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Review article

Parkinsonian-Pyramidal syndromes: A systematic review

Christine Tranchant, MD [a, c, *], Meriam Koob, MD PHD [b, d], Mathieu Anheim, MD PHD [a, c]

[a] Service de Neurologie, Hopital de Hautepierre, Strasbourg, France
[b] Service d'Imagerie 2-Radiopédiatrie, Hôpital de Hautepierre, Strasbourg, France
[c] Fédération de Médecine Translationnelle, Faculté de Médecine, Strasbourg, France
[d] Laboratoire ICube, UMR 7357, Université de Strasbourg-CNRS, France

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ABSTRACT

Introduction: Parkinsonian-Pyramidal syndrome (PPS), defined as the combination of both pyramidal and parkinsonian signs is a concept that recently emerged. PPS may manifest itself in numerous neurodegenerative diseases, many of these being inherited. Their diagnosis is a major challenge for the clinical management, for the prognosis, for genetic counselling and, in a few cases, which should not be neglected, for specific treatment.
Objective: Our objective is to provide a review of PPS and an algorithm in order to guide their diagnosis in clinical practice.
Methods: We performed an exhaustive PubMed and OMIM research matching the following key words: "Parkinsonism and pyramidal signs" or "Parkinsonism and spasticity" or "pallido-pyramidal syndrome" or "Parkinsonism and spastic paraplegia". English publications from the last ten years were included.
Results: We propose a pragmatic presentation based on several established classifications and we will distinguish inherited PPS found in complex hereditary spastic paraplegia, young onset parkinsonism, neurodegeneration with brain iron accumulation, primary familial brain calcifications, inborn errors of metabolism, and few rare others inherited neurodegenerative diseases, then non-inherited neurodegenerative PPS. We therefore suggest guidelines (based on age at onset, family history, associated clinical signs, brain MRI findings as well as certain laboratory investigations), for the diagnosis and the management of PPS. Many pathophysiological pathways may underlie PPS but the most frequent are those usually involved in both inherited Parkinson's disease and spastic paraplegia, i.e. mitochondrial pathway, vesicular trafficking including endosomal and lysosomal pathways as well as autophagy.
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1. Introduction

Parkinsonian Pyramidal syndromes (PPS), that could be defined as the combination of both parkinsonian (bradykinesia, rigidity or/and rest tremor) and pyramidal (increased reflexes, extensor plantar reflexes, pyramidal weakness or spasticity) signs, is a concept that recently emerged as the result of the explosion in the past few years, of literature devoted to either parkinsonism or spastic paraplegia. PPS may manifest mostly in numerous neurodegenerative diseases, many of these being inherited. Several of these PPS, have been described recently and may be ignored or misdiagnosed since specific biomarkers are lacking in most cases. Nevertheless, their diagnosis is a major issue in order to guide prognosis, genetic counselling and in a few cases specific treatment. Our objective is to provide a review of PPS and to propose algorithms in order to guide their diagnosis in clinical practice.

2. Methods

Our aim was to focus on neurodegenerative PPS, especially inherited forms. We thus performed an exhaustive PubMed and OMIM research matching the following key words: "Parkinsonism and pyramidal signs" or "Parkinsonism and spasticity" or "pallido-pyramidal syndrome" or "Parkinsonism and spastic paraplegia", and selected all the English publications (reviews and case reports) published between October 2005 and July 2016.

We suggest to leave out the term "Pallido Pyramidal syndrome" proposed in 1954 [1] on the basis of 5 patients who had pyramidal signs and parkinsonism. Indeed, the existence of the pallido

* Corresponding author. Service de Neurologie, Hôpital de Hautepierre 1, Avenue Molière, 67000 Strasbourg, France.
E-mail address: christine.tranchant@chru-strasbourg.fr (C. Tranchant).

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pyramidal syndrome as a distinct entity has been discussed [2] because in most patients the correlation between clinical signs and affected structures is missing.

We provide a pragmatic classification and will distinguish inherited PPS found in complex hereditary spastic paraplegia, young-onset parkinsonism, neurodegeneration with brain iron accumulation (NBIA), primary familial brain calcifications (PFBC), inborn errors of metabolism, and few rare other inherited neurodegenerative diseases, then non-inherited neurodegenerative PPS. Although certain diseases can interestingly belong to two of these groups (such as, PLAN (*PLA2G6* associated mutations) that can be classified among NBIA or young onset parkinsonism (PARK 14)), this presentation seems the most coherent with the clinical practice.

3. Results

3.1. Complex hereditary spastic paraplegia

SPG11 and SPG15 occur between 10 and 35 years of age with progressive spastic paraplegia, mental retardation and in some cases axonal motor neuropathy [3]. In a few cases, early levodopa responsive resting tremor and akinesia, is described [4,5]. Levodopa response decreases with time, but tremor disappears, masked by predominant spasticity. Patients become wheelchair bound following a mean disease duration of 14.9 ± 6.6 years for SPG11 and 18.8 ± 7.6 years for SPG15 [3]. In both diseases, brain MRI showed a moderate to severe thin corpus callosum, particularly in its anterior part, and frequent white matter hyperintensities (WMH) located in the anterior portion of the frontal horns named “ears of the lynx” shape (Fig. 1a,b,c). Mild cerebellar atrophy may be encountered in SPG15. Spatacsin(SPG11) and spastizin(SPG15) share a similar subcellular localization, are both components of a multi-protein complex and are implicated in vesicular trafficking and autophagy [6].

