A longitudinal study of patients with Parkinson's disease (ELEP): aims and methodology

ELEP Group [a]

A LONGITUDINAL STUDY OF PATIENTS WITH PARKINSON'S DISEASE (ELEP): AIMS AND METHODOLOGY

Summary. Introduction and development. *Parkinson's disease (PD) is a chronic and progressive disorder. It produces a significant burden not only for patients, but also for their family and caregivers, with a major socio-economic impact on society. Current knowledge on PD is characterized by scarce information about the evolutionary course of: 1) the non-motor PD features; 2) impact of non-motor PD features on disability and health related quality of life (HRQL) impairment; 3) factors related to disability and HRQL determinants; 4) factors that speed or slow the progression of PD; 5) differential long-term effect of available PD therapeutic schedules and their relationships with disability, complications, and HRQL; and 6) impact of the disease on patients' caregivers. In addition, heterogeneity in the metric quality of the applied measures and selection bias are frequently found.* Conclusion. *Due to the aforementioned limitations and from a multidimensional perspective, a new longitudinal study in PD is deemed necessary. The longitudinal study of PD patients (ELEP) includes a long-term follow-up of never before sistematically assessed aspects, will allow to increase the global knowledge about PD. [REV NEUROL 2006; 42: 360-5]*

Key words. *Assessment. ELEP. Long-term follow-up. Methods. Parkinson's disease.*

INTRODUCTION

Based on the results of door-to-door epidemiologic studies, the estimated total population of Parkinson's disease (PD) patients in Spain ranges from 100,000 to 150,000, and of these 30%-50% may not be diagnosed [1-5]. Current knowledge of PD suffers from major limitations as regards aspects concerning the development and evolution of non-motor features of the disease, the impact of such features on disability and health-related quality of life (HRQL), the evolution of certain determinants of disability and HRQL, differential factors linked to the speed of disease progression, the impact of PD on caregivers and society, etc. Due to these shortcomings, more in-depth knowledge is needed on the above aspects and their development over time.

With these general objectives in mind, the longitudinal study of patients with Parkinson's disease –*Estudio longitudinal de pacientes con enfermedad de Parkinson* (ELEP)– has been implemented. It is the Spanish contribution to the international EuroSCOPA-Propark project, the first phase of which –known as Scales for Outcomes in Parkinson's Disease (SCOPA and already concluded– was undertaken as an international collaboration for the purpose of reviewing, designing and analyzing specific measures for PD. EuroSCOPA-Propark will apply the assessment methods validated in the first phase of the project –some newly designed and targeted at evaluating aspects of the disease never before measured [6-15]– to a wide number of PD patients across a long-term follow-up.

In Spain, this project acquires a special dimension for two reasons, namely:

a) It stands at the activity interface of two research networks: *Red de Centros de Investigación en Enfermedades Neurológicas*, *Fundación CIEN*, and *Red de Investigación de Resultados en Salud*, *Red IRYSS*.
b) It is connected with another project, targeted at studying the development of complications, and genetic and neuroimaging aspects of PD (the VIP Project), which, together with the ELEP, constitute the program of the 'Spanish PD Consortium' (*Consorcio Español sobre la EP*) (Figure).

This paper seeks to: 1) describe the long-term follow-up protocol adopted by the ELEP for a multicenter series of PD patients and their caregivers; and 2) briefly outline the assessment instruments to be applied in this protocol.

