Quantitative, functional MRI and neurophysiological markers in a case of Gerstmann-Sträussler-Scheinker syndrome

Silvia Marino, MD, PhD\textsuperscript{a,b}  
Rosa Morabito, MD\textsuperscript{a,c}  
Simona De Salvo, MSC\textsuperscript{a}  
Lilla Bonanno, PhD\textsuperscript{a}  
Alessia Bramanti, MD\textsuperscript{a}  
Patrizia Pollicino, MD\textsuperscript{a}  
Roberto Giorgianni, MD\textsuperscript{a}  
Placido Bramanti, MD\textsuperscript{a}  

\textsuperscript{a} IRCCS Centro Neurolesi “Bonino Pulejo”, Messina, Italy  
\textsuperscript{b} Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina, Italy  
\textsuperscript{c} Biomedical Department of Internal and Specialty Medicine, University of Palermo, Italy

Correspondence to: Silvia Marino, MD, PhD  
E-mail: silvimarino@gmail.com

Summary

Gerstmann-Sträussler-Scheinker syndrome (GSS) is an inherited autosomal dominant prion disease, caused by a codon 102 proline to leucine substitution (P102L) in the prion protein gene (PRNP). We describe the case of a 40-year-old male, affected by a slowly progressive gait disturbance, leg weakness and cognitive impairment. Genomic DNA revealed a point mutation of PRNP at codon 102, resulting in P102L, and the diagnosis of GSS was confirmed. Somatosensory evoked potentials showed alterations of principal parameters, particularly in the right upper and lower limbs. Laser-evoked potentials were indicative of nociceptive system impairment, especially in the right upper and lower limbs. Conventional magnetic resonance imaging (MRI) revealed marked atrophy of the vermis and cerebellar hemispheres and mild atrophy of the middle cerebellar peduncles and brainstem, as confirmed by a brain volume automatic analysis. Resting-state functional MRI showed increased functional connectivity in the bilateral visual cortex, and decreased functional connectivity in the bilateral frontal pole and supramarginal and precentral gyrus. Albeit limited to a single case, this is the first study to assess structural and functional connectivity in GSS using a multimodal approach.

KEY WORDS: brain atrophy, functional connectivity, Gerstmann-Sträussler-Scheinker, laser-evoked potentials.

Introduction

The human prion diseases are fatal neurodegenerative disorders that include Kuru, Creutzfeldt-Jacob disease, Gerstmann-Sträussler-Scheinker syndrome (GSS) and fatal familial insomnia (Chen and Dong, 2016). Gerstmann-Sträussler-Scheinker syndrome is an inherited autosomal dominant prion disease, caused by a codon 102 proline to leucine substitution (P102L) in the prion protein gene (PRNP) (Takazawa et al. 2010, Salsano et al., 2011; Collins et al., 2001; Asante et al., 2015). Since GSS was first linked to a P102L mutation in PRNP, a variety of mutations in the allele on chromosome 20 have been described in association with this disorder (Collins et al., 2001; Asante et al., 2015; Webb et al., 2008). GSS is clinically characterized by a midlife onset and slow progression of cerebellar ataxia and dementia (Takazawa et al., 2009). The mean duration of the disease varies between 5 and 7 years (Ortega-Cubero et al. 2011).

To our knowledge, neurophysiological data on GSS are scarce. In the literature, motor evoked potentials and nerve conduction studies were normal in most cases (Salsano et al., 2010; Takase et al., 2001); somatosensory evoked potentials (SEPs) were normal or showed only minimal abnormalities, such as delayed N13-N20 interpeak and N20 latencies in the upper limbs (Takase et al., 2001). Electromyography showed slight chronic denervation signs in some cases, while electroencephalography (EEG) was usually normal. No studies have reported the use of laser-evoked potentials (LEPs). With regard to magnetic resonance imaging (MRI), no use of quantitative MRI or functional MRI (fMRI) has been reported.

