996)	8 cases 47–70 years	Dementia and severe ataxia in short illness duration (less than 1 year). Ataxia slowly evolving and no cognitive impairment over 3–4 years disease course	5 months–4 years	P102L–M/M129 (M/V129 in one case)	Normal or diffuse slow waves	Not known	Cortical atrophy	Available in 1 case, spongiform changes, multi-centric, uni-centric and “kuru-like” amyloid plaques
Bianca et al. (2003)	41-year-old male	Depression, psychosis, dysarthria, ataxia, after 2 years occurred gait disturbances, limb numbness, dementia	4 years	P102L–V129	Normal EEG	Not known	Normal MRI	Not performed
Cagnoli et al. (2008)	52-year-old female	Cerebellar ataxia, frequent falls, dysmetria, hyper-reflexia, normal cognition. Late akinetic mutism	5 years	P102L	Normal EEG	Not known	Normal MRI	Not performed
Chi et al. (2010)	3 cases in detail, cases mentioned retrospectively	Case 1: truncal ataxia and cognitive decline; Case 2: gait unsteadiness with early falls, dementia, personality changes, late decerebration; Case 3: dementia, behavioral changes, auditory hallucinations, gait ataxia, mutism, myoclonus, rigidity	5 months–13 years	P102L–M129	Multifocal spikes, intermittent slow waves, later independent spikes and sharps, background slowing. Normal EEG in Case 1	Not performed	Case 1: normal MRI; Case 2: atrophy and DWI restriction peritumoral and in temporo-parieto-occipital cortical regions; Case 3: FLAIR hyperintensities in caudate, putamen, pulvinar and cortices	Not performed

(Continued)

TABLE 2
(Continued)

Articles	Age at onset, gender	Clinical presentation	Duration of illness	Mutation	EEG	14-3-3	MRI	Neuropathology
De Michele et al (2003)	11 patients, 22-71 years, 3 cases more in detail	Case 1: limb dysesthesias, gait ataxia, nystagmus, dysmetria, dysarthria, depression, slowly progressive dementia; Case 2: cognitive impairment, disorientation, insomnia, apraxia, hyperreflexia, speech disturbance; Case 3: withdrawal behavior, dementia	3-7 years	P102L	Diffuse slowing and spikes in temporal lobes in Cases 2 and 3	Not performed	Brain and cerebellar atrophy in Cases 2 and 3	Hematoxylin-eosin cerebellar slides – decreased number of Purkinje cells, uni-centric kuru-type eosinophilic plaques, absence of spongiform changes, immunohistochemistry not performed
Giovagnoli et al. (2008)	31-year-old male	Headache, sweating, dysarthria, pyramidal signs, but no ataxia. Late dementia, mutism and myoclonus	25 months	P102L, 129 codon not known	Incomplete periodic synchronous discharges	Not performed	High intensities in bilateral caudate nuclei, thalami on T2 and in cerebral cortices on DWI	Not performed
Kretschmar et al. (1992)	1 family, 3 cases 39-51 years	Case 1: dementia, muscular atrophy, paralysis of cranial nerves IX, X, XI, neurogenic pattern on EMG, severe cerebellar ataxia; Case 2: fasciculations, EMG fibrillation patterns, atrophy of tongue with fasciculations, severe ataxia; Case 3: progressive ataxia, pyramidal signs, myoclonus, spasticity, cognitive deficit	2-4 years (N/A in case 3)	P102L	Not known	Not performed	Not known	Not given
Majtenyi et al. (2000)	3 cases: sisters – 56-66 years	Case 1: aphasia, visual agnosia, dysexecutive syndrome, hemiparesis, rigidity, upper extremity dystonia; Case 2: paresthesias, hemiparesis, dysarthria, memory loss, gait and truncal ataxia; Case 3: behavioral changes, visual loss, aphasia, dementia	2-2.5 months	P102L-M129	Generalized periodic spike and slow wave activity	Not performed	Not performed; CT was normal	Spongiform changes, PrP positive uni-centric “kuru” or multi-centric plaques, and abundant [beta]-A4-positive senile plaques

