Parkinsonism and Related Disorders 25 (2016) 58–64

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Neuropsychiatric symptoms are very common in premanifest and early stage Huntington's Disease

Saul Martinez-Horta [a, b, c, f], Jesus Perez-Perez [a, b, c], Erik van Duijn [e], Ramon Fernandez-Bobadilla [a, b, c, f], Mar Carceller [b, d], Javier Pagonabarraga [a, b, c], Berta Pascual-Sedano [a, b, c], Antonia Campolongo [a, b, c], Jesus Ruiz-Idiago [g], Frederic Sampedro [i], G.Bernhard Landwehrmeyer [h], Spanish REGISTRY investigators of the European Huntington's Disease Network, Jaime Kulisevsky [a, b, c, f, *]

[a] Department of Neurology, Movement Disorders Unit, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain
[b] Sant Pau Institute of Biomedical Research (IIB-Sant Pau), Barcelona, Spain
[c] Centro Investigación Biomedica en Red-Enfermedades Neurodegenerativas (CIBERNED), Spain
[d] Department of Psychiatry, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain
[e] Department of Psychiatry, Leiden University Medical Centre, Leiden, and Centre for Mental Health Care Delfland, Delft, The Netherlands
[f] Universitat Oberta de Catalunya (UOC), Barcelona, Spain
[g] Hospital Mare de Déu de la Mercé, Barcelona, Spain
[h] Department of Neurology, University of Ulm, Ulm, Germany
[i] Faculty of Medicine, Autonomous University of Barcelona, Spain

ARTICLE INFO

Article history:
Received 5 September 2015
Received in revised form
28 January 2016
Accepted 5 February 2016

Keywords:
Huntington's disease
Apathy
Behavior
Neuropsychiatry
Biomarker

ABSTRACT

Background: Neuropsychiatric symptoms are common features of Huntington's disease (HD). Whereas most studies have focused on cognitive and neuroimaging markers of disease progression, little is known about the prevalence of neuropsychiatric symptoms in premanifest mutation carriers far-from and close-to disease onset.

Methods: We obtained neurological, cognitive and behavioral data from 230 participants classified as premanifest far-from (preHD-A) and close-to (preHD-B) motor-based disease onset, early-symptomatic (early-HD), and healthy controls. Frequency and severity of neuropsychiatric symptoms were assessed with the short Problem Behaviors Assessment for HD (PBA-s). The odds-ratio (OR) to present symptoms in the clinical range was calculated using the control group as reference. Logistic regression analysis was used to explore relationships between neuropsychiatric symptoms and medication use.

Results: Prevalence of depression was similar in all groups. Apathy was already present in 32% of preHD-A increasing to 62% of early-HD patients. The probability of presenting apathetic symptoms was 15–88 times higher in preHD-A and preHD-B respectively than in healthy controls. Irritability and executive dysfunction were present in both preHD-B and early-HD.

Conclusion: Neuropsychiatric symptoms are highly prevalent in HD, already in the premanifest stage, with increasing prevalence of irritability, apathy and executive dysfunction closer to onset. Compared to controls, HD mutation carriers have the highest probability to develop apathy, with an increasing prevalence along disease stages. Our findings confirm the high prevalence of neuropsychiatric symptoms in HD, already many years before the onset of motor symptoms, with apathy as an early manifestation and core neuropsychiatric feature of the disease.

1. Introduction

Huntington's disease (HD) is an inherited, autosomal dominant, neurodegenerative disease resulting from a trinucleotide CAG expansion in the *HTT*. In people carrying the expanded gene

* Corresponding author. Department of Neurology, Movement Disorders Unit, Hospital de la Santa Creu i Sant Pau, Sant Antoni M. Claret 167, 08025 Barcelona, Spain.
E-mail address: jkulisevsky@santpau.cat (J. Kulisevsky).

http://dx.doi.org/10.1016/j.parkreldis.2016.02.008
1353-8020/

(CAG > 36 repeats), HD clinically manifests around mid-adulthood with a triad of progressive motor, cognitive and behavioral symptoms [1]. Formal neurological diagnosis of HD is based on the presence of unequivocal motor symptoms [1]. However, besides these characteristic motor symptoms and the progressive cognitive decline, neuropsychiatric disturbances are a common feature of HD [2,3]. Neuropsychiatric symptoms, including depression, apathy, and irritability, may already be present many years before motor symptoms appear [3,4]. While the etiology of these symptoms is unclear, the progressive nature of the neurodegenerative process, mainly involving the basal ganglia-thalamo-cortical circuits, is supposed to underlie the high prevalence of neuropsychiatric symptoms seen in patients with HD [5].

Since the availability of predictive genetic testing [6], it is possible to assess which individuals will develop the disease before motor symptoms are present [7]. Compelling evidence has shown that subtle cognitive and neuroimaging changes can be identified many years before motor-based diagnosis [8,9]. It has been suggested that these changes are potential early markers of disease progression that could be useful to monitor future disease-modifying therapies [10]. Previous studies found that apathy, depression and irritability are frequent neuropsychiatric symptoms of HD, and that their prevalence and severity are already increased in premanifest gene carriers (pre-HD) compared to healthy controls [4,11].