Only spectroscopic MRI and single-photon emission computed tomography (SPECT) have been performed: Konaka et al. (2000), in a \(^{1}H\)-magnetic resonance spectroscopy (\(^{1}H\)-MRS) study, described a decrease in the NAA/Cr ratio in the frontal lobe, cerebellum and putamen. Kepe et al. (2010), in an \(^{18}FDG\) PET study, showed a metabolic decrease in the neocortex and basal ganglia. Arata et al. (2006), in SPECT studies, demonstrated diffuse hypoperfusion, predominant in the occipital lobes. We here describe a case of a patient with GSS. Our aim was to assess resting-state fMRI activation, brain volume and neurophysiological markers in this patient, in order to evaluate cortical networks involved in the pathogenesis of this rare disorder.

Materials and methods

Neurological examination of a 40-year-old male showed mild truncal and limb ataxia, ataxic speech, sensory impairment and areflexia in the lower extremities. Pyramidal signs were identified. He also presented dysarthric and dysphagic disturbances and showed progressive
cognitive impairment (Montreal Cognitive Assessment 22/30). Genomic DNA was extracted from peripheral lymphocytes to perform genetic analysis and a point mutation of PRNP at codon 102, resulting in P102L, was identified.

Genetic analysis was negative for spinocerebellar ataxia types 1, 2, 3 and 6. In the family history, his mother had shown similar progressive symptoms, approximately 5 years previously, and genetic analysis had confirmed the same mutation. The P102L mutation was also detected in his asymptomatic younger sister.

Brain MRI acquisition was performed using 3T whole-body MRI equipment (Achieva, Philips Medical System, Best, the Netherlands) with a 32-element phased array sensitivity-encoding (SENSE) head coil. The MR system was equipped with gradients achieving a maximum slew rate of 200 mT/m and a maximum strength of 80 mT/m.

The imaging protocol included 3D T1-weighted fast field echo (FFE), 3D FLAIR, and two-dimensional axial DP/T2-weighted fast spin echo (FSE) sequences. The 3D T1-weighted FFE images were acquired with the following parameters: repetition time (TR) 8.2ms; echo time (TE) 3.7 ms; section thickness 1 mm; number of signals averaged 1, and reconstruction matrix 512x512. 3D FLAIR images were acquired with TR 12000 ms, TE 140 ms, inversion time (TI) 285 ms, section thickness 4 mm, number of signals averaged 1, and reconstruction matrix 512x512.

DP/T2-weighted dual FSE images were acquired with TR 2000 ms, TE 10 ms/TE 80 ms, section thickness 4 mm, and number of signals averaged 1. The scan parameters of the resting-state fMRI scan were as follows: TR = 3.0 sec; TE = 35 ms; flip angle = 90°; and voxel size 1.9 * 1.9 * 4.0 mm, scan duration 10 min. During the resting-state scan, the patient was instructed to lie still with his eyes closed and not to fall asleep.

SIENAX is the cross-sectional version of the structural image evaluation which uses the normalization of atrophy method (Smith et al., 2002) to estimate global and regional brain tissue volumes normalized for subject head size. The brain volume was calculated by measuring the volume differences inside a mesh over the exterior surface of the brain and inside the ventricles. Partial volume correction was employed to limit the impact of cerebrospinal fluid (CSF) within the cerebral sulci. The algorithm extracted the skull and brain masks from an image at a single time point. The brain image was then affine-registered to a canonical image (MNI-152 image) in a standardized space (using the skull image to provide the scaling cue), a procedure that provides a spatial normalization (scaling) factor for the single subject. Then, tissue-type segmentation with partial volume estimation was performed to calculate the total volume of brain tissue, including separate estimates of volumes of grey matter (GM), white matter (WM) and ventricular CSF (Smith et al., 2002). Finally, standard space masks were also used to provide estimates of ventricular CSF and “peripheral” grey matter volumes (De Stefano et al., 2003). All volumetric outputs are provided both normalized for head size and un-normalized. The primary output is referred to as total normalized brain volume (NBV).

