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An overview of parkinsonian syndromes: data from the literature and from an Italian data-base

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Abstract

Recent molecular biology research on neurodegenerative diseases, including parkinsonisms, has identified mutations in the genes that code for the proteins alpha-synuclein and tau, which have been used to classify them into synucleinopathies and tauopathies. The synucleinopathies include, besides the most common and well studied Parkinson's disease (PD), dementia with Lewy bodies, which accounts for approximately 20% of all cases of dementia in the elderly, and multiple system atrophy, whereas the tauopathies include rare and rapidly progressive syndromes, such as progressive supranuclear palsy and corticobasal degeneration.

Data we collected at our center in over 2900 parkinsonian patients show that PD accounts for no more than 70% of parkinsonisms.

The various syndromes have many features in common that make the differential diagnosis difficult in the early stages of disease. Our data are consistent with the findings reported in the international literature and provide additional information useful for differential diagnosis.

Keywords: Neurodegenerative disease; Parkinsonism; Parkinson's disease; Data-base; Disease progression

1. Introduction

In the last decade, molecular biology has produced a radical change in the approach to neurodegenerative disorders such as parkinsonian syndromes. Recent studies indicate that neurodegenerative diseases are associated with abnormalities in the structure of particular proteins that change their biological function [1].

The investigation of familial cases of Parkinson's disease (PD) has disclosed mutations in the gene coding for alpha-synuclein, a small protein that appears to contribute towards the transport of dopamine–laden vesicles from the cell body to the synapses; alpha-synuclein is one of the main fibrillar components of Lewy bodies found in neurons in PD and dementia with Lewy bodies (DLB) and in glial cells in multiple system atrophy (MSA) [2].

Studies of inherited frontotemporal dementia have revealed mutations of the tau gene that result in hyperphosphorylation and aggregation of tau proteins, an important component of the cytoskeleton [3]; it is now known that tau protein alterations are involved in Alzheimer's disease (AD), frontotemporal dementia, progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD).

As protein abnormalities appear to be the key to neurodegeneration, they are now used as a framework for the classification of neurodegenerative diseases into 'synucleinopathies' and 'tauopathies' [1,4].

At the Parkinson Institute at Istituti Clinici di Perfezionamento in Milan, 250 variables related to the follow-up of patients attending the center are regularly entered into a central data-base. The variables are collected using specific questionnaires administered by trained personnel under the supervision of a neurologist expert in movement disorders. They are the following: past medical history; symptoms at onset reported by the patient on a checklist; family history, which is considered to be positive when at least one relative is affected by a parkinsonian syndrome; history of exposure

Abbreviations: CBD, corticobasal degeneration; DLB, dementia with Lewy bodies; MSA, multiple system atrophy; PD, Parkinson's disease; PDD, Parkinson's disease dementia; PSP, progressive supranuclear palsy; VPD, vascular Parkinson's disease.

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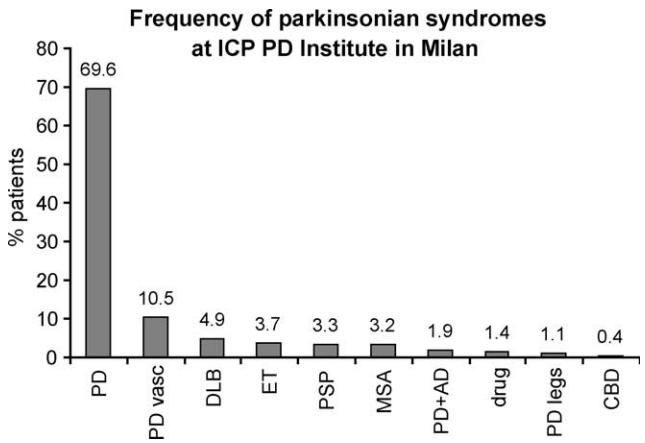

Fig. 1. Frequency of parkinsonian syndromes at ICP PD Institute in Milan.

to environmental agents based on information on occupation, area of residence and hobbies, as well as duration and extent of weekly exposure to calculate the overall exposure according to Beirne's scale [5]. The data-base is regularly up-dated during follow-up by inserting information on unified Parkinson's disease rating scale (UPDRS) scores, neuroimaging and cognitive function investigations, pharmacological and non-pharmacological treatments, response to dopaminergic therapy assessed by the levodopa test (considered to be positive when the motor score improves by at least 33%) and the apomorphine test (considered to be positive when the motor score improves by at least 20%).

