

# Pallidopyramidal Syndrome and Hereditary Spastic Paraplegia common features and diagnostic approach and therapeutic considerations

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## Abstract

The neurological diagnosis, can be, in some situations, a challenging one. Clinical presentation for neurological disease, which has no imagistic diagnosis criteria, can develop during several month or years. Therefore, the first evaluation of the patient with neurological symptoms is not always conclusive. Pallidopyramidal syndrome and hereditary spastic paraplegia (HSP) can present common features and diagnostic approach has to be careful. genetic assessment is the gold diagnosis method in some cases. Therapeutic strategies, following a correct diagnosis has to be addressed to improvement the patient's quality of life by rehabilitation methods and medication targeting the pathophysiological processes involvement. The aim of this paper is to discuss the clinical evolution and the diagnosis strategies in hereditary spastic paraplegia.

**Key words:** *pallidopyramidal syndrome, hereditary spastic paraplegia, extrapyramidal syndrome, neurodegeneration,*

## Introduction

Usually, the neurological diagnosis is based on several well –rounded stages: from clinical symptoms to syndrome diagnosis and topographical diagnosis. Quite often this sequence is sufficient for the diagnosis and therapeutic attitude. However, sometimes the patient presents myriads of symptoms and clinical signs apparently defy any logic. The association between extrapyramidal hypertonia, bradykinesia, resting tremor, motor deficiency in the lower limbs, pyramidal hypertonia at the same level, and pyramidal pathological signs stands as an example. There are some models of neurological pathology with a similar clinical presentation with or without known genetic cause but the current classification and nomenclature remain confusing (1). Moreover, the pathogenetic mechanisms of these disorders are not fully elucidated. But in the last few years, functional and genetic studies in the field of neurology have shown interesting links between Parkinson's disease, lysosomal storage disorders (LSD), neurodegeneration with brain iron accumulation (NBIA) and other neurodegenerative diseases (1,2,3). It is currently considered that

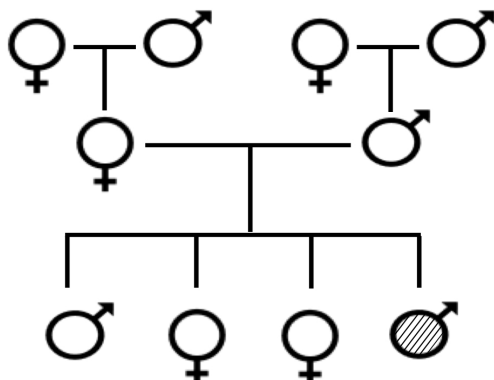
lysosomes and mitochondria form a “functional continuum” with great implications in neurodegenerative disease. (1,4,5). Metabolic pathways that depend on mitochondria and lysosomes are critical in the development of neurodegenerative pathology (5,6).

Pallidopyramidal syndrome is a rare genetic (7,8) or sporadic (9) neurological disorder characterized by the association of both parkinsonian signs (bradykinesia, rest tremor) and pyramidal signs (motor deficit in the lower limbs, spasticity at the same level, bilateral Babinski's sign), in varying proportions. Davison described five affected cases in three families (7). He also added a neuropathological description that revealed degenerative changes in the globus pallidus, thinning of the ansa lenticularis and early demyelination of the pyramids and crossed pyramidal tracts. (7). The onset of the clinical symptoms in the cases described by Davison occurs between the ages of 13 and 22. Furthermore, the first symptoms that occurred were the extrapyramidal ones. For this reason we believe that pyramidal symptoms, which appear later, can go clinical

unnoticed. Therefore, cases of association of extrapyramidal and pyramidal symptoms may be more numerous than previously believed. Juvenile parkinsonism has been described since 1899 (10,11,12). Interestingly, one of Hunt's patients developed Babinski's sign only later, resulting that Davison's patients might have been a variant of juvenile parkinsonism or a specific pallidopyramidal syndrome. Horowitz and Greenberg described two cases of pallidopyramidal syndrome with onset at 8 and 7 years of age respectively (8). In both cases the onset of the disease was through extrapyramidal symptoms and the patients responded well to levodopa therapy. Nisipeanu et al. (1994) reported two families in which two siblings had parkinsonian pyramidal syndrome with good therapeutic response at levodopa. (13), Panagariya et al (2007) reported a 19-year-old Indian man with pallidopyramidal syndrome with excellent therapeutic response at levodopa (14). The aim of this paper is to present a clinical case with pyramidal and extrapyramidal signs as an example of diagnosis approach for this rare neurological disorder.