Park et al. (2010)	46-year-old female	Slowly progressive ataxia, gait and cognitive decline, dysarthria, severe dementia, perioral dyskinesias; no myoclonus	3 years (still alive)	P102L	Non-specific generalized theta–delta slow waves	Positive	DWI and FLAIR hyperintensities over the entire hemispheric cortices; no putaminal signs	Not performed
Takazawa et al. (2010)	38-year-old female	Dysarthria, agraphia, cerebellar ataxia, late insomnia. Leg hyperreflexia as early sign	5 years (still alive)	P102L–M129	Diffuse theta and delta waves	Positive	Vermis atrophy, DWI and FLAIR fronto-parietal cortical hyper signal	Not performed
Tanaka et al. (1997)	6 patients in 1 family, 2 in detail 34-year-old male, 64-year-old male (father and son)	Case 1: mental deterioration, speaking and writing difficulties, important reduction in verbal fluence, mild ataxia and wide based gait; Case 2: unsteadiness in walking, dysdiadochokinesis in the left arm, normal cognition	4 years in Case 1 (N/A in Case 2)	P102L–E219K	Normal	Not performed	Atrophy in the cerebral cortex, normal cerebellum, in addition multiple ischemic lesions in case 2	No spongiform changes, no neuronal loss, mild to moderate gliosis, diffuse cortical plaques not stained with hematoxylin-eosin or Congo red
Yamada et al. (1999)	39-year-old female, 35-year-old female	Case 1: gait difficulty, dysarthria, ataxic gait, dysesthesia and painful paresthesias, no dementia; Case 2: gait and speech disturbances, truncal ataxia, dysarthria, nystagmus, areflexia in the legs, painful dysesthesias in the feet, normal cognition early (but late dementia)	3 years in Case 2 (N/A Case 1)	P102L–129M/M	Frequent bursts of theta waves in frontal leads without periodic synchronous discharges in Case 1 (N/A Case 2)	Not performed	Slight cerebellar atrophy (Case 1)	Spongiform changes in the cerebral and cerebellar cortices, kuru-type plaques, PrP deposits in brain and spinal cord

(Continued)

TABLE 2
(Continued)

<i>Articles</i>	<i>Age at onset, gender</i>	<i>Clinical presentation</i>	<i>Duration of illness</i>	<i>Mutation</i>	<i>EEG</i>	<i>14-3-3</i>	<i>MRI</i>	<i>Neuropathology</i>
Young et al. (1995)	2 cases 31 and 56 years (gender not mentioned)	Case 1: motor coordination deterioration mild degree of cognitive impairment, eyelid opening apraxia, nystagmus, cerebellar tremor and dysarthria, ataxic gait; Case 2: gait and balance disturbances, depression, cerebellar dysarthria and dysmetria, axonal neuropathy; late dementia	3–5 years	P102L–129M	Case 1: not performed Case 2: normal	Not performed	Normal	Amyloid plaques, spongiform changes, multi-centric PrP deposits
Young et al. (1997)	33-year-old male	Seizures as the presenting symptom, numbness on lower extremities, weakness, dysarthria, swallowing difficulties, no dementia	12 years	P102L–129V	Not performed	Not performed	Not performed	PrP positive amyloid plaque in cortex, hippocampi, caudate, putamen, thalamus. No spongiform changes.
Present case	44-year-old female	Early personality and behavior changes, followed by paresthesias and ataxia, later associated with memory problems, pyramidal signs, anosognosia and very late myoclonus, spasticity, and severe dysexecutive impairment	15 months	P102–129M/M	Generalized triphasic periodic complexes	Negative	FLAIR and DWI caudate, mesio-frontal and insular hyperintensities	Spongiform dystrophy, prominent amyloid plaques in the cerebellar and cerebral cortex as well as in subcortical gray matter structures, anti-PrP antibodies positivity, amyloid plaques

Cagnoli et al., 2008). In our case, with a very rapid progression, MRI findings were similar to sCJD findings (Bianca et al., 2003; Irisawa et al., 2007).