By May, 2002 demographic data related to 7500 patients had been inserted in the data-base of the center. All the data included from the beginning of 1998 to the end of 2000 were used for our analysis of parkinsonian syndromes, i.e. a total of 2931 patients. A total of 2041 (69.6%) had a diagnosis of idiopathic PD and 890 (30.4%) of parkinsonism. The most common parkinsonian syndromes besides idiopathic PD were 'vascular' PD (VPD) (10.5%), DLB (4.9%), PSP (3.3%) and MSA (3.2%) (Fig. 1).

The main features related to the various parkinsonian syndromes are described below, together with the data collected at the Parkinson Institute, ICP, Milan, which are summarized in Table 1.

2. Parkinson's disease

Idiopathic PD, the most common parkinsonian syndrome, is due to neuronal loss in the substantia nigra [6]. Recent epidemiological studies have shown that the prevalence of PD in the elderly population (≥65 years) is approximately 1.5–1.6% in Europe, with little variation among individual countries. The prevalence increases with age, ranging from 0.6 for those aged 65–69 years to 3.0 in those aged 80–84 years. The corresponding rates for Italy were 0.7 and 4.6, respectively [7].

The aetiology of PD has not been elucidated. The currently accepted hypothesis is that it is the result of an interaction between environmental insults and genetic susceptibility. Familial and environmental factors both appear to play an important role in its pathogenesis [8].

The histological hallmark of PD is the presence of intracytoplasmic, eosinophilic, neuronal inclusions made of neurofilament proteins, mainly alpha-synuclein and ubiquitin, located almost exclusively in the substantia nigra and locus ceruleus (Fig. 2) [8]. It is slightly more frequent in males than females. Familial forms of the disease usually develop in youth (<40 years) [9], whereas the idiopathic form develops on average in the late 50s. At onset the main signs and symptoms are asymmetrical, namely resting tremor, bradykinesia and rigidity [6]. In the later stages shuffling gait and postural impairment appear. A less known feature of the disease is daytime sleepiness associated with rapid eye movement (REM) sleep behavior disorder (RBD). This phenomenon is also present in other synucleinopathies and is considered to be a specific manifestation of this new class of diseases [10,11]. The diagnosis is based mainly on

Table 1
Main features of PD and parkinsonian syndromes at the Parkinson Institute, ICP, Milan

Diagnosis	Male sex (%)	Mean ± SD age at onset (years)	Mean ± SD duration of disease at first visit (years)	Positive family history (% pat)	History of exposure (% pat)	Mean ± SD degree of exposure (Beirne's scale) (5)	Symptom lateralization at onset (% pat)	Mean ± SD UPDRS motor score at sixth year of disease	Response to apomorphine (% pat)	Positive autonomic system test (% pat)	Response to levodopa (% pat)
PD	57.6	56.8 ± 10.7	6.7 ± 5.7	33.6	37.2	1.9 ± 3.4	87.0	22.9 ± 10.1	83.9	62.1	82.7
VPD	61.1	67.8 ± 8.1	5.4 ± 4.5	19.7	29.1	1.2 ± 3.0	57.5	29.6 ± 11.2	48.8	–	35.0
MSA	44.3	56.6 ± 8.5	4.5 ± 2.8	30.7	38.5	2.6 ± 3.8	66.2	38.5 ± 12.3	45.5	84.0	47.1
DLB	60.3	65.9 ± 9.1	5.9 ± 4.3	25.8	28.1	1.2 ± 2.9	57.1	35.2 ± 12.1	61.1	83.3	57.6
PDD	55.2	62.9 ± 9.4	8.3 ± 5.5	23.6	24.1	1.6 ± 3.6	58.9	26.8 ± 7.1	76.6	–	76.6
PSP	51.5	64.1 ± 8.4	4.9 ± 3.3	22.2	28.6	1.0 ± 2.6	44.4	38.5 ± 14.0	38.1	–	22.7
CBD	41.7	63.5 ± 6.0	4.1 ± 2.3	18.2	20.0	1.0 ± 3.2	66.7	42.0 ± 5.4	–	–	37.5
Drug-induced	38.1	66.4 ± 11.0	4.2 ± 3.5	17.6	13.8	0.25 ± 1.2	46.8	27.1 ± 16.0	–	–	40.9

