

EARLY ONSET PARKINSONISM

Oscar S. Gershanik

Sección Enfermedades Extrapiramidales, Centro Neurológico-Hospital Francés & Laboratory of Experimental Parkinsonism, Instituto de Investigaciones Farmacológicas, ININFA-CONICET, Buenos Aires, Argentina

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1. ABSTRACT

Early-onset parkinsonism refers to those patients with onset of a parkinsonian syndrome before age 40. These cases can be further subdivided into Young-onset (between ages 40 and 21) and Juvenile-onset (below age 21). In this review we will focus on the peculiar clinical features that distinguish these cases from classic late-onset parkinsonism, their characteristic response to medication, and their heterogeneous pathogenesis, including recent findings in the field of genetics that would suggest that a significant number of these patients are the result of genetic mutations.

2. INTRODUCTION

Parkinson's disease (PD) is a degenerative disorder of the Central Nervous System affecting approximately 1 in a 1000 individuals with a predominant age of onset between 55 and 65 years of age (1). Approximately 5 to 10% of cases have an onset below age 40 (2), and they are generally referred as early-onset parkinsonism (EOPD), comprising, according to presently accepted criteria, those between the ages of 21-40 (young-onset cases, YOPD) and those below 21 (juvenile onset cases, JP) (3). Analysis of this clinical subgroup of parkinsonian patients has mainly focused on several salient features: distinctive clinical presentation, a different natural history, peculiar response to medication, and disease

heterogeneity probably based upon a variable genetic background. The fact that Parkinson's disease could also affect younger individuals was recognized many years ago (2) and that knowledge has since generated a growing interest in this age segment, for it was believed and later confirmed that it could provide answers related to the genetics of the disease; the mechanisms underlying motor complications, both drug and disease-related; and whether the presence of cognitive decline in PD is disease or age-related. The number of papers that have been published on the subject of EOPD, since the first cases were described, reflects such interest.

It is however difficult to reach uniform conclusions on the nature of EOPD as different publications have used variable age limits to define the population under analysis making it almost impossible to perform a metanalysis capable of providing definitive results in comparing the different series. In the majority of cases reported in earlier publications, their correct clinical interpretation is often difficult due to the lack of clearly defined nosological criteria. Moreover, at the time these cases were published, modern laboratory (including genetic typification) and imaging techniques were not available, thus precluding a correct differential diagnosis and a more precise phenotypic/genotypic correlation.

In recent years, the contributions made by molecular genetics, pharmacology, physiology, and clinical neuropsychology have allowed us to make significant advances in the understanding of the pathophysiology and pathogenesis of PD as a whole, and of EOPD in particular. We are presently in a significantly better position to assign clinical categories to distinct disease entities with a precise underlying genetic background. It is against this setting that this review will focus on the problem of EOPD both in its juvenile and young-onset presentations.

3. HISTORICAL BACKGROUND

The development of parkinsonism in younger patients was first recognized as far back as 1875, when Huchard reported a case of a child with akineto-rigid symptomatology and identified it as childhood onset Parkinson's disease (2). This report was soon followed by a number of publications. Willige in 1910 (4) was perhaps the first to publish a series of cases, commenting on the clinical findings of 14 early-onset cases, the youngest one having started the disease at age 18, of which six had a positive family history. Although he believed his patients were in fact affected by Parkinson's disease, their age of onset and the presence of a positive family history made him propose that these cases should be classified separately from classical adult-onset Parkinson's disease. He coined a new term, "paralysis agitans juvenilis familiaris", underlining the need for a more strict nosological classification of PD cases based on their age of onset and family history.

Additional reports published until the 1950's (5-9), included isolated cases, familial cases, small series, epidemiological studies, and in some instances pathological observations (2). It became evident that no single disease could account for so much variation in clinical presentation and family background, and new disorders were thus described, such as "primary atrophy of the globus pallidus" (5, 6), and "pallidopyramidal disease" (7). Some of the cases were attributed to an encephalitic disease, but the idea that classical Parkinson's disease could eventually start at a very early age was never abandoned. The presence of family aggregation was believed to be the evidence of hereditary factors playing a role in the etiology of PD (2).

After the introduction of levodopa to the treatment of Parkinson's disease in the later part of the 1960's it became readily accepted that a positive response to the drug was the hallmark of Parkinson's disease. The effects of levodopa helped, to some extent, in distinguishing cases of parkinsonism with a positive response to the drug from those in which no response could be elicited. However, a positive response to levodopa did not necessarily help in distinguishing classic Lewy body parkinsonism (Parkinson's disease) from other disorders presenting with parkinsonian features but corresponding to a different etiology. Such was the case with dopa-responsive dystonia (DRD) first reported by Segawa in the late 1960's (10) and selected cases of juvenile parkinsonism with marked response to levodopa, in whom

post-mortem examination revealed nigral cell loss without the presence of Lewy-body type inclusions (11, 12).

