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Nosography of Parkinson's Disease

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Summary

Mean-age of onset of Parkinson's disease is 56 years. The older the patient is the more rapid is on average the progression of disability. In the early phase the motor symptoms respond well to therapy. Later, variations of response to therapy and side-effects of therapy occur (wearing-off, end-of-dose akinesia, end-of-dose dystonia, dopaminergic abnormal involuntary movements, pharmacogenic psychoses etc.). Due to the modern pharmacologic treatment of Parkinson's disease with dopaminergic substances disabling stages of the disease occur mean 3 to 5 years later than before levodopa-substitution was initiated. The incidence of depression, distinct cognitive deficits (impairment of memory, visuospatial deficits) and dementia increases in the course of the disease. The tremulous form of Parkinson's disease generally leads to less motor impairment than the rigid-akinetic form. Parkinson's disease of early onset (onset before the age of 40), may be regarded as a subtype of Parkinson's disease.

Benign and malignant types of Parkinson's disease may be distinguished, as well as overlaps with multisystem atrophies.

Introduction

James Parkinson was the first to publish an essay on shaking palsy which may even nowadays be regarded as an excellent nosography of the disorder (Parkinson, 1817). James Parkinson did not only accurately describe the symptomatology of early and advanced stages of the disease, but shed also light on the course and the final phase of shaking palsy and discussed etiological and therapeutic aspects. It was not until a striatal dopamine deficit was found to be the underlying pathologic substrate of Parkinson's disease and levodopa-substitution was initiated (Ehringer and Hornykiewicz, 1960; Birkmayer and Hornykiewicz, 1961) that the nosology of Parkinson's disease underwent an important change.

It became soon apparent that levodopa treatment may not sustainedly reduce rigidity and akinesia, but cause after some years fluctuations of the motor-performance and pharmacogenic psychoses. These therapy-related phenomena appearing in the course of Parkinson's disease, and the therapeutic improvement of motor-disability and various non-motor symptoms have meant a new clinical, neurobiochemical, and pharmacological approach to the understanding of the functions of the basal ganglia.

The aim of the present article is to make a general survey of epidemiology, onset, course, subtypes, and psychologic aspects of Parkinson's disease. Symptomatic and postencephalitic as well as drug-induced (neuroleptic, MPTP-induced) Parkinson-syndrome are not the subject of the article.

Some Remarks on Epidemiology of Parkinson's Disease

Mean age of disease onset is about 56 years (Hoehn and Yahr, 1967; Maier-Hoehn, 1983; Zetusky *et al.*, 1985). Both sexes are perhaps equally affected with Parkinson's disease (Schoenberg *et al.*, 1985). Depending on the employed methods of investigation prevalence ratios of Parkinson's disease range from a low of 65 to a high of 347 patients per 100,000 inhabitants (Schoenberg *et al.*, 1985, for review).

There is evidence from epidemiological studies that the number of Parkinson patients with late disease-onset is increasing, which is probably due to a general prolongation of expectation of life in the last few decades (Hoehn and Yahr, 1967). In a small group of patients onset of the disease occurs before the age of 40 (Parkinson's disease of early onset, "juvenile Parkinson's disease") (Hoehn and Yahr, 1967; Barbeau and Pourcher, 1981; Yokochi *et al.*, 1984). Due to some aspects discussed later this variant of early onset may be regarded as a subtype of Parkinson's disease (Barbeau and Pourcher, 1981). Otherwise, hereditary factors generally do not play an important role in Parkinson's disease (Duvoisin *et al.*, 1981; Martin *et al.*, 1973; Ward *et al.*, 1983).

Symptoms at Onset of Parkinson's Disease

Onset of Parkinson's disease is generally insidious. Therefore, figures on the incidence of symptoms regarded as primary symptoms are uncertain. Occasionally patients relate the onset of Parkinson's

disease, especially the onset of tremor, to emotional upsets, intercurrent infections or physical injuries. Frequently the first symptoms of Parkinson's disease are noticed by spouses, relatives, or friends, but not by the patients themselves. At the beginning gait may be slowed with increasingly short and shuffling steps, the trunk and the head mildly bent forward, and the automatic swing of the upper extremities diminished (for review Duvoisin, 1985). Tremor, impairment of finger-dexterity, and micrographia, are generally the symptoms which are recognized by the patients themselves. Therefore, they are frequently regarded as initial symptoms of Parkinson's disease. Onset of Parkinson's disease is often restricted to one side, however, symptomatology generally involves the other side within two years. Patients presenting with predominant rigidity and akinesia may complain of diffuse pain and stiffness of the back and the limbs so that the disorder may be misinterpreted as a rheumatic disease (Duvoisin, 1985; Hoehn and Yahr, 1967). Later reduced facial expression of emotions (hypomimia), mild dysarthria and hypophonia, and mild imbalance of gait become apparent.