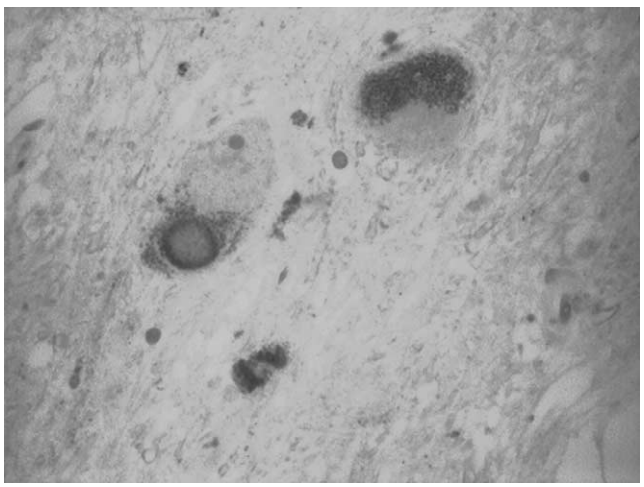

Fig. 2. Lewy body showing alpha-synuclein immunoreactivity in the substantia nigra.

clinical features and the response to levodopa. Treatment is symptomatic and consists mainly of dopaminergic therapy, which controls symptoms adequately for a mean period of 5 years, after which complications such as motor fluctuations and dyskinesias set in. The rate of progression of PD is generally slow, especially in juvenile forms.

Our data are consistent with those in the literature. The disease was slightly more frequent in males and the mean age at onset was 56.8 years (Table 1). The onset of disease was almost invariably asymmetric; we observed that the most common initial symptom was tremor, followed by bradykinesia. Other characteristic features of the disease, such as impairment of postural reflexes, usually developed in later stages of the disease. A little known symptom is pain, which was reported amongst the first symptoms in 5% of cases (Fig. 3(A)–(E)). The proportion of patients with a positive family history for parkinsonism was similar to the proportion with a history of exposure to environmental agents such as hydrocarbon solvents. Moreover, both a positive family history and exposure to hydrocarbon solvents were associated with significantly earlier onset of disease: patients with a history of exposure were on average three years younger at onset than those without (54.6 ± 11.0 versus 57.6 ± 10.4 years; $P < 0.0001$), and patients who had a positive family history were on average 1.5 years younger at onset (55.7 ± 10.6 versus 57.2 ± 10.7