It was Yokochi in 1979 (13) the first to draw attention to the high prevalence of "juvenile" and "young-onset" parkinsonism in Japan in a comprehensive report including 40 patients with a mean age of onset of 26.1 ± 9.6 (range 6-39) collected from different hospitals. He provided a detailed analysis of the clinical features, family history and response to medication in these patients. "Early-onset" parkinsonism cases amounted to almost 11% of all cases of parkinsonism seen in Japan and the frequency of a positive family history in these patients was surprisingly higher (42.5%) than previously reported for adult-onset cases (13, 14). The clinical features of these cases differed somewhat from those usually seen in adult-onset patients. Gait disturbances and dystonic postures of the feet were particularly frequent in the younger patients, whereas tremor and autonomic disturbances were rarely present. A dramatic response to levodopa with rapid development of fluctuations and dyskinesias appeared to be the rule.

Numerous reports originating in different regions of the world (3, 15-27) have been published providing detailed clinical descriptions of larger series of cases; allowing the comparative analysis of clinical presentation, pharmacologic response, development of complications, and natural history of the disease in contrast to classic adult-onset cases.

Our present concept of early-onset parkinsonism has been dramatically changed by the finding of genetic markers for "dopa-responsive dystonia" and autosomal recessive "juvenile" or "young-onset parkinsonism" (28-30). Both these disorders, now precisely defined on the basis of their corresponding genetic mutations, probably account for a large proportion of cases of parkinsonism of early-onset. We have now, at last, the possibility of making a correct diagnosis based not only on artificially defined age-limits or peculiar clinical manifestations.

4. CLINICAL FEATURES

Regardless of the underlying etiology, early-onset cases of parkinsonism have, in general, peculiar clinical features that differentiate them from late-onset cases. These differences tend to be more marked the lower the age of onset. In the many reports existing in the literature this issue has been extensively dealt with (2).

4.1. Distinguishing clinical features and response to medication

The majority of cases display predominantly rigid-akinetic forms of the disease, tremor is reported to be less frequent than in older patients, although there is great variability among the different reported series. In most reports originating in Japan tremor has been described as being predominantly of the postural type (14). Dystonia as a presenting feature, either alone and preceding the onset of bradykinesia, rigidity, and tremor, or in association with more typical parkinsonian symptoms, has been reported as

being more prevalent in younger patients (2, 31). Gait difficulties, are not often present at the onset of the disease, in contrast to older-onset patients in whom this complaint is in a high proportion of cases what brings them to seek medical help (26). However, in juvenile cases, there is frequently severe lower limb or foot dystonia causing significant interference with gait. Cognitive disturbances and autonomic symptoms have been reported to be less frequent than in older cases. In addition, diurnal fluctuations in symptomatology and marked sleep benefit may occur in early-onset cases, even prior to the introduction of levodopa (11, 14, 32).

Response to medication is a very distinctive feature of early-onset parkinsonism cases. Several reports have been published comparing early- and late-onset cases specifically focusing on late complications of levodopa therapy in the two patient populations. Early-onset cases show a marked to dramatic response to levodopa, even in low doses, but the benefit may be marred, early in the course of treatment, by the appearance of response fluctuations and sometimes severe dyskinesias (19, 20, 26, 27).

4.2. Natural history and progression

A small number of studies have provided follow-up information in a systematic fashion. In Yokochi's seminal report (13), a retrospective analysis of his so called "juvenile" cases allowed to infer that early-onset patients progressed at a slower rate and apparently had a benign prognosis. This is applicable to PD in general, irrespective of specific age group classifications. Goetz *et al.* (33) provided evidence that age at onset was the only contributory factor that helped distinguish the slowly from the rapidly progressing patients in a case-control study of factors influencing disease progression in PD. Similarly, Diamond *et al.* (34) concluded that younger patients undergoing levodopa treatment had significantly lower disability scores from the onset of treatment than older cases. This difference reached statistical significance after 4 years of treatment. At that time, the older-onset group had a 68% greater disability score. In addition, mortality ratios tended to be lower in the earlier-onset group confirming the more benign nature of the disease in these cases. In a prospective interventional study including a cohort of 800 "de novo" patients, Jankovic *et al.* (35) analyzed the variable expression of PD within this group. Although early-onset cases had a similar degree of disability than the older cases at the beginning of the study, they had a significantly longer estimated duration of symptoms. Moreover, those with a benign course were significantly younger. In addition, early-onset patients performed better than the older cases on a variety of neuropsychological tests, and those with late-onset disease were more occupationally disabled.

