Neurol Sci (2002) 23:S77–S78

Clinical predictors in Parkinson's disease

E. Gasparoli · D. Delibori · G. Polesello · L. Santelli
M. Ermani · L. Battistin · F. Bracco (✉)
Department of Neurological and Psychiatric Sciences, University of Padua, Padua, Italy

Abstract Parkinson's disease is characterized by heterogeneity of clinical presentations, association of signs and symptoms, rate of progression, and response to therapy. The aim of this prospective 5-year study was to evaluate whether clinical features at onset were predictive of the subsequent progression. Two courses were identified which differed in the characteristics at onset. Slow course was characterized by earlier age at onset, lateralization of motor signs, rest tremor, and absence of gait disturbance. Rapid course presented older age, less evident lateralization of signs, predominance of bradykinesia-rigidity and gait disturbance. Our results confirmed that PD is clinically heterogeneous and specific patterns of onset seem to be associated with different rates of disease progression. Predictive models based on these clinical characteristics have a good sensitivity in indicating a slow disease progression but are not reliable in indicating a rapid evolution.

Parkinson's disease (PD) is characterised by heterogeneity of clinical presentations, association of signs and symptoms, rate of progression of the disease, and response to therapy, suggesting the existence of different subgroups, possibly related to different underlying processes. In the pre-levodopa era, the clinical data of Hoehn and Yahr [1] revealed a great heterogeneity of disease progression: 37% of the patients whose duration of disease was less than 5 years were in stage III, while 34% of patients whose duration of disease was ten years were in stage I or II. The patients in the same stage had a large variation of disease duration.

Possible tools for monitoring disease progression are evolution of clinical pattern, modality of response to therapy, neuroimaging techniques and genetic research. In the case of autosomal recessive parkinsonism, genetic tests could predict the slow progression with good response to levodopa. Sequential neuroimaging techniques seem to be a useful tool in monitoring the intra-individual progression of dopaminergic cell loss in PD but cannot predict the kind of progression when performed only at onset. Currently, disease progression rate can be evaluated with clinical indicators: rate of impairment of motor signs and their temporal association, the presence of non-motor signs, the variation in the response to therapy, the presence of motor and non-motor complications, and comorbidity.

The aim of this study was to evaluate whether clinical features at onset and their different sequence of association could be predictive of the subsequent rate of disease progression. The pattern of disease progression may define the prognosis and influence therapeutic strategies.

A prospective longitudinal study was carried out in 103 patients (69 men) with a diagnosis of PD according to the Parkinson's Disease Society Brain Research Centre's clinical diagnostic criteria. The exclusion criteria were atypical parkinsonism (at onset and follow up) and dementia at onset. At onset the following parameters were recorded: sex, age at onset, main motor sign, lateralization of motor signs, association of signs/symptoms, presence of depression, and presence of gait disturbance. At the 5-year follow-up, impairment of motor score was evaluated by Unified Parkinson's Disease Rating Scale (UPDRS) and cognitive impairment was measured by MMSE (Mini-Mental State Examination). Complications of therapy (motor fluctuations and dyskinesia), impairment of postural reflexes, functionally limiting gait disturbance and cumulative dose of levodopa were recorded to evaluate the severity of disease progression.

Cluster analysis was used to identify two groups of patients based on UPDRS motor score, presence of motor fluctuations and dyskinesia at 5 years. This distinction in two groups was used to give a prognostic meaning to the characteristics evaluated at onset. To evaluate the prognostic meaning of the variables at onset, the progress of each component of progression, the UPDRS motor score and possible relationships between each parameter of onset and presence of fluctuations and dyskinesias were analyzed. The characteristics significantly correlated with the outcome were used to obtain a predictive model using logistic regression.

For statistical analysis chi-square tests were used for all dicotomic variables and Student's *t* test was used for all continuous variables. All variables were then subjected to cluster analysis.

Two disease courses (slow and rapid) were identified by cluster analysis. Patients with a slow evolution (61%) were characterized by earlier age at onset, lateralization of parkinsonian signs, prevalence of rest tremor and absence of gait disturbance. Patients with rapid progression (39%) had an older age, absence of lateralization of parkinsonian signs, predominance of bradykinesia-rigidity and gait disturbance (Table 1).