**Case presentation**

We report the case of a 41 year old man, Caucasian, the first of the four children born admitted to the Rehabilitation Hospital, in 2014, who signed an informed consent related to this data presentation. The age difference between the first born (the patient presented in this paper) and the last born of the family is seven years (another brother and two sisters between). All three of them currently do not present any neurological symptoms (Fig 1).



**Fig. 1.** Patient's genealogy study. The grandparents were without symptoms. The same line descendents are also without symptoms. The genetic transmission appears to be autosomal recessive.

In his medical history here is no other known family history of neurological disease or history of a consanguinity. Our patients had a good health condition until the age of 16, when he developed relatively slow bradykinesia and distal tremor in the upper right limb. These symptoms progressed slowly and were followed by the onset of gait disturbance, approximately at the age of 21-22 years. The symptoms had worsened progressively in the following years, affirmatively without cognitive degradation. Several successive neurological examinations - up until the ages of 27-29 years have led the diagnosis to Parkinson's disease. But levodopa treatments and anticholinergic medication (trihexyphenidyl hydrochloride), low doses did not result in clinical improvement.

After the age of 30, the patient describes the occurrence of motor deficit in the lower limbs, accentuating hypertonia at the same level and consequent alteration of walking. Clinical symptoms have progressed slowly, but steadily over the last 10 years. In the last 2-3 years walking can be done only with unilateral support. Considering the cardiovascular functions, the patient is normal (blood pressure: 120/80 mmHg with no tendency to orthostatic hypotension). Neurological examination revealed an alert and fully orientated patient. Taking in consideration that bradykinesia and cognitive impairment can occur associated with thyroid hypo function (15), TSH and T4 were assessed and were found normal. Cognitive functions and memory were also normal. The patient presents a particular attitude with anterior flexion of the head and thorax. In the state of repose the patient shows a 4-5 /second "pill-rolling" tremor, more accentuated in the right upper limb. Olfactory function is good. There are no changes of visual acuity, of visual field and of oculomotor nerves function. The patient's face is inexpressive (hypomimia). The usual blink rate is reduced to 8-10/minute and Meyerson's sign was present. Hearing is normal and there are no signs of nystagmus. There are no functional changes in the territory of the bulbar nerves distribution. Ortostation is relatively difficult without support and the Romberg test cannot be performed. The patient demonstrated a scissors gait, with small steps. Walking is impossible without unilateral support. Muscle strength examination is normal in the upper limbs (5/5); however, there is a motor deficit in the lower limbs (4-/5 proximal, 3/5 distal). The patient also presents an important bradykinesia. Alternating

movements to the upper limbs are affected (supination and pronation). The arising from the chair test and pull test are positive. The muscular tonus has different changes in the upper limbs compared to the lower limbs. The upper limbs present extrapyramidal hypertonia with present cogwheel sign, whereas the lower limbs show pyramidal hypertonia. The tendon reflexes are exaggerated in the lower limbs. The patient demonstrates bilateral Babinski's sign. The vibratory sensitivity is diminished distally in the lower limbs. Occasionally, the patient has urinary sphincter disorders. He has a parkinsonian speech (soft and monotonous). Praxia is normal. Other systemic examinations were normal.