Patients sometimes report early in the course of the disease on loss of initiative, fatigue, forgetfulness and depression (Duvoisin, 1985; Mayeux *et al.*, 1981; Malgin *et al.*, 1977; Mayeux and Stern, 1983; Robins, 1976).

Typical Parkinson tremor is a resting agonist-antagonist tremor with a frequency of 3 to 7 beats per second (Selby, 1968). Tremor of the head, the eye-lids, the chin, the tongue, and the voice are rare in Parkinson's disease. Tremor occurs in the majority of Parkinson patients, but is generally not severe enough to disable the patient. However, evidence of tremor may have a great psychological impact on the patient.

Autonomic symptoms such as seborrhea, sialorrhea, orthostatic hypotension, constipation, impairment of micturition and sexual dysfunction (Rajput and Rozdilsky, 1976) do not play an important role in the early phase.

Levodopa, generally in combination with a peripherally acting decarboxylase-inhibitor, is the treatment of choice in early Parkinson's disease. Levodopa alleviates rigidity and akinesia, which are the basic pathologic motor symptoms causing the motor-disability of Parkinson's disease. It may also improve seborrhea (Baas *et al.*, 1985; Streifler *et al.*, 1980), Parkinson-related sleep disturbances (Kendel

et al., 1972; Schneider *et al.*, 1984), loss of libido (Duvoisin, 1981), and at least transiently the cognitive dysfunction (Barbeau and Pourcher 1981). Tremor, rigidity, sialorrhea, and sweating respond to anticholinergic agents. Both levodopa and to a lesser degree anticholinergics are usually well tolerated in early Parkinson's disease. Treatment in the early stage with dopaminomimetic ergot derivatives in the place of levodopa may also be practized (Lees and Stern, 1981).

Lack of appropriate therapeutic agents in the predopa-era led to a sustained deterioration of rigidity and akinesia, impairment of gait with festination and sudden falls, loss of finger dexterity, serious dysphagia, dysarthria, and in the end complete immobility (Parkinson, 1817).

Studies have shown that levodopa treatment results in an attenuation of the progression of the symptoms of Parkinson's disease and does not influence the disease-process itself. (Stages III, IV, and V according to the classification of Hoehn and Yahr postponed by mean 3 to 5 years) (Maier-Hoehn, 1983; Markham and Diamond, 1981).

Different Phases of Parkinson's Disease

The levodopa substitution therapy and treatment with dopaminomimetic ergots are nowadays well established in Parkinson's disease. Therefore 3 phases of the disease may be delineated with respect to the therapeutic effect obtained.

1. Phase of Early Parkinson's Disease

The phase of early Parkinson's disease is characterized by mild motor symptoms, which are either not treated, or successfully treated with dopaminergic substances without evidence of therapy-related fluctuations and with maintenance of complete autonomy of the patient.

2. Phase of Advanced Parkinson's Disease

In the phase of advanced Parkinson's disease therapy-related fluctuations occur which may necessitate personal help in critical situations, however, not longer than for a few hours a day. Generally, the fluctuations become apparent 3 to 4 years after initiation of levodopa treatment.

Response to levodopa appears increasingly delayed and duration of response to levodopa progressively decreases (wearing-off). Early

morning akinesia is observed and noctural akinesia become apparent, frequently combined with painful leg cramps and early morning foot dystonia. Increasingly lower dosages of levodopa lead to abnormal involuntary movements, appearing either as onset-and-end-of-dose dyskinesias or as peak-dose dyskinesias (Lhermitte *et al.*, 1977; De Jong and Meewaldt, 1984; Rajput *et al.*, 1976). There is some evidence from clinical studies that primary treatment with dopaminomimetic substances may diminish and postpone the fluctuations of the motor-performance, however, response to dopaminomimetic therapy seems to be generally less pronounced than that to levodopa treatment (Lees and Stern, 1981; Rinne, 1985).

In the phase of advanced Parkinson's disease rigidity, akinesia, and dyskinesias are frequently associated with deterioration of tremor and autonomic symptoms, like paroxysmal sweating, sialorrhea, impairment of micturition, and orthostatic hypotension, the latter being frequently aggravated by dopaminergic treatment. Cognitive impairment, especially memory disturbances and depression may increase to such an extent, that the patients are rendered handicapped in social and occupational functions. Vivid nocturnal dreams or nightmares may indicate the propensity to pharmacogenic psychoses (Moskowitz *et al.*, 1978), which may not only be induced by dopaminergic agents, but also by anticholinergics and amantadine.