More recently, in reviewing the natural history and mortality of a group of young-onset PD cases (a number of which were included in Quinn *et al.*'s original publication) (3), Schrag *et al.* (27), found that after 10 years, only 5% of patients were experiencing falls and 30% freezing, but all patients had developed levodopa related

fluctuations and dyskinesias. Cognitive function was fairly well preserved in the majority of patients after a median duration of 18 years, more so in those who were less than 60 at the time of the second evaluation. In contrast to what was expected, mortality was twofold compared to the general population, which is coincidental with the findings of Diamond *et al.* (34), who found a higher ratio for the older-onset group. The authors conclude that mortality in parkinsonism starting before the age of 40 is increased in comparison to the normal population and similar to the general PD population irrespective of age. Intellectual function and postural reflexes appear to remain well preserved despite a long history of the disease and the frequent occurrence of levodopa related complications.

Similarly, Gomez Arévalo *et al.* (26) found that younger-onset patients (onset before age 40), irrespective of the duration of the disease, had a better response to levodopa and less involvement of postural stability and gait than those with disease onset after 60. They speculated that the presence of a higher residual motor score, compounded by the presence of postural instability and gait disturbances in older patients, was indicative of the presence of non-dopaminergic involvement related to aging. This is in agreement with Blin *et al.*'s (36) hypothesis on the mechanisms underlying a worsening of the response to levodopa with age. There are no clear indications as to what specific neurotransmitters other than dopamine would be responsible for this. The hypothesis is mainly based on the fact that certain symptoms become less responsive to the beneficial effects of dopamine replacement therapy, while others continue to respond irrespective of the passing of time.

4.3. Diagnostic challenges

We should be particularly careful in applying the label "Parkinson's Disease" to patients presenting with a rigid-akinetic syndrome of early-onset without the necessary thorough imaging and laboratory workup, including the search for known genetic mutations. Even the presence of a positive and sustained response to levodopa is not enough to warrant such a diagnosis. Based on recent findings, it is becoming evident that the term idiopathic parkinsonism is not necessarily synonymous with PD (Lewy body parkinsonism, sporadic or familial). Early-onset parkinsonism is a heterogeneous category including a variety of idiopathic or primary disorders in addition to secondary or symptomatic causes.

4.4. Differential diagnosis

Table 1 includes a list, albeit incomplete, of known causes of early-onset parkinsonism (young-onset and juvenile-onset). Although many of the diseases listed in the table are rare or infrequent they have been reported in the literature and deserve to be included (2).

Patients starting with parkinsonian symptomatology around or under the age of 40 should be thoroughly evaluated. In addition to the usual criteria (both inclusionary and exclusionary) used in the diagnosis of PD, special attention has to be paid to the presence of clinical features that appear to be characteristic of some of the

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Table 1. Differential diagnosis of Young-onset and Juvenile parkinsonism

Young-onset parkinsonism (<40)	Juvenile parkinsonism (<21)
Parkinson's disease (Lewy body) sporadic	Dopa-responsive dystonia (DRD)
Autosomal recessive parkinsonism (PARK 2)	Autosomal recessive parkinsonism (ARP) (PARK 2)
Parkinson's disease (Lewy body) familial (PARK 1)	Juvenile parkinsonism/dystonia (Lewy bodies)
Diffuse Lewy body disease	Rapid-onset dystonia-parkinsonism
Rapid-onset dystonia-parkinsonism	Post-encephalitic parkinsonism
X-linked Dystonia Parkinsonism (Lubag)	Juvenile parkinsonism/dystonia (ARP) (Neurofibrillary tangles)
MPTP and other toxins	Defects of the biosynthesis of DA (infantile forms of dystonia-parkinsonism)
SCA 3 (Machado-Joseph's disease)	Pallidopyramidal disease
Post-encephalitic parkinsonism	Neuronal Intranuclear Hyaline Inclusion disease
Dominantly inherited early-onset parkinsonism	Others: Wilson's disease, Huntington's disease, Mitochondrial cytopathies, Niemann-Pick type C
Chromosome 17 linked-Frontotemporal dementia and parkinsonism	
Multiple System Atrophy	
Hemiparkinsonism/hemiatrophy	
Others: Wilson's disease, Huntington's disease, Mitochondrial cytopathies, Prion's disease	

