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Akinetic Mutism, Spastic Tetraparesis and Rapidly Progressive Dementia of Subcortical Frontal Topography as a form of Presentation of Progressive Supranuclear Palsy

García Granado JF[1] and Pérez García MDP[2]*

[1]Department of Neurology, Hospital Universitario de Gran Canaria Doctor Negrín (HUGCDN), Spain

[2]Department of Primary Care, Hospital Universitario de Gran Canaria Doctor Negrín (HUGCDN), Spain

Abstract

Progressive Supranuclear Palsy (PSP) is a neurodegenerative disease characterized by progressive supranuclear ophthalmoplegia, gait disturbance and postural instability, dysarthria, dysphagia, stiffness and frontal cognitive impairment. Its definitive diagnosis is neuropathological but clinical features and rational screening for other rapidly progressive neurodegenerative diseases can establish the diagnosis if validated diagnostic scales and criteria are properly applied. The present case is a 77-year-old female patient with chronic parkinsonism and postural instability classified as Parkinson's disease. She was admitted with a clinical picture of rapidly progressive neurological deterioration with functional limitation. Physical examination revealed spastic tetraparesis, akinetic mutism and subcortical frontal profile cognitive impairment with associated frontal release reflexes. Frontal atrophy in cranial MRI, alteration of the bilateral presynaptic dopaminergic pathway in cerebral SPECT, frontal and basal ganglia hypometabolism in PET-CT and negativity of levodopa test are findings suggestive of this disease, which allowed the diagnosis to be established. Assessment by a multidisciplinary team and the application of symptomatic treatments were the main focus of the therapeutic approach to this patient.

Keywords: Progressive supranuclear palsy; Akinetic mutism; Spastic tetraparesis; Frontal cognitive impairment

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Correspondence:
Juan Francisco García Granado, Department of Neurology, Hospital Universitario de Gran Canaria Doctor Negrín (HUGCDN), Canary Islands, Spain

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Introduction

Progressive Supranuclear Palsy (PSP) is a neurodegenerative disease that occurs in people aged 30 years and older, with a usually gradual progression [1]. It is the most common of the degenerative forms of atypical parkinsonism, with an estimated prevalence of 3 to 7 per 100,000 adults [2].

As originally described, PSP was characterized by progressive supranuclear ophthalmoplegia, gait disturbance and postural instability, dysarthria, dysphagia, rigidity and frontal cognitive impairment [3]. Consistent pathological features of PSP consist of neuronal loss, globose neurofibrillary tangles, tau-positive inclusions found in tufted astrocytes and gliosis mainly in the basal ganglia, cerebellum, brainstem and, to a lesser extent, cerebral cortex [4], with astrocytic plaques and abnormal fiber tufts being highly characteristic of typical PSP [5]. Its etiology corresponds to a 4-repeat tauopathy in the microtubule-binding domain, although the mechanism is not known in detail [6].

Neuropathological examination remains the gold standard for definitive diagnosis. The pathological diagnosis of PSP is based on the identification of a high density of neurofibrillary tangles and neuropil threads in the basal ganglia and brainstem [7,8]. However, in 2017, the Movement Disorder Society (MDS) proposed new diagnostic criteria for PSP. These MDS-PSP criteria include a set of core features (inclusion and exclusion criteria) required for diagnosis, four core functional domains (ocular motor dysfunction, postural instability, akinesia and cognitive dysfunction) as characteristic manifestations of PSP, supportive clinical features that increase confidence in the diagnosis, operational definitions for core and supportive functions and four levels of diagnostic certainty [9].

There are no treatments that alter the natural history of the disease in PSP and no drugs that provide significant symptomatic benefits as seen with levodopa in Parkinson's disease. A multidisciplinary approach involving healthcare professionals from neurology, physiotherapy, occupational therapy, speech pathology, nutrition, neuropsychology, psychiatry, social work and

palliative care is essential [10].

The purpose of this review is to present a clinical case of PSP treated at the Hospital Universitario de Gran Canaria Doctor Negrín (HUGCDN). The aim is to expose and emphasize the rare form of presentation objectified in this case, manifesting as an akinetic mutism, a rapidly progressive spastic tetraparesis and dementia of frontal topography.

Case Presentation

A 77-year-old woman with a history of hypertension and type 2 diabetes mellitus. She was diagnosed with probable Parkinson's disease with a negative levodopa test. She was admitted for a clinical picture of chronic neurological deterioration starting approximately 2 years ago, but with a rapid and marked worsening in the last 3 to 4 months. The clinical manifestations began with frequent falls, marked gait instability, cognitive deterioration with progressive frontal subcortical profile and functional limitation, as well as epileptic seizures of uncertain origin.