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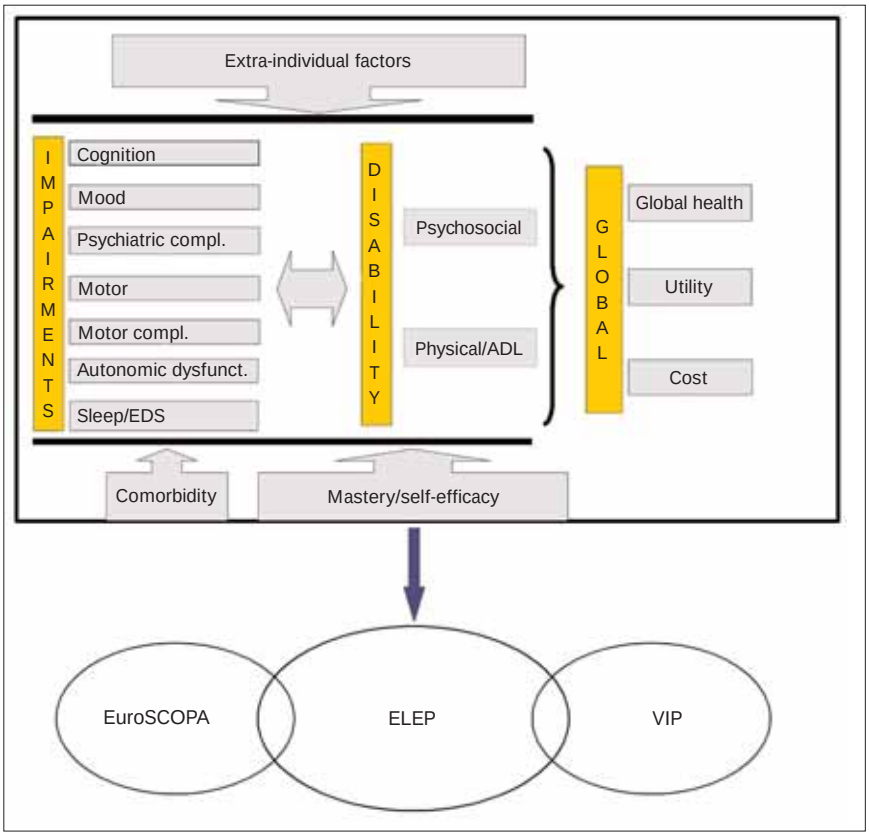

Figure. Longitudinal study of patients with Parkinson's Disease Project (with the authorization of the head of research of SCOPA Propark project, Dr. J.J. van Hilten. Leiden University Medical Center. Leiden, The Netherlands).

METHODS

Design

This is a nation-wide, observational, multicenter study, using a longitudinal long-term follow-up (6 years) with repeated (annual) cross-sectional assessments across the study period.

Population

'Study unit' is defined as the pair consisting of the patient and principal caregiver (PPC). PD will be diagnosed by a neurologist specialized in movement disorders, as per the modified United Kingdom Parkinson's Disease Society brain bank diagnostic criteria for Parkinson's disease (BCUKPDS) [16] (Table I).

'Principal caregiver' (principal informal caregiver) is defined as 'any person who usually cohabits with the patient and is in some way directly involved in the care of the patient or suffers the impact of the latter's health problem (even though this may not require care), without being a professional or belonging to a social support network'.

PPCs will be selected on the basis of the primary inclusion of patients in accordance with the criteria specified in table II. Furthermore, account will be taken of the sample distribution plan, based on patient characteristics, detailed below.

Sample

Characteristics

PPCs will be included according to a plan that stratifies basic aspects from a clinicoepidemiologic stance, i.e., age at PD onset, duration of disease at date of entry into the study, and sex. The aim is to obtain a balanced sample, in which account is taken, from the outset, of primary historical and demographic characteristics, so as to prevent traditional PD selection biases, such as inclusion based on level of severity as per Hoehn & Yahr staging (typically asymmetric, with overrepresentation of stage-2 and -3 and practical absence of stage-5 patients), treatment goals (studies with questionable external validity), presence of complications, etc. Blocks of 8 patients will be included as per the breakdown shown in table III.

Sample size

Psychometric analysis criteria applicable to the measures used will be taken as the base for calculation. To this end, it is estimated that a minimum of around 40 patients will have to be computed in each box of the above-mentioned sampling distribution, making 320 patients in all. Not only does this figure allow for score distributions to be reliably analyzed and statistics with satisfactory confidence levels to be applied, but it also allows for the performance of methodologic aspects to be checked in successive evaluations, e.g., aspects such as standard error of measurement calculated on the basis of reliability index (Cronbach's α in cross-sectional studies versus intraclass correlation coefficient in re-tests), for which samples greater than 300 patients may be required [17]. Furthermore, the proposed figure seeks to ensure a minimum number of 30 cases per box, totally computable at the end of the study, which would enable data to be analyzed for purposes other than psychometric analysis, without any correction for small sample sizes.