disorders presenting within this age range. Among these features dystonia deserves a separate comment (12, 29). The rate of occurrence of dystonia in parkinsonism increases with decreasing age. Thus very early onset cases (infancy or early adolescence) with predominant dystonic features and mild parkinsonian features, in some cases associated with marked diurnal fluctuations in symptomatology (morning better than evening, rest-dependent improvement) should evoke a diagnosis of Hereditary Progressive Dystonia or DRD (10, 29). In older cases, with more marked parkinsonian features, the presence of lower limb dystonia, brisk deep tendon reflexes and a history of consanguinity in their parents, or presence of affected siblings, is highly suggestive of the autosomal recessive forms of parkinsonism (ARP) linked to chromosome 6 (PARK 2) (37-39). Although this last group also presents with diurnal fluctuation in disability, the response to levodopa is somewhat different. DRD cases show a dramatic response to very low doses of levodopa and rarely if ever develop long term motor complications. On the contrary, ARP cases in spite of having an excellent response to the drug, and a somewhat benign course, very early on in the course of the treatment develop motor fluctuations and dyskinesias. Dystonia may also be present as a prominent feature in cases of classic Lewy body PD of early onset (EOPD), and similar to what happens in ARP, early appearance of dyskinesias and response fluctuations is a pattern frequently observed in these cases (2). Non routine metabolic studies (CSF biochemistry, fluorodopa PET scanning, and dopamine transporter density measured with SPECT) may be helpful in distinguishing these cases. Furukawa *et al.* (29) were able to separate cases of classic PD, from early onset parkinsonism with prominent dystonia and DRD, on the basis of CSF levels of total bipterin, total neopterin, and fluorodopa PET scanning. CSF total bipterin levels were more markedly reduced both in early-onset cases and DRD cases, while neopterin was reduced only in DRD. Fluorodopa PET scanning showed reduced striatal uptake both in PD and early-onset parkinsonism, being normal in DRD. Bipterin is a

cofactor of tyrosine hydroxylase (TH), the rate limiting enzyme for the synthesis of dopamine, while neopterin is an intermediate in the synthesis of bipterin. Both are used as markers for the detection of abnormalities in the synthetic metabolic chain of bipterin. A defect in the synthesis of bipterin is the biochemical substrate of DRD. At the time these studies were performed, it was not possible yet to identify the genetic background of early-onset cases and it may well be that this group included both Lewy body parkinsonism and non-Lewy body ARP cases. More recently, Jeon *et al.* (40) measured the density of the dopamine transporter (DAT) by means of [123I]β-CIT SPECT in genetically confirmed cases of DRD and compared it with juvenile parkinsonism cases. DRD cases were shown to have normal levels of DAT, which corresponded with the absence of nigral cell loss found in post-mortem studies in these cases (41), whereas in JP the levels of DAT were markedly decreased.

Table 2 provides a comparison of clinical, biochemical and pathological findings of cases of ARP, EOPD and DRD. The pathology will be discussed in more detail in the following section of this review.

The presence of atypical features (excluding dystonia), and/or the lack of response to levodopa will determine the need of a more extensive search of alternative diagnosis (Table 1)

A comprehensive laboratory work up is always mandatory and should include serum ceruloplasmin and urinary copper excretion. Wilson's disease, caused by a disturbance of copper metabolism leading to deposition of this metal in the striatum, although infrequent should be ruled out from the beginning as it entails a bad prognosis if left untreated. The same is true for imaging techniques and electrophysiological investigations that will be helpful in detecting structural damage or more extensive involvement of the central and peripheral nervous system. In selected cases, obtaining a biopsy specimen (muscle, peripheral nerve, bone marrow, brain) will be helpful in the diagnosis

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Table 2. Clinical, biochemical and functional differences between Autosomal Recessive Parkinsonism (ARP), Early-onset Parkinson's Disease (EOPD), and Dopa-responsive Dystonia (DRD)

	ARP	EOPD	DRD
Heredity	AR	None	AD
Mean age at onset (yrs)	20s	30s	<10
Sleep benefit	+	-/+	++
Tremor	Fine, postural	Coarse, rest	Fine, postural
Dystonia	+	+	++
Effect of levodopa	+++	++	++++
Drug-induced dyskinesias	+++	++	-
Fluctuations	+++	++	-
CSF biopterin	↓↓	↓	↓
CSF neopterin	→	→	↓↓
Fluorodopa PET scanning	↓	↓	→
DAT/SPECT	↓	↓	→
Neuronal loss and gliosis in SN	Focal	Diffuse	None
Lewy bodies in SN	None	Diffuse	None
Depigmentation in SN	++	+	++
Neuronal loss in LC	+	++	-
Neurofibrillary tangles	+	-	-

AR: Autosomal recessive; AD: Autosomal dominant, DAT: Dopamine transporter

of cases of early onset parkinsonism associated with more rare disorders (mitochondrial cytopathies, metabolic diseases, prion's disease, etc.).