Summing up, during the patient's clinical evolution, extrapyramidal symptoms were first onset, and were followed by the pyramidal symptoms. Both are evident at this moment of evaluation. This is the reason why at the first admission to our clinic, four years ago, the diagnosis was pallidopyramidal syndrome. The patient started the treatment with levodopa/carbidopa (250/25 mg) three times/ day, propranolol – 40 mg/ day, and trihexyphenidyl – 6 mg/ day, but with little benefit.

In December 2018 the patient was once again admitted to our clinic. From a clinical point of view, there is a degree of evolution of the symptoms (especially an increase in motor deficit of the lower limbs). During this time the siblings were genetically tested. A homozygous mutation in the SPG11 gene was identified in our patient, while the patient's brother and one of his sisters were found to carry a heterozygous mutation in the SPG11 gene.

Basic hematological and biochemical investigations, including the level of ceruloplasmin, copper level in blood and urine, liver function tests and thyroid hormones, were normal. Blood protein electrophoresis, lipids profile and serological witnesses of viral infections were all normal. Neurophysiological examinations (electroencephalography, electroneurography, visual evoked potential) were also within normal limits. The study of central motor conduction (by transcranial magnetic stimulation assessment) for abductor digiti minimi was normal (4.5 ms). The same test applied for the inferior limbs (anterior tibial muscle) was found to be slightly prolonged (12.8 ms). At the first admission to our hospital, a cranial CT was performed, which did not show any abnormalities. Moreover, during the last hospitalization, the

differential diagnosis with vitamin B12 deficiency (although no megaloblastic anemia features were evident in the laboratory tests), structural spinal cord disorders (multiple sclerosis, compressive spinal cord injury) or dopa-responsive dystonia, was raised. Upon evaluation, serum vitamin B12 levels were normal (268 pg/ml). In addition, spinal cord MRI examinations were performed at cervical and dorsal level showing no significant changes or spinal cord compressions. Although, interestingly, there appeared to be a spinal cord thinning at D6 level on sagittal plane (5.8 mm instead of 7.5-8 mm) (Fig 2).

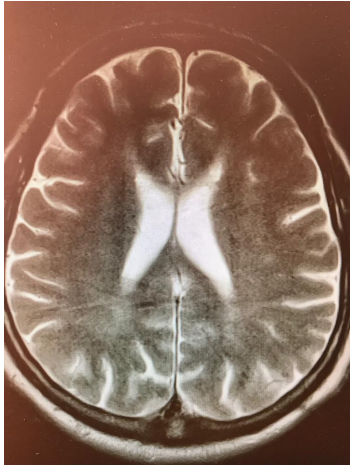


**Fig. 2.** MRI of the spinal cord T2 weighted on sagittal plane at D6 level (the spinal cord may appear small – 5.8 mm on the antero-posterior diameter).

The cranial MRI examination revealed: important atrophy of the corpus callosum (Fig 3) and a relatively large area of signal modification at the periventricular area (Fig 4).



**Fig. 3.** Cranial MRI on sagittal plane (FLAIR) reveal important atrophy of the corpus callosum.



**Fig. 4.** Cranial MRI on axial plane T2 weighted – signal changes in periventricular white matter.

These changes, through the appearance, exclude the etiology of multiple sclerosis.

These new elements once again raise the problem of diagnosis. But at the same time the question arises whether the pallidopyramidal syndrome is indeed a real clinical entity.

### Discussions

The identification of the SPG11 gene mutation accurately clarifies the diagnosis. It is about a genetic variant of hereditary spastic paraplegia (HSP) (16,17). Spastic paraplegia type 11 is part of these heterogeneous neurodegenerative and inherited disorders.