Replacement

To offset the attrition of the baseline sample that is inevitable in long-term longitudinal studies, particularly among elderly populations, replacement of losses will be permitted during the first 3 years of the study. Bearing in mind that, as from the 3rd year, losses can rise as high as 10%, a minimum of 350 patients will be included. In view of the variability of expression of PD, however, it is highly advisable for these minima to be exceeded, since stratification for certain analyses (e.g., effect of stereotaxic surgical treatment) could be hindered by a lack of cases.

Data collection and ethical aspects

Assessments will be made once a year, over the total duration of the longitudinal 6-year follow-up. This time interval is felt to be sufficient to study the progression of PD on the basis of the various levels established, by sample distribution block, in respect of aspects such as disease expression, disability, HRQL, and socioeconomic impact.

The information obtained on each PPC will be based on a purpose-designed code and anonymously recorded in a database.

Table I. Diagnostic criteria for Parkinson's disease (based on the United Kingdom Parkinson's Disease Society brain bank diagnostic criteria for Parkinson's disease, modified version [16].

1. Diagnosis of Parkinsonism
Bradykinesia (slowness in initiating voluntary movements, with progressive reduction in speed and amplitude of repetitive actions, and at least one of the following signs:
Muscular rigidity
4–6 Hz resting tremor
Postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction.
2. Parkinson's disease exclusion criteria
History of repeated strokes with stepwise progression of parkinsonian features
History of repeated head injury
History of definite encephalitis
Oculogyric crisis
Neuroleptic treatment at onset of symptoms
Sustained remission
Strictly unilateral features after 3 years
Supranuclear gaze palsy
Cerebellar signs
Early severe autonomic involvement
Early severe dementia with disturbances of memory, language and praxis
Babinski's sign
Presence of a cerebral tumor or communicating hydrocephalus on computed tomography scan
Negative response to large doses of levodopa (if malabsorption excluded)
MPTP exposure
3. Criteria that support a diagnosis of Parkinson's disease
Three or more of the following criteria required for diagnosis of definite Parkinson's disease:
Unilateral onset
Rest tremor present
Progressive disorder
Persistent asymmetry affecting the side of onset + evident and lasting response to levodopa and/or dopaminergic agonists
Severe levodopa-induced chorea

This database, like the PPC check list, will be protected in accordance with prevailing statutory requirements (Organic Act 15/1999 of 13 December). The central database will be located in the Applied Epidemiology Section of the National Center for Epidemiology, at the Carlos III Institute of Public Health, Madrid. Each assessor will be responsible for keeping personal information and codes assigned to PPCs confidential, with the head researcher having overall responsibility for the central database.

Table II. ELEP project inclusion/exclusion criteria for PD patients and caregivers.

Patients	Caregivers
Inclusion criteria	Inclusion criteria
Age 30 years or over.	Full legal age
Both sexes	Both sexes
Diagnosis of idiopathic PD	Compliance with definition of principal caregiver
Informed consent	Capable of answering self-assessment questionnaires in a personal or proxy capacity.
	Adequate fluency in Spanish
	Informed consent
Exclusion criteria	Exclusion criteria
Failure to meet any given inclusion criterion	Failure to meet any given inclusion criterion
Lack of stable caregiver	
Any medical or psychiatric comorbidity barring proper assessment of PD	

Table III. ELEP-patient inclusion plan [a].

	Men		Women	
	30-60 years	> 60 years	30-60 years	> 60 years
PD duration ≤ 5 years	1	1	1	1
PD duration > 5 years	1	1	1	1

[a] Modified after an investigators meeting held on December 15, 2005.

Patients and caregivers will be required to give their informed consent to participating in the study. The project has been approved by the Research Committee of the Carlos III Institute of Public Health, and the Clinical Research Ethics Committee of the Princesa Hospital (Madrid).

Assessments

The measures to be applied, for which there are validation studies for specific use on PD patients and their caregivers (SCOPA Project and other studies) [6-15,18-23], are set out in table IV. In order to analyze the performance of the new PD assessment scales to be used in the ELEP project, pilot feasibility, transcultural validation and independent validation studies have been conducted, some already published or currently in press. Table V shows data, for the most part preliminary, on essential metric characteristics (internal consistency and convergent construct validity) of the measures included in the ELEP project.