In a large cross-sectional study, apathy was the only symptom that increased significantly with disease progression [12], whereas another cross-sectional study found a clear increase of apathy along disease stages and a more modest increase of obsessive compulsive behaviors, depression, irritability and psychosis [13]. Thus, apathy shows the strongest linear association to disease progression, indicating a direct relation with progressive neurodegeneration [13,14]. However, the study of van Duijn et al. assessed the prevalence of neuropsychiatric symptoms in a mixed population of premanifest and manifest mutation carriers [13]. The study from Duff et al. also explored the occurrence of neuropsychiatric symptoms in premanifest individuals. However, the sample included symptomatic individuals and the behavioral assessment was done using the Symptom Checklist 90 Revised (SCL-90-R), a good but non-specific for HD instrument. Moreover, they neither controlled for the influence of pharmacological management nor estimated time to disease onset [12].

Many HD studies used instruments that measure both frequency and severity of neuropsychiatric symptoms, including the behavioral component of the Unified Huntington's Disease Rating Scale (UHDRS) and the Problem Behaviors Assessment (PBA). Both scales are specifically designed for HD populations and measure common neuropsychiatric symptoms of HD [4,15].

To assess the prevalence of neuropsychiatric symptoms in relation to the presence of motor symptoms, we measured the occurrence of neuropsychiatric symptoms using the PBA-s in a large sample of well characterized pre-HD individuals, early symptomatic patients and non-carriers enrolled in the Spanish cohort of the REGISTRY Study [16].

2. Methods and materials

2.1. Sample

Two-hundred and thirty subjects from Spain who provided written informed consent to participate in the European REGISTRY Study from the European Huntington's Disease Network [16] were included in the analysis. REGISTRY is a large, prospective study observing the natural course, clinical spectrum and management of HD in European countries [16]. In the current study, cross-sectional data from baseline visits was used. HD gene carriers from the REGISTRY dataset with a UHDRS [15] total motor score below 5 points were classified as premanifest individuals. We then calculated the disease burden score (age x [CAG_n − 35.5]) which is proposed as an index of burden of pathology due to lifetime exposure to mutant huntingtin. Then, the estimated time to disease onset with a probability of 0.6 was calculated using the conditional probability model developed by Langbehn et al. [17] As assumed in previous studies, premanifest individuals with estimated years to diagnosis over 10.8 years were classified as far-from (preHD-A) and below 10.8 years as close-to disease onset (preHD-B) [7].

Those with a UHDRS total motor score over ≥5 and a Total Functional Capacity (TFC) score between 11 and 13 were classified as early symptomatic (early-HD). Controls were identified as: (i) people who had a history of being at-risk for HD but were genetically confirmed to be non-carriers, and (ii) partners/principal caregivers of a gene-positive individual, without family history of HD. This control group experienced the same stressors that are related to HD: the verified non-carriers grew up in the same family circumstances and experienced the psychological stress of being at risk, whereas the partners/caregivers currently live in similar circumstances and experience the same disease related stressors.

Sociodemographic characteristics included were age, sex and years of education. Pharmacological treatment with antidepressants, benzodiazepines, neuroleptics, anticonvulsive drugs, and anti-choreic medication (tetrabenazine or amantadine) was recorded. We excluded participants with a previous diagnosis of major chronic psychiatric disorder (two cases of schizophrenia in non-carriers; one case of bipolar disorder in a premanifest mutation carrier). We also excluded participants with diagnosis of neurological disorder other than HD or a history of head trauma.

2.2. Neurological and functional assessment

The UHDRS motor subscale was used to assess the presence of a wide range of motor alterations characterizing HD. It includes measures for oculomotor function, dysarthria, chorea, dystonia, parkinsonism, postural instability, and gait. The UHDRS total motor score is the sum of all individual item scores, with higher scores indicating greater impairment [15].

Functional capacity was assessed using the Total Functional Capacity scale (TFC) of the UHDRS [18]. This instrument measures the possibility to independently perform activities of daily living. The TFC score ranges from 0 to 13 with higher scores indicating better functional capacity.

2.3. Cognitive assessment

Cognitive functioning was assessed using the UHDRS cognitive score [15]. Cognitive functioning is presented with the sum of the scores of five cognitive tasks: the Verbal Fluency Test (VFT; using three letters: FAS), the Stroop word naming, the Stroop color naming, the Stroop interference, and the Symbol Digit Modality Test (SDMT), as has been done in previous studies [7].

2.4. Behavioral assessment

The PBA-s was used to obtain behavioral data [4]. The PBA-s is an 11-item semistructured interview, specifically designed to cover a wide range of neuropsychiatric symptoms related to HD. This scale is administered in presence of the main caregiver or a proper companion and rates the severity (0 = absent, 1 = questionable, 2 = mild, 3 = moderate and 4 = severe) and frequency (0 = never/almost never, 1 = seldom, 2 = sometimes, 3 = frequently and 4 = daily/almost daily for most or all the day) of depressed mood,