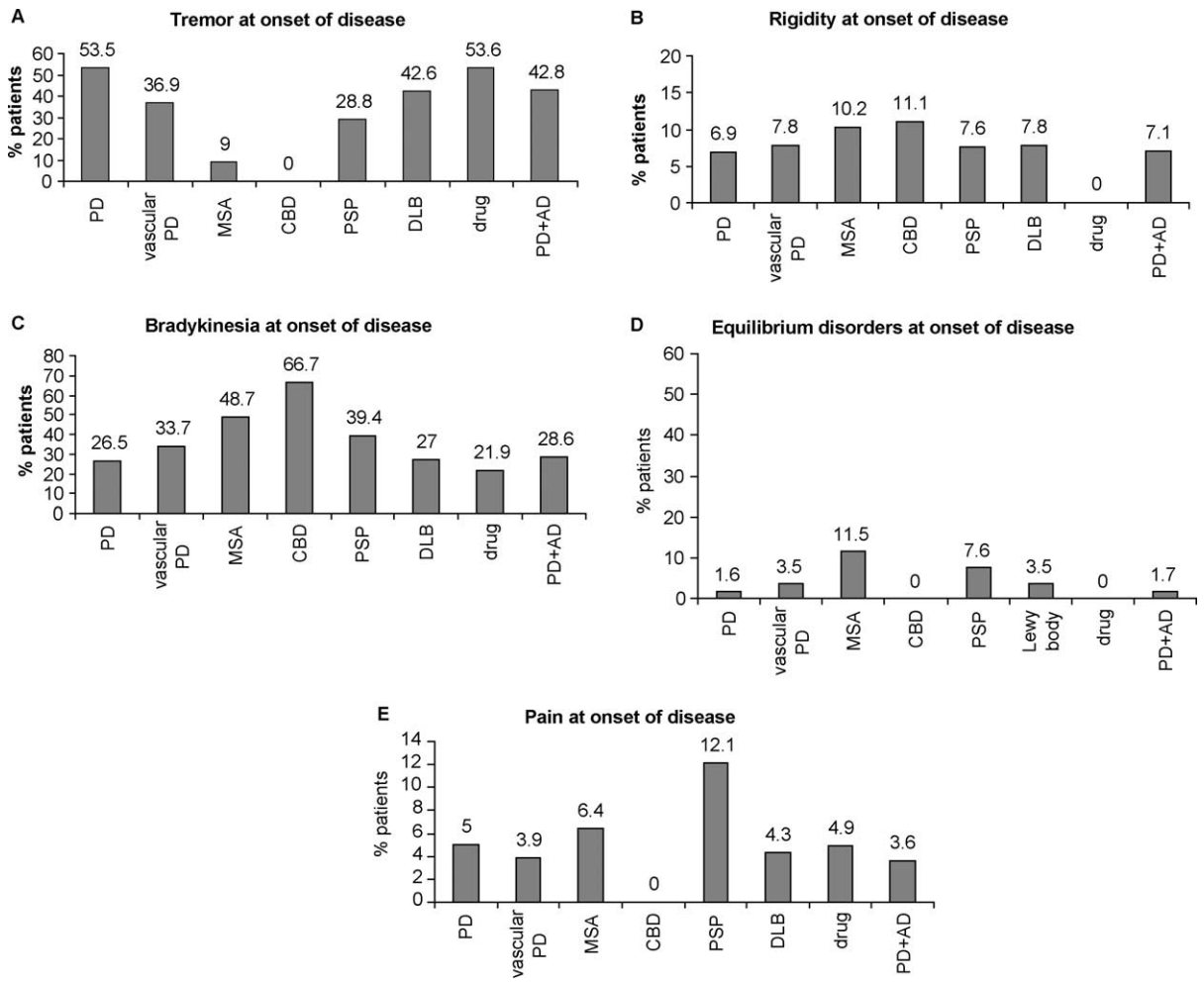

Fig. 3. (A) Tremor at onset of disease, (B) rigidity at onset of disease, (C) bradykinesia at onset of disease, (D) equilibrium disorders at onset of disease, and (E) pain at onset of disease.

years; $P < 0.005$) than those who did not (Table 1). Exposure to hydrocarbon solvents was associated with earlier onset of PD in a previous study; the extent of anticipation was the same [12].

Most of our patients responded positively to levodopa and also to the apomorphine test, response being defined as a 20% improvement in the UPDRS motor score. The response to chronic dopaminergic therapy is also important for the diagnosis of PD [13]. Neuroimaging plays an important role, albeit to a lesser extent than with other parkinsonian syndromes; it yielded useful findings in approximately 3 out of 4 cases. The mean UPDRS part III motor score at the first visit after 6 years of disease was 22.9 ± 10.1.