The discovery of specific genetic mutations in a significant number of cases of juvenile or young onset parkinsonism has greatly facilitated the diagnostic process. Mutations in the parkin gene (PARK 2) are diagnostic of ARP while those corresponding to GTP cyclohydrolase I will certify a diagnosis of DRD (28, 30). The recent identification in two European families of mutations in the DJ1 gene (PARK 7) in ARP cases linked to chromosome 1, leading to absence or inactivation of the DJ1 protein, will probably add an additional genetic marker for the diagnosis of early-onset cases (42). There are, however, numerous cases of early-onset parkinsonism with obvious familial incidence in which no specific mutation has been detected as yet, including the recently published ARP cases linked to chromosome 1 (PARK 6), and autosomal dominant cases linked to chromosomes 4 and 12 (PARK 4, PARK 8) (43, 44).

5. PATHOLOGY

Initial autopsy reports of cases with parkinsonism of early onset will not be considered in this review, as the pathological concept of PD was not firmly established at the time these observations were made. These include the so called "primary atrophies of the pallidal system" (5, 6) and "pallidopyramidal disease" reported by Davison in 1947 (7).

After excluding cases with a specific pathology, corresponding to degenerative, metabolic, toxic, or

infectious disorders, the pathology of primary parkinsonism of early onset is almost restricted to the substantia nigra (SN) causing a syndrome of dopamine deficiency and can be subdivided into three main categories: Lewy body disease (familial or sporadic), nigral cell loss without Lewy bodies and immature nigral cells with poor melanization.

5.1. Lewy body disease (familial or sporadic)

There have been reports of several cases with onset between ages 20 to 40 in which the autopsy findings were indistinguishable from classic late-onset PD. These include: a) severe neuronal loss in the SN pars compacta (SNpc), with Lewy bodies in some of the remaining neurons; b) extracellular melanin and inside macrophages, together with marked gliosis of the SN; c) mild to moderate cell loss, gliosis, and Lewy bodies in the locus ceruleus (LC), dorsal motor nucleus of the vagus, and substantia innominata (12, 17, 45). Pathological features such as these have been found in sporadic cases of early onset and in autosomal dominant PD (PARK 1/alpha-synuclein mutation) in which early-onset cases have been documented (46).

5.2. Nigral cell loss without Lewy bodies

A few cases of juvenile or young onset parkinsonism with age at onset between 10-24 years have come to autopsy. In these cases the post-mortem findings differed considerably from classic Lewy-body parkinsonism. The neuropathological features of these cases included marked depigmentation of the SN and LC, neuronal loss with gliosis and extraneuronal free melanin in the ventrolateral and medial part of the intermediate group of the SNpc. The remaining neurons of the SNpc and those of the LC had smaller size and a reduced melanin content. Lewy bodies were not found anywhere in the central nervous system, even by ubiquitin immunostaining. In one of the cases, in addition, the use of specific stains and immunohistochemical techniques revealed the presence of neurofibrillary tangles (NFT) in the SNpc, LC, red nucleus, posterior hypothalamus, and several cortical regions (38, 47, 48). All of these cases had a positive family history with an autosomal recessive mode of transmission (ARP). Genetic studies performed later in some of these cases detected mutations of the parkin gene (PARK 2) (48).

An exception to this is the case reported by Dwork *et al* (49). This patient whose symptoms started at age 28 died at age 46 after receiving an autologous adrenal transplantation, due to glioblastoma multiforme. Autopsy findings revealed severe neuronal loss in the and pars reticulata of the SN, with prominent gliosis. The remaining neurons in the SNpc were poorly pigmented, and no Lewy bodies or NFT were present in any of the regions studied. This case differed from the previous ARP cases discussed, in that the hereditary mode of transmission was autosomal dominant (13 additional family members in three generations were affected, some with onset in early childhood). No genetic mutation has been detected in these cases as yet.

5.3. Immature nigral cells with poor melanization

Only two patients with these neuropathological features have been published and correspond to childhood

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onset cases. One was reported by Rajput in 1994 (41) and clinically fulfilled the criteria of DRD. In this case, the nigral cell population was normal except for reduced melanin content, especially in the ventral tier. Neurochemically, however, the levels of dopamine as well as the TH protein and the activity of TH were severely reduced in the striatum. In contrast, the SN showed normal levels of TH protein, normal TH immunoreactivity despite a substantial reduction of dopamine content.