In SPG10 (*KIF5A* gene) age at onset is from 2 to 51 years [7]. Patients may experience, besides spastic paraplegia, sensori-motor axonal neuropathy, and more rarely, severe upper limb amyotrophy, intellectual deficiency, deafness and in a few cases, levodopa responsive resting tremor and bradykinesia. MRI shows spinal cord atrophy and in some cases WMH [8]. Most patients are still able to walk without help after more than 40 years of disease duration. *KIF5A* encodes a kinesin which interferes with cargoes [9].

3.2. Young onset inherited parkinsonism

PARK15 (*FBXO7* gene), sometimes named Parkinsonian Pyramidal disease [10] starts between 10 and 30 years of age with parkinsonism as well as pyramidal signs. Levodopa is effective but induces dyskinesia and behavioral disorders. Oculomotor apraxia or vertical supranuclear gaze palsy (VSGP) are frequent as well as psychiatric features, dystonia or action tremor [10–12]. Recently, two cases with a later onset (41 and 52 years) and a typical levodopa responsive Parkinson's disease have been reported [13]. The clinical course is slow and brain MRI is normal. FBXO7 is involved in the ubiquitin proteasome system and its mutations promote protein aggregation in mitochondria and inhibit mitophagy [14].

PARK9 or Kufor Rakeb syndrome *(KRS)* (*ATP13A2* gene) usually begins before age 20 with unilateral levodopa-responsive akinetic and rigid syndrome as well as cognitive decline. Pyramidal signs and dystonia are frequent. VSGP or slow saccades, visual hallucinations, and facial or finger minimyoclonus are common [15]. Ataxia and axonal neuropathy are rarer. Levodopa induces dyskinesias and hallucinations. Disease progression is from slowly (decades) to rapidly progressive (months to years). Cerebral MRI may reveal diffuse atrophy or rarely show iron deposition [16] (Fig. 1d), which led to consider KRS as a NBIA. Cytoplasmic membrane bound lamellar inclusions have been described in muscle, skin, Schwann and neural cells and a post-mortem cerebral pathological aspect of neuronal ceroid lipofuscinose (NCL) in one family [17]. Since *ATP13A2* mutations have been associated with NCL in dogs [18] a continuum spectrum ranging from NCL to KRS has been suggested. *ATP13A2* encodes a lysosomal transmembrane protein belonging to the 5P-type ATPase subfamily but it has been demonstrated that mutant forms localize to the endoplasmic reticulum [15].

PLAN may manifest with 3 overlapping phenotypes: infantile neuroaxonal dystrophy, atypical neuroaxonal dystrophy classified among NBIA and dystonia parkinsonism syndrome (PARK14). PARK14 is a young onset (10–40 years) parkinsonian syndrome, which is usually associated with cognitive decline, psychiatric features, dystonia, pyramidal signs, dysarthria and dysphagia [19]. A pure, young onset parkinsonism has been reported [20]. VSGP and eyelid opening apraxia are described in one patient [11]. Cerebral MRI may demonstrate slight cerebellar atrophy (Fig. 1e) without iron deposits. Levodopa induces early-onset dyskinesia and its efficacy progressively disappears. Disease progression may be rapid with some patients becoming wheelchair bound 4–6 years after the onset. Pathology revealed widespread Lewy body and accumulation of hyperphosphorylated Tau protein. *PLA2G6* encodes a mitochondrial calcium independent phospholipase A2 and loss of normal *PLA2G6* gene activity leads to lipid peroxidation and mitochondrial dysfunction [21].

In PARK19 (*DNAJC6* gene) [22], patients display early, rapidly progressive parkinsonism including rest tremor. Mental retardation, pyramidal signs and epilepsy have been reported in one family [23] where brain MRI demonstrated generalized atrophy. Levodopa induced motor and psychiatric side effects and patients became wheelchair bound or bedridden with anarthria and global akinesia following 10–15 years. *DNAJC6* encodes the neuronal co-chaperone auxilin whose reduction impairs the clathrin mediated endocytosis (CME) and the clathrin-dependent trafficking of cargo from the Golgi apparatus to the lysosome [22].

Mutations in the *vacuolar protein sorting 13C*(*VPS13C*) gene were found in patients with early onset (25–46 years) typical levodopa-responsive parkinsonism [24]. Disease worsening was rapid, with loss of response to treatment, cognitive decline and dysautonomia. Pyramidal signs and motor deficits were present in 2/3 patients who were bedridden 15 years after onset. Brain MRI demonstrated late bilateral cortical atrophy. One post-mortem examination showed diffuse alpha-synuclein and ubiquitin positive-Lewy bodies and Tau-immunoreactive neurofibrillary tangles. VPS13C proteins play a role in mitochondrial maintenance.

In X-linked Parkinson's disease spasticity (*ATP6AP2* gene) [25], age at onset is between 14 and 58 years. Spasticity was the first sign in 3 patients who later displayed asymmetrical rest tremor and akinesia. Two others experienced a pure parkinsonian syndrome [26]. Cerebral MRI was normal. Pathology found a significant 4-repeat tauopathy in the striatum in one patient died at age 86.

G51D *SNCA* heterozygous mutation [27], has been associated with mild to moderate levodopa-responsive parkinsonism with pyramidal signs (enhanced tendon reflexes with extensor plantar reflexes or severe spasticity), and in some patients cognitive decline and dysautonomia. Age at onset was between 28 and 68 years. Progression confined the patients in wheelchair following 5–14 years. Brain MRI showed diffuse atrophy. Pathology revealed alpha-synuclein immunoreactive neuronal inclusions resembling Lewy body as well as glial inclusions mimicking MSA. It has been demonstrated *in vitro* that G51D mutation decreases alpha synuclein aggregation and could have a distinct toxic mechanism to other *SNCA* mutations [28].

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