On inspection, the patient had a surprised facies with hypercontraction of the bilateral frontalis muscle and facial dystonia. There is a limitation of the upper vertical gaze, spastic tetraparesis in all 4 limbs with global bradykinesia and generalized tremors of distal predominance, of the lower limbs and slightly more intense on the left side. He also presented with akinetic mutism, marked frontal release reflexes with glabellar and palmomental reflex present and striatal 1st finger sign of the left lower limb.

A complementary diagnostic study was carried out using cranial MRI, which showed no conclusive neuroradiological data, except for hydrocephalus, probably in the context of bilateral symmetrical hemispheric atrophy of predominantly anterior frontal and temporal poles (ex-vacuo hydrocephalus). In order to complete the study, a CSF evacuation test was performed, extracting 40 ml of CSF, with no subsequent clinical improvement. The CSF biomarker study showed a pattern according to the ATN (Amyloid/Tau/Neurodegeneration) A+ T- N+ classification, without establishing conclusive clinical or neuroradiological data of Alzheimer's disease. The study was completed with DATSCAN which showed alteration of the bilateral presynaptic dopaminergic pathway. Given these findings and the clinical context suggestive of advanced neurodegenerative disease with rapidly progressive deterioration, the first possibility of an atypical parkinsonian syndrome in the context of Progressive Supranuclear Palsy was raised, showing severe bilateral frontal and anterior and posterior cingulate hypometabolism in the cranial PET-CT scan, in the right precuneus and upper and lower parietal region, and severe decrease in the uptake of both striates, predominantly on the left, findings compatible with this disease. After coordination with the Geriatrics team and the Social Worker, the patient was treated at an approved center, with symptomatic treatment and died 3 weeks