The second case deserves a separate comment as this patient has been reported and discussed in several publications and the conclusions differ significantly from one another (50-52). This patient started at age 6 with gait disturbances and frequent falls, associated with inversion of the feet. She further developed generalized rigidity and limb dystonia even prior to receiving levodopa. At age 24 a left sided thalamotomy provided relief of both rigidity and dystonia on the right side. After levodopa became available the patient showed marked improvement but went on to develop left-sided involuntary movements that were subsequently relieved with a right sided thalamotomy. From age 31 to 38 when she died with peritonitis, she functioned almost normally with small doses of levodopa and bromocriptine. The patient's younger brother was also affected, but had milder dyskinesia on levodopa. Neuropathological reports differ considerably, with one of the publications emphasizing a reduced number of neurons in the SNpc, with numerous immature-appearing round cells, reduced melanin content comparable to that of a child 2 to 3 years old, and absence of microglial proliferation or fibrillary gliosis. In contrast, other authors found almost total nerve cell depletion and severe astrocytic gliosis in the ventrolateral part of the SNpc, presence of Lewy bodies, and reduced melanin content. These contradictory observations led to different interpretations of the pathogenetic mechanisms underlying this case, hypoplasia or dysgenesis vs. degenerative process. The question is still unresolved.

6. EPIDEMIOLOGY AND GENETICS

There are no systematic epidemiological surveys of parkinsonism of early onset, however, most reports agree that in the western hemisphere, approximately 5 to 7% of patients with PD in referral populations develop their symptomatology before age 40 (2, 53). This figure is almost double in reports from Japan where confounding factors could be attributed to the inclusion of very early onset cases (childhood or juvenile) probably corresponding to ARP and DRD (11, 12, 31).

6.1. Incidence

The annual incidence of new cases of PD occurring between ages 35 and 39 is about 0.15 cases per 100,000 population, which is about 1/10 the incidence between ages 60 and 64, the age interval of peak occurrence of the disease (1, 53). Although informally it has been noticed that the mean age of patients being referred to specialized clinics has decreased, an analysis of the medical records of the Rochester, MN, population, showed no difference in the distribution curves according

to age of onset when comparing the years 1935 to 1966, 1945 to 1954, and 1967 to 1979. It is argued that this apparent decrease in the mean age of patients with PD seeking medical treatment is due to an improvement in public awareness, bringing patients to consultation sooner after onset (1, 53).

As for the etiology, prevailing hypotheses propose that most cases of PD, including those of early onset, are the result of the combined interaction between genetically determined neuronal vulnerability and exogenous toxic factors or the "wear and tear" of endogenous dopamine metabolism. Analysis of risk factors have yielded conflicting results with some studies finding an association between early onset and rural living and well-water consumption, others with occupational exposure to herbicides or pesticides, and finally some failing to find an association with either rural living or toxic exposure but with a positive family history of PD or head trauma (33, 54-58).

6.2. Familial aggregation

A higher incidence of familial cases has always been considered to be a distinctive feature of parkinsonism of early onset. However, most of the reports originating in the western hemisphere had failed to find any indication of a predominant hereditary component to this disorder, as the majority of published cases were apparently sporadic, with only 1/5 of the cases having at least one affected relative. In contrast, Japanese publications report a significant number of familial cases among their early-onset parkinsonism patients. Ten out of 15 cases were familial in Yamamura's series (32); in the series of Yokochi and Narabayashi (14), 42.5% of patients with onset of parkinsonism between ages 6 and 39 had a 1st- or 2nd-degree relative with PD; Ishikawa (37) found that 10 out of 17 cases with a mean age at onset of 27.8 years had an affected sibling. The main differences between Western and Japanese cases are, a younger onset (large number of patients with either childhood or juvenile onset), and an apparent autosomal recessive pattern of inheritance (11, 12, 31). This difference could be presently explained by the large number of ARP (PARK 2) cases found in Japan, and perhaps the erroneous inclusion of DRD cases among them.

6.3. Genetic aspects

In contrast to previously prevailing ideas, a genetic contribution to the etiology of young-onset PD and juvenile parkinsonism is now well established. This is not only based on the demonstration of familial aggregation of the disease found in several case-control studies, and on the description of large multigenerational families with an autosomal dominant mode of transmission, or families in which multiple siblings were affected (recessive), but in the discovery of specific genetic mutations linked to the causation of the disease (42-44, 59).

A gene locus has been mapped to the long arm of chromosome 4 (4q21-23) in a few families of greek-italian descent that manifested the disease in an autosomal dominant mode and were found to have typical Lewy body pathology at autopsy (46, 60). These families carried a

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Table 3. Response to medication and motor complications in Young-onset (YOPD) and Juvenile Parkinsonism (JP)