Data analysis

Based on the measures used

– Quality and acceptability of data: percentage of missing and final computable data, observed versus possible range, measures of central trend and dispersion, floor and ceiling effects, etc.

Table IV. ELEP project assessments.

Self-assessment by patient	
Mental status and mood	Hospital Anxiety and Depression Scale
Autonomic dysfunction	SCOPA-AUT
Sleep disorder	SCOPA-Sleep
Psychosocial impact	SCOPA-Psychosocial
Quality of life	EuroQoL
Fatigue	Visual Analogue Scale (VAS)
Pain	VAS intensity, VAS frequency
Assessment by researcher	
Cognitive status	SCOPA-Cognition
Motor aspects	SCOPA-Motor
Psychiatric complications	Parkinson Psychosis Rating Scale - Modified
Comorbidity	Cumulative Illness Rating Scale-G
Disease stage	Hoehn & Yahr Classification
Global assessment	Clinical Impression of Severity Index-PD
Cost	SCOPA-Costs - Modified
Assessment by caregiver	
Demography and relationship with patient	
Data on care	
Burden	Zarit's Caregiver Burden Scale
Health-related quality of life	EuroQoL
Depression / Anxiety	Hospital Anxiety and Depression Scale

– Scale assumptions: distribution of scores, and item convergent and discriminant validity.
– Internal consistency –Cronbach's α, item-total correlation, homogeneity– and stability –κ coefficient, intraclass correlation coefficient (ICC), Kendall's concordance coefficient, etc.
– Concurrent criterion validity where possible, since there may be a 'gold standard': correlation coefficient.
– Convergent and divergent construct validity: correlation coefficients, multitrait multimethod analysis.
– Known groups validity: ANOVA, Kruskal-Wallis test.
– Cross-sectional (α-based) and longitudinal (ICC-based) precision –standard error of measurement (SEM)–.
– Sensitivity to change: standardized mean response, effect size, SEM.
– Interpretability, based on distribution of score differences and categorization vis-á-vis external comparative measures.

Based on the clinical and evolutional aspects of the cohort

– Descriptive statistics for quantitative and qualitative variables.
– Comparative analyses: *t*-test, Wilcoxon/Mann-Whitney, chi-squared tests, etc., and cluster studies to identify subgroups.
– Correlation and multiple regression in the successive cross-sections to identify associations.
– Variance analysis for repeated measures.
– Survival analysis (Kaplan-Meier) and Cox's regression for data on successive intervals.

CONCLUSIONS

Available information on the longitudinal course of PD is characterized by a number of limitations, which can be summarized under three heads:

– The traditional approach taken by studies, their tendency to focus on the disease's motor manifestations in detriment to the others, has meant that existing empirical information on the impact of non-motor symptomatology over the course of disease progression is relatively sparse.
– The frequent use of assessment instruments with clinimetric flaws –and, occasionally, even unvalidated scales– whose results may have been deemed acceptable and used for decision-making with little questioning.
– A tendency to reflect findings based on populations selected for the study of specific aspects (e.g., clinical trials) or samples drawn from specialized units, despite the presence of selection bias that excluded a part of the PD population (e.g., patients in the most advanced phases).

The ELEP seeks to improve knowledge of PD in aspects that have been little explored or poorly evaluated until now, by means of a systemized longitudinal follow-up, with proper instruments. To this end, the ELEP has been proposed as a nation-wide collaboration, incorporating a large team of neurologists specialized in PD and movement disorders.

The objectives are twofold, and are: on the one hand, to furnish data on the metric attributes of a series of scales that constitute a complete PD assessment system, the components of which could prove useful for other studies in the future; and on the other, to obtain data through this system of assessment which serve to enhance knowledge on PD, in terms of long-term evolutional aspects and others on which current information is found wanting. The results of the ELEP could be considerably strengthened by parallel projects (the VIP Project and EuroSCOPA), since both use similar clinical protocols.

It is evident that patients to be included in the ELEP do not correspond to those constituting a representative sample of PD in the general population. This is the result of a sample design that has been expressly tailored to the designated study objectives. Long-term analysis will enable the evolutional profile of the disease to be reconstructed in respect of aspects analyzed in terms of basic epidemiologic elements. Thanks to the balanced patient-inclusion design, information will be sought on aspects which, until now, have been little known due to the use of biased selection methods with scant representation of extremes.