HSP was first described in 1880 by Adolf Strumpell (18). A few years later, Maurice Lorrain (1888) published a contribution to the clinical and anatomical study of HSP (19). Ever since then, HSP has been known as Strumpell-Lorrain disease. Rhein (1916) was the first who drew attention to the clinical heterogeneity of the Strumpell-Lorrain disease (20). The terminology Strumpell-Lorrain disease was reserved only for patients with spastic paraparesis (21). The term hereditary spastic paraplegia was imposed by Anita Harding in 1983 (22). Harding, who was an important pioneer in the field of molecular neurogenetics has introduced a new classification of HSP in pure HSP and complicated HSP (22). Pure HSP is clinically manifested by paraparesis, spasticity in the lower limbs and decrease in distal vibratory sensation in the lower limbs. Complicated HSP associates spasticity and motor deficit with other neurological changes: muscle atrophy, optic atrophy, mental retardation,

extrapyramidal symptoms, ataxic syndrome, peripheral neuropathy and epilepsy (22,23). The genetic transmission pattern may be autosomal dominant, autosomal recessive and rarely X-linked (23,24). SPG11 mutation were first described in patients with autosomal recessive HSP, with thin corpus callosum and cognitive impairment (24,25). To date have been identified over 70 genotype for HSP (26). The genes are designed SPG (SPastic Gait gene). With all this progress made by neurogenetics in the recent years, 40% of HSP have not yet a precise cause identified (27). the prevalence of HSP varies in different studies, depending on the used diagnostic criteria. Some studies in which the diagnosis criteria suggested by Harding were used, found the prevalence of HSP to be 2-4.3/100000 (28,29).

The major neuropathological aspect in HSP is the long axonal pathways degeneration. The corticospinal tracts, the spinobulbar and spinocerebellar tracts are interested (30). The histopathology characteristic suggested that a process of "dying back" is occurring with degeneration beginning from the end of the axon to the cell's body (31). De Luca et al describes the large pictures of neuropathological features for 6 patients with HSP (32). They support the same concept as Schwarz: axonal loss in HSP is tract specific (32).

In the last decade molecular neurogenetics has clarified many aspects of intimate knowledge of HSP. More than 102 SPG 11 mutation have been described (33). SPG 11 gene encoding spatacsin it is a protein consisting of 2443 amino acids whose function is not entirely known (25). Mutation of the same gene is responsible for some rare forms of Charcot-Marie-Tooth disease and juvenile onset amyotrophic lateral sclerosis (34). It is interesting how mutation of the same gene can lead to different phenotype expression.

Spatacsin together with spastizin, a protein encoded by SPG 15 gene are co localized on lysosome/autolysosome endosomal endoplasmatic reticulum (35). Previous studies have shown increased involvement of spatacsin in outgrowth of spinal motor axons and suggests that this protein maybe is important for formation of neuromuscular junction (36). Spatacsin is localized in cytoskeleton and synaptic vesicles of neuron axon and dendrites (33). Experimental studies on cortical rat neurons, in conditions of lowering level of spatacsin, indicated that the anterograde axonal transport was decreased

(33,37). One of the theories of the pathophysiological mechanisms involved in neurodegeneration is represented by the contribution of redox imbalance that can may lead to overproduction of reactive oxygen and nitrogen species (ROS/RNS) and subsequent oxidative tissue damage, a critical event in neurodegeneration process (38,39). It is still not fully understand the importance of oxidative stress as a primary trigger and as a consequence of neurodegenerative process. There are studies that support the contribution of oxidative stress to neuronal death initiation and also as an to neurodegenerative process augmentation. Therefore the anti oxidative therapy (39,40) and cholesterol lowering drugs added to anti spastic therapy , K<sup>+</sup> channel blocker drugs, levodopa therapy, folic acid therapy and other rehabilitation therapies (41,42,43,44,45,46) could constitute a future strategy for improving the quality of life for this patients.

### Conclusions

The diagnostic aspects and pathophysiological mechanisms associated with hereditary spastic paraplegia can constitute a real challenge. Because of the extrapyramidal syndrome presence on the disease onset, the complicated forms of HSP can be confused with juvenile Parkinson's disease. Autosomal recessive transmission of this disease lead to very rare incidence and the genealogy analysis is not always useful. Therefore the genetic diagnosis is crucial. Because there is no specific treatment for this disease a lot of various therapeutic strategies targeting pathophysiological involved mechanisms could bring hopes for this patients.

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