The statistical correlation between the variables at onset and the UPDRS motor score after 5 years suggested a significant correlation of age at onset (p=0.01), main motor sign (p=0.02), lack of lateralization of clinical signs (p=0.001) and presence of gait disturbance (p=0.03). Age at onset (51.0±15.3 years vs. 61.5±9.1) was significantly correlated with presence of dyskinesias (p=0.001), while no other characteristic at onset was significantly correlated with the later presence of motor fluctuations.

Predictive models based on these clinical characteristics have a good sensitivity (87.3% of correct prediction) in indicating a slow disease progression but poor sensitivity in indi-

Table 1 Characteristics of PD patients at onset, by type of progression

	Slow progression (n=63)	Rapid progression (n=40)
UPDRS motor score[a]	11.9 (3.9)	25.1 (5.1)
Motor fluctuations, %	19.0	52.5
Dyskinesias, %	15.8	30.0
Age at onset, years[a]	56.0 (11.0)	63.5 (11.0)*
Lack of lateralization, %	17.4	45.0*
Main motor sign, %		
Tremor	58.8	42.5
Rigidity	41.2	57.5
Depression, %	9.5	12.5
Gait disturbance, %	3.2	10.0

*p=0.002

[a] Values are mean (SD)

cating a rapid evolution (37.5% prediction of correct response).

Our results confirm that PD is clinically heterogeneous and suggest that specific patterns of onset may be associated with different rates of disease progression. Several studies have addressed the question of clinical heterogeneity by proposing subgroups distinguished by age at onset, variable progression, family history, patterns of motor symptoms and associated non-motor findings such as dementia and depression. In these studies the disease progression was evaluated considering the progression of single signs, and not the sequential association of signs. Homogeneous predictive criteria were not found and their results show that early disease onset [2, 3] with tremor dominance correlates with slow progression, while older age at onset and presentation with bradykinesia are predictive of a more aggressive course [4].

Cluster analysis was used to identify subgroups [5]: in our study two different groups of patients (slow 60% and rapid 40%) were identified. Our results provide a predictive model which reliably predicts only a slow disease progression, but not a rapid evolution. We found that age at onset was significantly associated with dyskinesias, while no other characteristic at onset was significantly correlated with the later presence of motor fluctuations. This supports the hypothesis of possible different pathogenic mechanisms.

In the previous studies [6, 7], the motor complications were considered in correlation with the disease stage, the duration and the kind of exposition to levodopa more than with the progression rate of disease.

The existence of different subtypes of disease is not only revealed by the characteristics at disease onset but also by the response to therapy. In a long-term study on the efficacy of dopamine agonist vs. levodopa in the treatment of early previously untreated PD patients [8], 35% of patients in monotherapy remained clinically improved for 4 years, showing that there are patients who respond better to therapy and/or with a more slowly progressing course of disease. Our results confirm this hypothesis.

The possibility of predicting, at disease onset, the rate of progression of symptoms, the quality of therapy response and latency and severity of motor and non-motor complications may give a instrument to identify the most appropriate initial therapeutic strategy of the single subgroups. This method is useful in consideration of both efficacy in pharmacological control and presence of complications in long-term therapy.

References

1. Hoehn MM, Yahr MD (1967) Parkisonism: onset, progression, mortality. Neurology 17:427–442
2. Goetz CG et al (1988) Risk factors for progression in Parkinson's disease. Neurology 38:1841–1844
3. Jankovic J, McDermott M et al (1990) Variable expression of Parkinson's disease: a baseline analysis of the DATATOP cohort. Neurology 40:1529–1534
4. Jankovic J, Kapadia AS (2001) Functional decline in Parkinson's disease. Arch Neurol 58:1611–1615
5. Graham JM, Sagar HJ (1999) A data-driven approach to the study of heterogeneity in idiopathic Parkinson's disease: identification of three distinct subtypes. Mov Disord 14:10–20
6. Goetz CG, Stebbins GT, Blasucci LM (2000) Differential progression of motor impairment in levodopa-treated Parkinson's disease. Mov Disord 15:479–484
7. Schrag A, Quinn N (2000) Dyskinesias and motor fluctuations in Parkinson's disease. A community-based study. Brain 123:2297–2305
8. Rinne UK, Bracco F, Chouza C et al (1988) Early treatment of Parkinson's disease with cabergoline delays the onset of motor complications. Results of a double-blind levodopa controlled trial. Drugs 55[Suppl]:23–30