No. of cases	Degree of response to Levodopa	Dyskinesias	Fluctuations	Latency	Reference
Group 1 (10)	Dramatic	++++	No mention	No mention	11
Group 2 (22)	Marked	+++	No mention	No mention	
13	Marked (low doses)	+++ (76%)	No mention	After 1 year (D)	15
JP (4)	Marked (80%)	+++ (100%)	+++ (96%)	After 1 month (20%) (D)	3
YOPD (56)	(group as a whole)	(group as a whole)	(group as a whole)	After 1 year (55%) (D) After 1 month (10%) (F) After 1 year (38%) (F) After 6 years (96%) (F)	
23	Not mentioned	+++ (16/23)	+++ (22/23)	After years of treatment (D, F)	18
60	Good (8.7%) at 6mo. Moderate (39.6%) at 6mo. Poor (51.7%) at 6mo.	++ (78%) (motor side-effects considered as a whole)	++ (78%) (motor side-effects considered as a whole)	No mention	19
30 (<48y)	No mention	++(8/30)	++(8/30)	Evaluation at 6 years (D, F)	22
JP (8)	Dramatic	+++	No mention	After 4 years (83%)(D)	21
YOPD (17)	Dramatic	+++	No mention	After 7 years (100%)(D)	
25	No mention	+++	+++	After 2 years (48%)(D) After 5 years (96%)(D) After 2 years (40%)(F) After 5 years (80%)(F)	20
221	No mention	+++(>40%)	+++(>50%)	No mention	24
JP (7)	Excellent(28%), Good(72%)	+++	+++	After 6 months (33%)(D)	25
YOPD (16)	Excellent(50%) Good(22%),Poor (28%)			After 6 months (50%)(D)	
34	Excellent (100%)	+++	+++	After 5 years (82%)(D) After 5 years (82%)(F)	26
JP (10)	Excellent (100%)	+++	+++	After 1 week (25%) (D/F)	27
YOPD(13)	Excellent (81%)	++(91%)	++(92%)	After 6 months (40%)(D/F)	
9)	Good (15%) Poor (4%)			After 5 years (91%) (D/F) 100% at 10 years (D/F)	

D: dyskinesias, F: fluctuations

mutation in the gene encoding the synaptic protein alpha-synuclein. The mutation leads to an amino acid exchange in the alpha-synuclein protein (Ala53Thr) (61). This familial form of PD has been designated PARK 1 as it was the first gene locus to be identified for this disorder. A different mutation in the same gene causing a proline for alanine substitution (Ala30Pro) was later identified in a single German family (62). Younger cases in these pedigrees fall within the range of young-onset PD (21-40 years). Two additional loci, one in chromosome 4 and the other in chromosome 12, causing autosomal dominant forms of the disease (PARK 5, PARK 8), have been also identified. In both, the age range includes young-onset cases (43, 44).

Cases with an earlier age of onset, generally in the 20s and 30s, and having an autosomal recessive mode of transmission with a high degree of parental consanguinity have been found to correspond to a gene locus in the long arm of chromosome 6 (6q25.2-27) (30, 39, 63). The protein encoded by this gene has been

denominated *parkin*, and different mutations (single or multiple exon deletions, point mutations, etc.) lead to a defect in the synthesis of this protein (30, 64, 65). The pathology in these cases differs from classic Lewy body parkinsonism in that there is a selective and severe degeneration of dopaminergic neurons in the SNpc, but without Lewy bodies (see sections on differential diagnosis and pathology) (48). More recently two additional autosomal recessive forms of PD of early onset have been reported corresponding to loci identified in chromosome 1, which have been designated PARK 6 and PARK 7 (43, 44). A mutation in a gene designated DJ1 leading to the absence or inactivation of its encoded protein has been only just reported in two families with the PARK 7 form of ARP (42)

In addition to these, cases of DRD that occasionally present with prominent parkinsonian symptomatology at a very early age carry a gene abnormality on chromosome 14q that results in partial

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reduction of the GTP-cyclohydrolase I (GTP-CH I) activity in the nigrostriatal dopaminergic neurons (28, 29, 66). GTP-CH I is a crucial enzyme in the synthesis of tetrahydrobiopterin, which, as we previously mentioned, is a necessary cofactor for the synthesis of TH.

Furthermore, there are several reports of familial forms of either juvenile or young-onset parkinsonism in which genetic factors, as yet undiscovered, play a role. Such is the case of the “Dominantly inherited, early-onset parkinsonism” reported by Dwork (48), the family reported by Ishikawa (67) with “Hereditary Juvenile Dystonia-Parkinsonism” with an autosomal dominant mode of transmission.

Atypical forms of early-onset parkinsonism have also been reported in which hereditary transmission is evident or genetic factors have been determined. The “pure” form of Diffuse Lewy Body disease may present initially with parkinsonian features of juvenile onset and later development of dementia or psychosis and familial incidence (68). The cases of “Rapid-onset dystonia parkinsonism” studied by Dobyns *et al* (69) with onset between 14 and 45 years have been proposed as a distinct nosological entity with an underlying genetic background as yet undiscovered. “Lubag” or X-linked Dystonia Parkinsonism is a disease that affects Filipino men originating principally from the Panay Island. Linkage analysis has confirmed the mode of inheritance and localized the disease gene to the proximal long arm of the X-chromosome (70). Infantile forms of parkinsonism-dystonia have also been reported and are most commonly caused by inborn errors of metabolism affecting the dopamine biosynthetic pathway (GTP-CH I deficiency, 6-pyruvoyltetrahydropterin synthase deficiency, dihydropteridine reductase deficiency, aromatic amino-acid decarboxylase deficiency, and TH deficiency) (71).