We decided to define the co-existence of vascular disease with PD as VPD. The features of this form of PD are slightly different. The prevalence of the male sex was slightly higher and the onset of disease occurred on average 11 years later than in idiopathic PD. A positive family history and a history of exposure to toxins was less frequent (Table 1), but the significant impact of exposure on onset of disease was present, and actually stronger: in exposed patients onset of disease occurred on average 4.2 years earlier (64.4 ± 7.9 versus 68.6 ± 7.9 years; $P < 0.0001$). However, family history did not induce an earlier onset of disease. The most common manifestations of the disease at onset were similar to idiopathic PD—tremor and bradykinesia (Fig. 3(B) and (C)), but onset was more frequently bilateral (Table 1). Neuroimaging, especially brain magnetic resonance imaging (MRI), was an essential part of the diagnostic work-up, as it produced useful information in nearly all cases. This form of PD was less responsive to dopaminergic therapy: only one third of patients responded to levodopa and the apomorphine test was positive in less than half (Table 1).

3. Multiple system atrophy

MSA is an atypical form of parkinsonism characterized by the co-existence of autonomic failure/urinary dysfunction, cerebellar ataxia and corticospinal dysfunction [14]. Approximately 70% of patients with MSA report sleep disorders, mainly sleep fragmentation, vocalization, REM sleep behavior disorders and nocturnal stridor; these symptoms are amongst the common symptoms at onset and tend to be associated with more severe motor function impairment [15]. MSA is a fairly rare syndrome, with a prevalence of 4–5 cases per 100 000 persons; it has been estimated that in Italy the absolute prevalence is 4900 cases [16]. MSA is reported to affect both sexes and to develop generally in middle age. Onset is often symmetrical, but may also be asymmetrical [14]. The syndrome has been subdivided into three types, according to the prevalence of cerebellar, autonomic or parkinsonian signs, i.e. MSA-C, MSA-A and MSA-P, respectively [17]. Characteristic neuropathological findings consist of oligodendroglial cytoplasmic inclusions, which are ubiquitin-, tau- and alpha-synuclein positive. In addition, there are widespread signs of neurodegeneration in some or all of the following structures: putamen, caudate nucleus, globus pallidus, substantia nigra, locus ceruleus, inferior olives, pontine nuclei, cerebellum, autonomic nuclei of the brainstem and the intermediolateral cell columns and Onuf's nucleus in the spinal cord [14]. The presence of sleep disorders reflects the extension of the neurodegenerative process [15]. The aetiology of MSA is unknown; the influence of family history and exposure to environmental toxins has not been established.

MRI yields useful information not only for the diagnosis of MSA but also for the subdiagnosis into the three types mentioned above [17], whereas PET has documented widespread metabolic abnormalities [18]. The response to levodopa is fair in 40–60% of patients; other antiparkinsonian drugs, such as dopamine agonists and amantadine, are not more effective than levodopa. In addition, specific therapeutic measures are required to mitigate orthostatic hypotension and genitourinary symptoms as much as possible in order to improve quality of life [19]. The median time from initial symptom to combined motor and autonomic dysfunction is 2 years, with considerable variability (range: 1–10 years); this interval is a predictor of subsequent deterioration and survival, which amounts on average to 9 years. Functional impairment is usually worse in MSA-P than in MSA-C, but survival is similar [20].

The data collected for our patients are similar to the findings reported in the literature on MSA. The diagnosis was more frequent in middle-aged women. Onset was usually unilateral (Table 1). At onset, patients usually reported bradykinesia and, to a lesser extent, equilibrium disturbances, rigidity and tremor. Pain was also reported early in the disease (Fig. 3(A)–(E)). The frequency of a positive family history and a positive history of exposure to environmental toxins was similar, but these factors did not have a significant impact on age at onset as they do with PD. Neuroimaging, mainly brain MRI, was useful for the diagnosis of MSA in most cases; testing of the autonomic system (tilting) was also revealing (Table 1). According to our data, the disease was less responsive to levodopa than is PD. Less than half of our patients responded satisfactorily to the levodopa and apomorphine tests (Table 1). The disease had a more severe and more rapid course than PD. The mean UPDRS motor score at presentation in our center was 38.5 ± 12.3 (Table 1).

4. Dementia with Lewy bodies

DLB is the most common disorder presenting with both cognitive impairment and extrapyramidal symptoms. Autopsy discloses Lewy bodies in the cortex of 15–25% of elderly demented patients, with or without concomitant AD. The extrapyramidal symptoms include rigidity,

shuffling gait, stooped posture, postural instability and, less frequently, tremor, whereas cognitive impairment fluctuates and is associated with symptoms of psychosis, especially visual hallucinations [21–23].