The fMRI data were processed with FSL (FMRIB’s Software Library, www.fmrib.ox.ac.uk/fsl). Using different modules of the FSL software package, the following pre-processing procedure was applied: the pre-processing of the resting-state data consisted of motion correction (Jenkinson et al., 2002), brain extraction (Smith, 2002), spatial smoothing using a Gaussian kernel with a full width at a half maximum of 8 mm. After pre-processing, the functional images were registered to the corresponding high-resolution echo planar images, which were registered to the T1-weighted images and the 2 mm isotropic MNI-152 standard space image (Jenkinson et al. 2002). These registration parameters were combined to obtain the registration matrix from native (fMRI) space to MNI space and its inverse (from MNI space to native space). The functional connectivity analysis was performed using the dual regression method of FSL, a technique that allows a voxel-wise comparison of resting-state functional connectivity (Filippini et al., 2009).

We compared the results of our patient with those of a group of five sex- and age-matched healthy subjects. Resting-state EEG recordings were performed with electrodes placed according to the standard 10-20 International System. Laser-evoked potentials were recorded after skin stimulation at dorsum of feet and hands using a Nd:YAP laser device (EL.EN, Florence, Italy). Stimulus intensity was set up at 2.75J, corresponding to an energy transfer of 21.54J/cm2; the handle of the stimulator was held perpendicular to the skin surface. LEPs were recorded by two surface Ag-AgCl electrodes placed along the midline (Fz and Cz according to the 10-20 International System) and by one electrode in the left or right temporal region (T3 and T4), contralaterally to stimulation site. The reference electrode was placed on the nose and the ground electrode on the forehead (Fpz). SEPs were also recorded in upper and lower limbs.

Results

Conventional MRI examination revealed marked atrophy of the vermis and cerebellar hemispheres, associated with enlargement of the subarachnoid spaces, and mild atrophy of the middle cerebellar peduncles and brainstem (Fig.1).

Automatic analysis of brain volumes was performed using SIENAX, and showed a decrease in the NBV (1376.5 cm3), GM (699.0 cm3) and WM (677.4 cm3) values, compared with the corresponding values recorded in five age- and sex-matched male healthy controls, (41±2 years, NBV 1659.7±3821.0 cm3, GM 901.7±259.5 cm3 and WM 758.0±125.7 cm3, p<0.01). A MELODIC analysis found 43 components in the patient. For our analysis, the artifact components were removed and five networks were included: default mode network, right attention network, left attention network, medial visual network, lateral visual network. The patient showed increased functional connectivity in the bilateral visual cortex, bilateral superior parietal cortex, and a decrease in primary somatosensory cortex compared with the control group (Fig. 2, Table I). In addition, the patient showed decreased functional connectivity in the bilateral frontal pole, primary somatosensory cortex, supramarginal and precentral gyrus (Table II).
Electroencephalogram traces showed frequencies between 8-10 Hz, symmetrical, especially in parietal-occipital areas. Furthermore, we recorded sharp wave and polymorphic theta in both hemispheres (Fig. 3). Visual evoked potentials and brainstem auditory evoked potentials were normal, whereas SEPs showed alterations of principal parameters (latency and amplitude), particularly in the right upper and lower limbs. LEPs were indicative of nociceptive system impairment, after laser stimulation of the right upper and lower limbs (Fig. 4).

Discussion

The human transmissible spongiform encephalopathies (TSEs) are generally sporadic neurodegenerative disorders, but can also occur in genetic and acquired forms (Chen and Dong, 2016; Collins et al., 2001; Park et al., 2010; Huang et al., 2015; Araújo 2013). The human PRNP on chromosome 20 governs most of the clinical and pathological features of prion disease and plays an important role in the determination of host...
susceptibility (Takazawa et al. 2010). Gerstmann-Straussler-Scheinker syndrome is a rare genetic form of TSE that was originally described in a large Australian family and is characterized by autosomal dominant inheritance (Collins et al., 2001; Park et al., 2010). A variety of mutations in the allele of chromosome 20 have been described in association with this disorder. In particular, seven point mutations, of PRNP codon 102, 105, 117, 145, 198, 202 and 217, have been detected in GSS patients. The most frequent is point mutation P102L (Takazawa et al., 2010; Collins et al., 2001; Ortega-Cubero et al., 2013; Kraus et al., 2015).