7. RESPONSE TO MEDICATIONS, THERAPEUTIC STRATEGIES

In discussing the clinical aspects of early onset parkinsonism it has already been mentioned that the pattern of response to medication is a characteristic feature of these patients. Table 3 provides a summarized review of all published cases in the literature in which an analysis of the response to levodopa was made.

Younger patients respond to medication differently than older cases. These patients show a more complex pattern of pharmacological response, with more severe dyskinesias, and a shorter duration of action of levodopa. The degree of improvement with levodopa therapy is qualitatively and quantitatively greater, when compared with older cases. These differences are probably age related and depend on central pharmacokinetics or pharmacodynamics or by the involvement of nondopaminergic systems in older patients (26).

Whatever the reason underlying these differences, younger patients require a more cautious approach to medication. Levodopa sparing strategies are

mandatory in these cases, and de novo treatment with dopamine agonists is preferable, as it has been demonstrated that their use reduces significantly the incidence of levodopa related motor complications in the long term. Whenever the use of levodopa becomes necessary it should be carefully introduced at the lowest dose necessary. It is advisable to maintain a stable therapeutic regime for as long as possible. Younger patients should receive psychological support (psychotherapy, support groups) and be stimulated to engage regularly in physical activity and preserve as much as possible an active life.

8. SPECIAL SITUATIONS AND NEEDS CONFRONTING THE YOUNG PATIENT

Younger patients face special psychosocial problems and are often faced with difficult situations in order to cope with a disease that has been traditionally associated with advanced age. The issue of acceptance is paramount and the question “Why me?” is a frequent complaint. The most valuable references on this topic will be found in personal accounts on how to live with PD when you are young (72, 73). People with PD at a young age are often reluctant to participate in support groups for the fear of facing the truth of what lies ahead for them. They feel conspicuous and out of place and feel they do not share the same concerns with people of older age. The issues of family adjustment, marital and sexual life, concerns of being unable to continue being the provider of the family, etc., although not unique for younger patients are more relevant within this age range.

8.1. Menstrual related fluctuations and pregnancy

Although infrequent, one of the specific issues that have to be dealt with in younger patients is the influence of menstruation on the clinical status of younger females still in the premenopausal stage. The menstrual cycle is associated with variations in disability and response to medication. Female patients often refer a worsening of symptomatology and reduced response to levodopa for a few days before menstruation that recurs with each menstrual cycle. This matter requires clarification and appropriate management (15, 53, 74, 75).

Although there have been no reports of an excess incidence of complications of gestation or parturition in pregnant women with PD, there appears to be a tendency for the symptomatology to worsen during pregnancy which often does not return to baseline after delivery. However, activities of daily living or the ability to take care of the child does not appear to be compromised significantly in these cases. Fortunately there has been no increased incidence of neonatal defects associated with the use of levodopa or other antiparkinsonian drugs, although no comprehensive studies on the subject have been performed (53, 76-78).

8.2. Job related demands

The needs of many of our young parkinsonian patients that have to continue working and are subject to special demands at the workplace deserve a final

consideration. They are faced with a dilemma, here they are confronted with a chronic, disabling disorder but they need to and want to continue living an active and productive life. The presence of conspicuous symptomatology often puts them at risk of losing their jobs not only because of their physical disability but because of fear of being discriminated. On account of these factors the treating physician often feels tempted to institute an aggressive treatment strategy, however, in order to prevent the appearance of long term complications it is advisable to exercise a cautious approach to treatment. A careful analysis of the risk-benefit ratio of any therapeutic intervention in these cases is mandatory and should therefore be thoroughly discussed with the patient.

9. ACKNOWLEDGEMENT

The "Seccion Enfermedades Extrapiramidales" & Laboratory of Experimental Parkinsonism is affiliated to and supported by the National Parkinson Foundation, Miami, Fla., USA.

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Key Words: Parkinson's disease, Early-onset, Clinical features, Therapeutics, Genetics, Review

Send correspondence to: Oscar S. Gershanik, MD, Professor and Chairman, Department of Neurology, Centro Neurologico, Hospital Frances, La Rioja 951, (1221) Buenos Aires, Argentina, Tel: 5411-4957-6984, Fax: 5411-4957-6984, E-mail: gersh@movi.com.ar