It has recently been established that DLB, like other synucleinopathies, is associated with REM sleep behavior disorder [11]. Its neuropathologic hallmarks are Lewy bodies in the parahippocampus, in several neocortical areas and subcortical nuclei, as well as abnormal ubiquitinated neurites in the hippocampal CA2 sector; in many cases senile plaques and neurofibrillary tangles coexist with Lewy bodies. The syndrome affects men more frequently. Age at onset ranges from 50 to 83 years [22]. Brain cholinergic system dysfunction is pronounced in DLB and there is preliminary evidence that anti-cholinesterases are effective in ameliorating cognitive symptoms of the disease [24].

DLB was amongst the most frequent syndromes recorded in our data-base (Fig. 1). Patients were mostly men, who mainly reported tremor and bradykinesia (Fig. 3(A)–(E)), slightly more frequently confined to one side, at onset in their late 60s; depression was also characteristically frequent. Family history and exposure to environmental toxins did not appear to have an impact on age at onset. Neuroimaging, primarily brain MRI and single-photon emission computed tomography (SPECT), produced useful diagnostic information in nearly all cases. Responses to the levodopa and apomorphine tests were positive in approximately 60% of cases. Mean UPDRS motor score at the sixth year of disease was 35.2 ± 12.1. On average, nearly 6 years elapsed from the onset of disease to the first consultation at our center (Table 1).

5. Progressive supranuclear palsy

PSP is an akinetic-rigid form of parkinsonism characterized by early falls and abnormalities of extraocular movements. This syndrome is rare, its prevalence being 1.4–4 patients per 100 000. Individual manifestations vary considerably as a result of heterogeneous anatomical involvement. Multiple anatomical sites are involved, mainly the subthalamic nucleus, the globus pallidus interna and externa, the pontine nuclei, the periaqueductal gray matter and the substantia nigra. The histological hallmark is the presence of intraneuronal neurofibrillary tangles made of abnormally phosphorylated tau protein. According to the data in the literature, PSP is more frequent in men and usually develops after the age of 50. The onset of the disease is usually symmetrical, the most common initial symptoms and signs being gait difficulty and falls, dizziness, bradykinesia, changes in personality, dystonia and, less frequently, tremor. The aetiology of the syndrome is unknown. There are anecdotal reports of toxin exposure and rare cases of familial PSP, but no clear association has been found between these two factors and PSP. Multiple pathways and neurotransmitters are involved in the pathological process, so dopaminergic therapy is not very effective and benefit is usually short-lived. A number of alternative agents have been used with variable and generally poor results. The progression of disease is rapid, and mean survival is approximately 9 years [25].

Our data are consistent with the reports in the literature. We observed prevalence in males and recorded onset of disease mainly in the 60s (Table 1). The onset of disease was usually symmetrical; the patients reported bradykinesia as the most disturbing symptom, at times associated with muscular pain at onset, and equilibrium disturbances less frequently as the first symptom of disease (Fig. 3(A)–(E)). Relatively few patients had a positive family history or a history of environmental exposure (Table 1) and these factors did not have a significant impact on age at onset. Neuroimaging, brain MRI and SPECT produced useful information for diagnostic purposes in most cases, as is reported in the literature [25]; the apomorphine test, performed in the early stage of the disease was also useful, as it is characteristically negative. Only 22.7% of our patients responded to chronic treatment with levodopa. We found a high mean UPDRS motor score at the sixth year of disease of 38.5 ± 14.0 (Table 1).

6. Corticobasal degeneration

CBD is a rare form of parkinsonism with both motor and cognitive dysfunction. The main parkinsonian symptoms are akinesia, rigidity and apraxia; dystonia and alien limb phenomena are also reported. Symptoms at onset are usually asymmetrical bradykinesia and limb dystonia. Symptoms are usually poorly responsive to levodopa and progression of the disease is rapid. Its neuropathologic hallmark consists of filamentous inclusions, present both in neuronal tissue and the glia, which are made of hyperphosphorylated tau. Other characteristic findings are asymmetric frontoparietal neuronal loss and gliosis with ballooned, achromatic cortical neurons, nigral degeneration and variable subcortical involvement [26,27].