Another interesting point is the finding of generalized sharp complexes on EEGs that are typical features associated with sCJD (Knight & Will, 2004) and are one of a major diagnostic signs for probable CJD (WHO Manual, 2003). In GSS similar abnormalities are rare. In a study of three patients with GSS, similar to our case (Majtényi et al., 2000), later stage EEGs showed generalized periodic spikes and slow wave activity, but unfortunately, MRIs were not done. Conversely, the majority of GSS cases with MRI hyper-intense signal changes, similar to CJD, have normal EEG patterns (Irisawa et al., 2007; Kovacs et al., 2002; Webb et al., 2008). Our finding may again be related to the relatively severe cortical spongiform dystrophy that was found neuropathologically and which is not typical in most GSS cases.

Neuropathologically, prominent hallmarks of prion disease mostly cortical, cerebral and cerebellar spongiform dystrophy are characteristic of CJD. This picture is consistently present in GSS P102L–M129 (but not in P102L–V129; Bugiani et al., 2000). We hypothesize that the presence of spongiform changes could account for both cortical hyper-intensities on MR images and generalized triphasic sharp complexes on the EEG in our case.

In summary, there are several interfaces between CJD and GSS in this case. Clinically, CJD is more homogenous in presentation and shorter in evolution. The recently proposed Centers for Disease Control and Prevention (CDC's) criteria for sCJD (http://www.cdc.gov/ncidod/dvrd/cjd/diagnostic_criteria.html) were adapted from the original WHO 1998 criteria (WHO Manual, 2003). The updated criteria (Zerr et al., 2009) now consider probable sCJD in rapidly progressive dementia with at least two out of the four listed features: (i) myoclonus, (ii) visual or cerebellar signs, (iii) pyramidal/extrapyramidal signs, and (iv) akinetic mutism; and at least one positive laboratory result: (i) EEG periodic patterns, (ii) positive 14-3-3 in patients with a disease duration of less than 2 years, and (iii) MRI hyper-intensities in caudate nucleus and/or putamen on DWI or FLAIR. Moreover, MRI in sCJD may also include cortical ribboning in the temporal, parietal or occipital cortices (Zerr et al., 2009).

GSS is very heterogeneous, occasionally even within the same family; the duration is often 5 or more years, however, a rapid decline over a few

months has been reported (Webb et al., 2008). Ataxia is usually the first and/or predominant manifestation and cognitive decline can be mild or absent (Arata et al., 2006). MRI scans may show atrophy or even a normal pattern; however, subcortical hyper-intensities indistinguishable from findings in CJD, although rare, can occur (Mittal et al., 2002). Finally, EEG patterns of generalized sharp complexes typical for CJD are rare in GSS (Knight & Will, 2004). In contrast to the highly variable clinical picture, the neuropathological pattern of GSS is quite typical: numerous PrP positive uni- and multi-centric amyloid plaques and diffuse deposits are present in the cerebellum and cerebral hemispheres combined with varying degrees of spongiform changes, neuronal loss and reactive astrogliosis (Bugiani et al., 2000).

Therefore, our observation demonstrates that genetic prion diseases, even GSS, can look not only like other neurodegenerative diseases (i.e., atypical Parkinson's diseases, Multiple system atrophy, Alzheimer's disease, and others), but also like sCJD. This highlights the importance of genetic testing and neuropathology of all suspected sCJD cases and/or atypical neurodegenerations. The genetic origin of the disease in our patient could have easily gone unrecognized, without an autopsy.

CONCLUSIONS

The presented case of GSS differed from the typical presentation of the syndrome not only in terms of rapid disease course, early cognitive impairment, and late onset of ataxia, but also in neuroimaging and EEG findings. The clinical picture together with abnormal EEG and MRI were highly suggestive of CJD. The family history in our patient was unclear since data concerning her mother was rather sparse. Only a detailed *post mortem* neuropathological investigation with PRNP genetic analysis established the correct diagnosis. Our case broadens the spectrum of atypical GSS phenotypes and further strengthens the need for autopsies in patients with neurodegenerative disorders, since subsequent family counseling in inherited forms of disorders is fundamentally important.

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