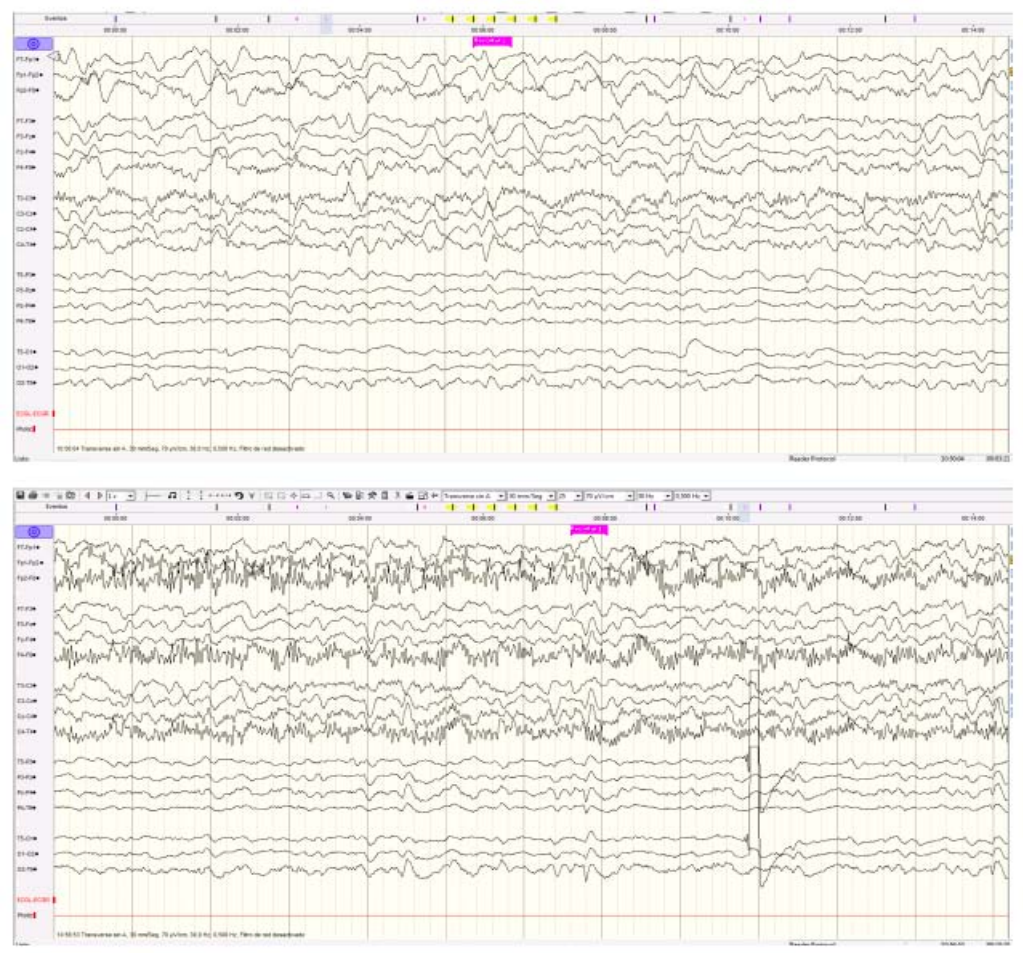

Figure 1: Electroencephalogram. Transverse bipolar assembly. EEG tracing with base rhythm at 2 Hz to 5 Hz where epileptiform discharges in the form of acute and triphasic waves with diffuse distribution are seen.

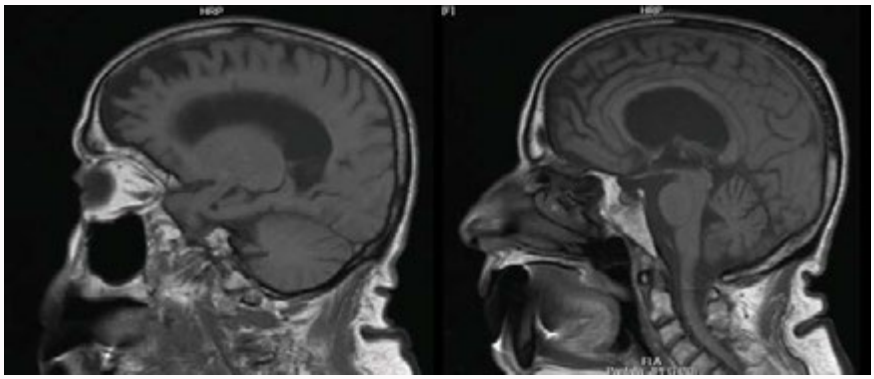

Figure 2: Brain MRI in T1 sequence, sagittal section. Cerebral hemispheric atrophy predominantly anterior frontal with associated ventriculomegaly.

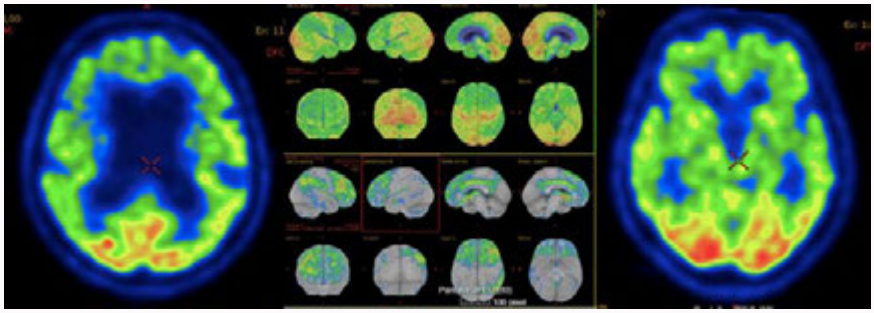

Figure 3: PET-TC. Severe bilateral frontal hypometabolism and anterior and posterior cingulate hypometabolism. Moderate/severe hypometabolism in the precuneus and the right superior and inferior parietal regions. Severe decrease in uptake of both striatal nuclei, predominantly left.

after discharge from hospital.

Complementary tests

Blood tests: General biochemistry: Glucose, ions, renal and hepatic function within normal parameters. C-reactive protein 65.88 mg/L (0.0-5.0). Hemogram, folic acid, vitamin B12, thyroid hormones and urinalysis with results within normal parameters.

Cerebrospinal fluid (CSF): Colorless and clear. Cellularity with 5 leukocytes/mcL; 1200 red blood cells/mcL; Glucose 102 mg/dL (40-70); Total protein 16.43 mg/dL (15-45). CSF culture negative. Protein study in biological fluids with TAU Protein 223.00 pg/mL (146.00-410.00), TAU Phosphorylated Protein 20.20 pg/mL (21.50-59.00), Beta amyloid peptide 1 to 42 of 198.00 pg/mL (725.99-1777.00), Beta amyloid peptide 1 to 40 of 2551.00 pg/mL (7755.00-16715.00), Beta amyloid peptide 1 to 42/beta-amyloid 1 to 40 ratio of 0.08 (0.069-0.155). CSF prionopathy study with positive CSF prion protein 14-3-3.