Our patients were of both sexes, with a slight prevalence of women; the syndrome usually appeared in their early 60s (Table 1). Symptoms at onset were usually asymmetrical, the most common being bradykinesia; other symptoms reported at onset were rigidity, dystonia and confusion. None of the patients reported tremor at onset, unlike most other parkinsonisms (Fig. 3(A)–(E)). The proportion of patients who responded to levodopa was low; mean UPDRS motor score was 42.0 ± 5.4 (Table 1). The severity of the motor and cognitive symptoms justified the short interval between onset of symptoms and consultation at our center, on average after 4.1 years (Table 1).

7. Parkinson's disease dementia

PDD is a syndrome characterized by slowing of cognitive and motor function, executive dysfunction and memory retrieval impairment, developing no earlier than 2 years after the appearance of parkinsonian symptoms in about 30% of PD patients, especially in the elderly and in patients with severe motor symptoms. It accounts for 1.2–3% of all dementias [28,29]. Correction of dopamine deficiency does not improve cognition in PDD patients, so it is likely that other neurotransmitters are involved. At present no specific anatomical alterations have been correlated with PDD. Degeneration of the nucleus basalis of Meynert is present, as in AD, so cholinergic deficiency may contribute to PDD; the data of a preliminary therapeutic clinical trial suggest that this is the case [21].

In our patients, PDD was slightly more frequent in males; onset occurred on average in the early 60s (Table 1), with primarily asymmetrical motor symptoms. The most common initial symptoms were resting tremor and bradykinesia, as in patients affected by idiopathic PD (Fig. 3(A)–(E)). The response rate to levodopa and the proportion of patients with a positive apomorphine test at onset of disease were similar to the proportion in idiopathic PD. Neuroimages yielded useful diagnostic information in a greater number of cases (Table 1). The mean UPDRS motor score at the sixth year of disease was 26.8 ± 7.1—worse than in idiopathic PD.

8. Drug-induced parkinsonism

Several pharmacological agents may induce parkinsonian symptoms. Among the most commonly used are compounds that belong to the following pharmacological classes: phenothiazines (chloropromazine), butyrophenones (haloperidol), thioxanthines (flupentixol) and substituted benzamides (sulpiride, metoclopramide). Drug-induced parkinsonism is usually characterized by bradykinesia and amimia, whereas resting tremor is less common. Neuroleptics characteristically display a mixture of akathisia, stereotypies and parkinsonism associated with orofacial or respiratory dyskinesia. The syndrome generally responds poorly to levodopa. It is reversible and usually regresses once the offending drug has been discontinued [6].

The vast majority of our cases were women in their late 60s. Symmetrical onset of symptoms was slightly more frequent than an asymmetrical onset (Table 1). By far the most common initial symptom reported by patients was tremor followed by bradykinesia. No patients reported rigidity or impairment of postural reflexes at onset, whereas a small number reported pain (Fig. 3(A)–(E)). The majority of patients responded poorly to levodopa treatment (Table 1).

9. Conclusions

Parkinsonian syndromes include a number of diverse diseases, which recent acquisitions in the field of molecular biology have now classified into synucleinopathies and tauopathies, according to the type of protein predominantly involved. Aside from the most common and well-studied PD, the synucleinopathies include DLB, which accounts for approximately 20% of all cases of dementia in the elderly, and MSA; the tauopathies include rare and rapidly progressive syndromes such as PSP and CBD. Data collected at our Parkinson center show that PD accounts for no more than 70% of parkinsonisms.

Parkinsonian syndromes are multisystemic diseases that produce not only motor and cognitive function impairment, but also other disorders that require the intervention of specialists other than the neurologist.

The various syndromes have many features in common that make the differential diagnosis difficult in the early stages of disease. The data collected at our center, besides confirming the findings reported in the international literature, provide additional information that is useful for differential diagnosis.

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