It is essential to have valid measures that cover the clinical spectrum of the disease. Table V sets out some basic characteristics, for the most part preliminary (some obtained from pilot studies), of the scales included in the ELEP. Based on currently available data, these measures as a whole comply with commonly accepted standard criteria.

Table V. Characteristics of ELEP-project assessment measures

Scale	Number of items	Method of administration	α coefficient (Cronbach)	Item-total correlation	Convergent validity (correlation coefficient)
SCOPA-COG [a]	10	Cognitive test	α = 0.82	0.41-0.64	MMSE *r* = 0.54 CISI-PD *r* = –0.59 PPRS *r* = –0.40 HY *r* = –0.27 SCOPA-AUT *r* = –0.33 SCOPA-Motor *r* = –0.65 SCOPA-CISI-PD *r* = –0.53 SCOPA-Sleep *r* = –0.41 HADS total *r* = –0.52 SCOPA-Psychosocial *r* = –0.49
SCOPA-AUT [a]	25	Self-administered	α = 0.79	0.05-0.65	HY *r* = 0.38 MMSE *r* = –0.14 PPRS *r* = 0.40 SCOPA-COG *r* = –0.33 SCOPA-Motor *r* = 0.58 CISI-PD *r* = 0.65 SCOPA-Sleep *r* = 0.15 HADS total *r* = 0.37 SCOPA-Psychosocial r=0.36
Pain [a]	2	Self-administered	α = 0.85	0.74 (inter-item correlation)	PDSS *r* = –0.54 HY *r* = 0.18 SCOPA-COG *r* = –0.12 SCOPA-Motor *r* = 0.13 CISI-PD *r* = 0.19 MMSE *r* = –0.13 SCOPA-AUT *r* = 0.25 HADS total *r* = 0.12 SCOPA-Sleep *r* = 0.006 SCOPA-Psychosocial *r* = 0.06
PPRS [a]	6	Interview with caregiver	α =0.70	0.10-0.67	CISI-PD *r* = 0.69 HY *r* = 0.56 MMSE *r* = –0.45 SCOPA-COG *r* = –0.40 SCOPA-AUT *r* = 0.40 SCOPA-Motor *r* = 0.46 SCOPA-Psychosocial *r* = 0.15 SCOPA-Sleep *r* = 0.36 HADS total *r* = 0.02
SCOPA-Psychosocial [a]	11	Self-administered	α = 0.84	0.17-0.70	MMSE *r* = 0.01 HY *r* = 0.25 PPRS *r* = 0.15 SCOPA-Motor *r* = 0.60 SCOPA-Sleep *r* = 0.28 CISI-PD *r* = 0.56 SCOPA-AUT *r* = 0.36 HADS *r* = 0.69 SCOPA-COG *r* = –0.49 Dolor *r* = 0.06
SCOPA- Motor [a]	Section I: 10 Section II:7 Section III:4	Interview + motor test	Section I: α = 0.78 Section II: α = 0.89 Section III: α = 0.86	Section I = 0.07-0.67 Section II = 0.49-0.87 Section III = 0.62-0.82	HY *r* = 0.49 MMSE *r* = –0.34 PPRS *r* = 0.46 SCOPA-COG *r* = 0.58 SCOPA-AUT *r* = 0.58 SCOPA-Sleep *r* = 0.30 CISI-PD *r* = 0.87 HADS total *r* = 0.36 Dolor *r* = 0.13
SCOPA-Sleep [a]	Nighttime sleep [5] Daytime sleepiness [6]	Self-administered	Nighttime sleep α = 0.92 Daytime sleepiness α = 0.83	Nighttime sleep = 0.68-0.88 Daytime sleepiness = 0.49-0.74	MMSE *r* = –0.28 HY *r* = 0.34 SCOPA-COG *r* = –0.41 PPRS *r* = 0.36 SCOPA-AUT *r* = 0.15 Dolor *r* = 0.006 SCOPA-Psychosocial *r* = 0.28 SCOPA-Motor *r* = 0.30 CISI-PD *r* = 0.40
CISI-PD [a]	4	Interview	α = 0.84	0.60-0.88	MMSE *r* = –0.39 HY *r* = 0.58 SCOPA-COG *r* = –0.59 PPRS *r* = 0.69 Dolor *r* = 0.19 SCOPA-Psychosocial *r* = 0.56 SCOPA-Motor *r* = 0.87 SCOPA-Sleep *r* = 0.40 HADS *r* = 0.40
Fatigue (VAS) [23]	1	Self-administered	NA	NA	Global perception of fatigue *r* = –0.47 General fatigue *r* = –0.47 D-FIS *r* = –0.62

[a] Unpublished preliminary data, obtained from the pilot study. NA: not applicable.