CSF extraction test (Tap Test): No clinical signs of clinical neurological improvement after evacuation of 40 ml of CSF. No intracranial hypertension.

Chest-abdomen CT scan: Normal findings and no signs of neoplastic disease.

Electroencephalogram (EEG): Trace with base rhythm of irregular morphology and globally and significantly slowed, with occasional presence of epileptiform discharges in the form of diffuse and triphasic waves of acute morphology (Figure 1).

Cranial MRI: Symmetrical atrophy in the cerebral hemispheres, predominantly in the anterior frontal and temporal poles. No microvascular lesions or signs of leukoaraiosis. There are no signal changes in the diffusion study suspicious for prion disease. Ventriculomegaly with increased periventricular T2 signal. Moderately prominent Sylvian fissures and relative collapse of sulci in convexity (Figure 2).

Brain PET-CT: Severe bilateral frontal and anterior and posterior cingulate hypometabolism. Moderate/severe hypometabolism in precuneus and right superior and inferior parietal regions. Severely decreased uptake in both striate nuclei, predominantly left (Figure 3).

Brain SPECT with 5 mCi of 123I-FP-CIT: Altered presynaptic dopaminergic radiotracer uptake in striatal nuclei, left predominant. There is a marked decrease in activity in putamen and right caudate, as well as sharpening of the left putamen with apparent preservation of the left caudate. Findings compatible with alteration of the bilateral presynaptic dopaminergic pathway.

Discussion

Progressive Supranuclear Palsy is a rare late-onset neurodegenerative disease characterized by oculomotor dysfunction, postural instability, akinesia-rigidity and cognitive dysfunction.

With this clinical case we want to emphasize the importance of establishing a correlation between the present symptomatology and the lesional topography objectified with PET-CT findings, where hypometabolism in the frontal region could explain the rapidly progressive and atypical onset of this patient's symptoms: An akinetic mutism with spastic tetraparesis and frontal cognitive dysfunction.

We would also like to emphasize that the common symptoms of classic PSP are not always present (progressive supranuclear

ophthalmoplegia or slowing of vertical saccadic movements, axial rigid-kinetic syndrome and postural instability, gait disorder, dysarthria, dysphagia, among others) but that on many occasions the symptoms present will depend on the lesional topography congruent with the onset of neurodegeneration, which does not always begin in the mesencephalic territory. In fact, the preservation of the volumetric morphology of the midbrain in the neuroimaging tests performed in this patient is striking, an unusual finding, with a predominance of degeneration in other areas of the central nervous system such as the striatum and the frontal, prefrontal, insular, premotor and supplementary motor areas.

The anamnesis should play a relevant role in the diagnosis of these diseases, as in this case, where the history of falls and the data on postural instability at the onset of the disease guided the diagnosis. This case therefore emphasizes the importance of establishing differential diagnoses with other neurodegenerative diseases or prion diseases, this process being more complex the more advanced the disease is due to the overlapping of common symptoms with other diseases, which is a clinical-diagnostic challenge.

The specificity of 14-3-3 prion protein in CSF is currently 80%, so a positive result of this marker in CSF should not assume the diagnosis of Creutzfeldt-Jakob Disease (CJD) where the low prevalence of the disease and the low specificity of the test leads to the conclusion that the vast majority of positive tests will represent false positives [11]. Therefore, the detection of 14-3-3 protein in CSF should be considered a complementary rather than diagnostic test for the diagnosis of prion diseases [12].

Progressive dementia, pyramidalis in the form of spastic tetraparesis, akinetic mutism and CSF 14-3-3 protein positivity are findings that, according to the criteria of the Centers for Disease Control and Prevention (CDC) [13], would establish the diagnosis of probable CJD, but we consider that further diagnostic investigations point to the diagnosis of PSP due to the following reasons: clinical course for more than 2 years, previous history of falls and postural instability, CSF prion protein un-specificity and the results of nuclear medicine tests with bilateral presynaptic dopaminergic involvement and the profile of neurodegeneration in frontal territory and basal ganglia.

Conclusion

Progressive supranuclear palsy is a rare neurodegenerative disease characterized by oculomotor dysfunction, postural instability, akinesia-stiffness and cognitive dysfunction. Establishing a differential diagnosis with other neurodegenerative diseases is crucial where anamnesis, physical examination and complementary tests play a relevant role. Frontal profile cognitive dysfunction, akinetic mutism and rapidly progressive spastic tetraparesis as a manifestation of PSP have not been described in the literature at present.

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