Due to progressive shortening of the on-periods the patient is increasingly rendered dependent on personal assistance in critical situations. In this phase patient is frequently no more able to cope with the requirements of his occupation.

3. *The Phase of Late Parkinson's Disease*

In late Parkinson's disease on-periods become increasingly unpredictable with respect to the time of intake of the medication and the dosage (on-off phenomenon) (Fahn, 1974; Marsden, 1980). Therefore, the patients get more and more dependent on personal assistance. The total duration of on-periods become progressively shorter. Towards the final stage of the disease the patients are either wheel-chair-bound or bed-ridden. Food intake becomes difficult because of either akinesia-related dysphagia or oral abnormal involuntary movements. Frequently patients have to be artificially fed via gastric tubes or have to be administered intravenous infusions.

Progressive urinary incontinence or neurogenic inhibition of micturition may necessitate catheterization. Intercurrent infections like bronchitis and pneumonia have to be early diagnosed and treated as they may lead to lethal complications.

Dementia is a general feature in late Parkinson's disease. Deliria may occur even at minimal dosages of various anti-parkinsonian substances or at drug-free states.

Death in Parkinson's disease may either be caused by a lethal akinetic crisis, which is frequently accompanied by delirium and vegetative disinhibition, or by intercurrent diseases not related to the disease (cardiac failure, myocardial infarction, vascular lesions of the central nervous system) or facilitated by the disease (marasm, pneumonia) (Hoehn and Yahr, 1967; Martilla and Rinne, 1980; Schneider *et al.*, 1981). The risk of mortality is higher in Parkinson's disease than it is in the general population (about 1.5 : 1 ratio). Due to modern pharmacologic treatment in the last decades, mortality has been improving especially among those patients responding well to levodopa treatment; they are generally of younger age-at-onset of the disease than those not improving through levodopa (Maier-Hoehn, 1983; Martilla *et al.*, 1977; Schneider *et al.*, 1981).

Subtypes of Parkinson's Disease

There is evidence from several studies that the tremulous form of Parkinson's disease is more favourable with respect to progression of motor-disability and the occurrence of dopaminergic side-effects than is the rigid-akinetic form (Hoehn and Yahr, 1967; Zetusky, 1985; Ransmayr *et al.*, 1985). The differentiation of a rigid-akinetic type, a tremor-dominance type, and an equivalence type of Parkinson's disease has been suggested (Poewe, Gerstenbrand, Ransmayr, 1983).

Dementia, and pharmacogenic psychoses are also likely to occur less frequently in tremulous cases than in those presenting with predominant rigidity and akinesia (Gil and Lefevre, 1979; Mortimer *et al.*, 1982). Studies have revealed that patients with early onset respond generally better to dopaminergic treatment than patients with late onset of the disease (Birkmayer *et al.*, 1979; Birkmayer and Riederer, 1985). The distinction of Parkinson's disease accompanied by dementia and Parkinson's disease without dementia has also been suggested (Lieberman *et al.*, 1979).

Parkinson's disease of early onset may also be regarded as a subgroup of Parkinson's disease due to its high heredity and the observed coincidence with thyroid dysfunction and diabetes.

Parkinson's disease may be combined with symptoms predominantly occurring in so-called multisystem atrophies (Parkinson plus, for review see Duvoisin *et al.*, 1981; Fischer, 1984). Patients presenting with symptoms like vertical gaze palsy (possible overlap with progressive supranuclear palsy), orthostatic dysfunction, sexual impotence, impairment of micturition, and anhidrosis (possible overlap with Shy-Drager syndrome) or dementia and motoneuron symptoms (possible overlap with Parkinson-amyotrophic lateralsclerosis-dementia complex) generally respond badly to therapy and deteriorate rapidly (Poewe, Gerstenbrand, Ransmayr, 1983).

Psychic Aspects of Parkinson's Disease

It has been hypothesized that certain premorbid personality-traits may be common in Parkinson's disease (loyality, accuracy, introversion, psychic inflexibility, marked self-control etc) (Poewe, Gerstenbrand, Ransmayr, Plörer, 1983). As a possible factor in the development of Parkinson's disease chronic emotional distress has been discussed (Todes, 1984). Incidence of smokers seems to be lower among parkinsonians compared to the general population (Mayeux *et al.*, 1981).

These findings and hypotheses may indicate that Parkinson's disease is frequently associated with a spectrum of psychic irritability, which has to be taken into consideration in the treatment of the patients.

Hopefully, new developments in the treatment of Parkinson's disease will increasingly improve the disability of the patients.

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