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ESTUDIO LONGITUDINAL DE PACIENTES CON ENFERMEDAD DE PARKINSON (ELEP): OBJETIVOS Y METODOLOGÍA

Resumen. Introducción y desarrollo. *La enfermedad de Parkinson (EP) es crónica y progresiva. Desde la perspectiva sociosanitaria, representa una fuente de sufrimiento para el paciente y sus cuidadores, así como una importante carga para la sociedad. La información actual sobre la EP es limitada en cuanto al conocimiento del curso evolutivo relacionado con: 1) el desarrollo y la evolución de los aspectos no motores de la enfermedad; 2) el impacto de estas manifestaciones sobre la discapacidad y la calidad de vida relacionada con la salud (CVRS); 3) los determinantes de la discapacidad y de la pérdida de CVRS; 4) los factores relacionados con la velocidad de progresión de la enfermedad; 5) las pautas de aplicación y la repercusión diferencial a largo plazo (sobre complicaciones, discapacidad, CVRS) de las medidas terapéuticas disponibles; y 6) el impacto de la EP sobre los cuidadores. Además, en la información existente se detecta heterogeneidad en la calidad de las propiedades métricas de los instrumentos de medida aplicados y de los sesgos de selección.* Conclusión. *Debido a las limitaciones señaladas, se estima necesario profundizar en el conocimiento longitudinal detallado de la EP, desde una perspectiva multidimensional. El estudio longitudinal de pacientes con la enfermedad de Parkinson (ELEP), que incluye un seguimiento a largo plazo de algunos aspectos nunca anteriormente evaluados de forma sistemática, permitirá incrementar el conocimiento global sobre la enfermedad. [REV NEUROL 2006; 42: 360-5]*

Palabras clave. *Enfermedad de Parkinson. ELEP. Evaluaciones. Métodos. Seguimiento a largo plazo.*

ESTUDIO LONGITUDINAL DE DOENTES COM DOENÇA DE PARKINSON (ELEP): OBJECTIVOS E METOLOGOLOGIA

Resumo. Introducção e desenvolvimento. *A doença de Parkinson (DP) é crónica e progresiva. De uma perspectiva socio-sanitária, representa uma fonte de sufrimento para o paciente e seus cuidadores, assim como uma carga importante para a sociedade. A informação actual sobre a DP é limitada em quanto ao conhecimento do curso evolutivo relacionado com: 1) o desenvolvimento e a evolução dos aspectos não motores da doença; 2) o impacto destas manifestações sobre a discapacidade e a qualidade de vida relacionada com a saúde (QVRS); 3) os determinantes da discapacidade e da diminuição de QVRS; 4) os factores relacionados com a velocidade de progressão da doença; 5) as pautas de aplicação e a repercursão diferencial a longo prazo (sobre complicações, discapacidade, QVRS) das medidas terapêuticas disponíveis; e 6) o impacto da DP sobre os cuidadores. Além disso, na informação disponível há uma heterogeneidade na qualidade das propriedades métricas dos instrumentos de medida aplicados e dos enviesamentos de selecção.* Conclusão. *Devido às limitações assinaladas, pensa-se que é necessário aprofundizar o conhecimento longitudinal detalhado da DP, numa perpectiva multidimensional. O estudo longitudinal de pacientes com doença de Parkinson (ELEP), que inclui um seguimento a longo prazo de alguns aspectos nunca antes avaliados de forma sistemática, permitirá aumentar o conhecimento global sobre a doença. [REV NEUROL 2006; 42: 360-5]*

Palavras chave. *Avaliações. Doença de Parkinson. ELEP. Métodos. Seguimento a longo prazo.*