Mutations of the PRNP gene induce a change in the conformation of the normal PrPc protein to the pathological form PrPSc (Chen and Dong, 2016; Huang et al., 2015; Araújo, 2013; Kraus et al., 2015). The resulting accumulation of PrPSc in the lysosomes causes them to swell and eventually burst, thereby releasing the damaging proteolytic enzymes and PrPSc into the cell (Araújo, 2013). PrPSc is neurotoxic and its accumulation leads to apoptosis and cell death (Araújo, 2013).

Although quite rare, GSS may result in pronounced and sometimes rapid cognitive, motor and clinical decline. Our patient showed slowly progressive cerebellar ataxia accompanied by spastic paraparesis, and extrapyramidal signs. In addition, he presented moderate cognitive impairment, which correlated with the brain cortical and cerebellar atrophy. In addition, automatic analysis of cortical volume revealed a decrease in total volume, but also in GM and WM, when compared with normal controls. These findings seem to suggest a neurodegenerative process that could explain the neurological symptoms and cognitive decline, due to cortical GM microstructural abnormalities. In addition, cerebellar atrophy could also explain the cognitive impairment, since the cerebellum is known to contain several cognition-related sub-regions involved in different functional networks.

With regard to functional studies, a decrease in the NAA/Cr ratio in the frontal lobe, cerebellum, and putamen has been shown on 1H-MRS examination, even in the absence of other abnormal imaging results (Konaka
PET studies using F-18FDG have shown a metabolic decrease in the neocortex, basal ganglia and/or thalamus (Kepe et al., 2010). Altered diffusion in the striatum, thalamus and frontal and occipital cortices was observed in most genetically confirmed GSS patients (Ortega-Cubero et al., 2013).

Albeit limited to a single case, this is the first study to explore quantitative MRI and fMRI markers in GSS. At present, there are no studies large enough to permit meaningful analysis of neuroimaging results, and findings from the few studies that have been completed are not sufficiently homogeneous to be useful in diagnosis. In comparison with the control group data, resting-state fMRI showed increased functional connectivity in the bilateral visual cortex and bilateral superior parietal cortex, and a decrease in the primary somatosensory cortex. In addition, the patient showed decreased functional connectivity in the bilateral frontal pole, primary somatosensory cortex, and supramarginal and precentral gyrus. The supramarginal gyrus is part of the somatosensory association cortex, which interprets tactile sensory data and is involved in the perception of space and limb position in space. The frontal pole is connected to the higher-order sensory association cortex. Recent studies found novel evidence suggesting that the frontal pole in humans is connected to the posterior visual cortex (Orr et al., 2015). These findings seem to be consistent with our fMRI data, which showed functional connectivity between the frontal pole and visual cortex.

The precentral gyrus is also referred to as the primary motor area or primary motor cortex, although it is most commonly called the motor strip. It is located in the frontal lobe and on both sides of the brain. The decreased connectivity shown by all these areas in our patient suggests a functional impairment in GSS, correlated with clinical assessment.

Our neurophysiological data showed right LEP abnormalities which might be considered to indicate a dysfunction of the posterior roots or columns of the spinal cord, including the dorsal horns and proximal peripheral nerve, even though lumbosacral MRI was normal (data not shown). These findings correlated with the SEP recordings, as latency and amplitude in the right upper and lower limbs were abnormal. Both LEP and SEP
recordings showed a right impairment and correlated with resting-state functional connectivity, which was decreased in the left primary somatosensory cortex. In conclusion, we described the case of a GSS patient. Our aim was to examine resting-state functional MRI activation, brain volume and neurophysiological markers in this patient in order to shed light on cortical networks involved in the pathogenesis of this rare disorder, and clarify a multimodal approach that could be useful for performing differential diagnosis and for detecting specific disease alterations. However, future studies might provide additional and important new insight into the pathology underlying prion diseases, and also monitor potential drug and rehabilitation treatments.

References