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The preclinical stage of movement disorders

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ABSTRACT

Findings from both cross-sectional and longitudinal studies have indicated a long preclinical period characterizing most neurodegenerative diseases. The study of presymptomatic movement disorders has implications for our understanding of their pathophysiology, early functional compensation and subclinical disease progression. This might lead to earlier diagnosis, might shift current disease staging and might help define at-risk populations amenable to preventive or disease-modifying therapeutic intervention. Here, we provide an up-to-date overview of the current knowledge about the preclinical stages of common movement disorders.

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1. Introduction

As a unifying theme in neurodegenerative diseases has emerged over the past years that the disease process obviously starts much earlier than symptoms appear. While the length of the presymptomatic period may differ, there is substantial evidence particularly from Huntington disease, Parkinson disease or Alzheimer disease that the gradual build-up of pathology leads to the appearance of characteristic symptoms only many years later.

Studies on the presymptomatic period of neurodegenerative disorders might shed light on individual disease susceptibility, pathophysiology or biomarkers, might lead to improved disease-staging and might eventually contribute to attempts at disease prevention or disease modification. To date, for none of the diseases covered in this review a potent neuroprotectant has been identified.

This review aims to provide an overview of the current knowledge on the preclinical stages of neurodegenative movement disorders, with an eye to the current or future diagnostic armamentarium available to the clinician confronted with the task of identifying of at-risk individuals or diagnosis in very early disease stages.

2. Methods

We undertook a MEDLINE search (1966–2015) with the search terms "preclinical", "presymptomatic", "asymptomatic", "prediagnostic", "premotor", "premanifest", "prodrom*" or "carrier*" in title, in combination with "neurodegenerative", "Parkinson*", "multisystem atrophy", "progressive supranuclear palsy", "corticobasal", "Huntington*", "Wilson*", "degenerative ataxia", "hereditary ataxia", "spinocerebellar ataxia", "Friedreich*" and "essential tremor". Some additional references were detected by hand-searching the reference lists of seminal reviews. Abstracts were screened for information relevant to diagnosis or therapy of these conditions with respect to their preclinical stages, and information from appropriate papers was extracted.

3. Terminology

Different terms characterizing the period before overt disease manifestation have been used, sometimes interchangeably [1,2] [e.g. 1,2]. We suggest to subdivide the preclinical stage of disease using the following terms, generally in line with the suggestions made by Reilmann et al. [2]:

- Presymptomatic: no clinical signs and no subjective symptoms, possible abnormalities on specific tests (at-risk individual, disease carrier status).
- Prodromal: the gradual appearance of subtle signs and/or symptoms (e.g. premotor stage of PD with prominent non-motor symptoms).

4. Early manifestation of disease under stress

From a clinical standpoint, neurodegenerative motor diseases are characterized by their relentless clinical progression. Prior to disease onset, some individuals at risk might become symptomatic only under specific challenging conditions: Mild gait disturbance in presymptomatic Parkinson might become apparent only during cognitive tasking [3], or Parkinson disease might transiently become manifest due to its neuroleptic sensitivity. In Huntington disease, Levodopa-induced chorea identified mutation carriers in early studies before the advent of genetic testing [4]. Similarly, SCA10 mutation carriers may initially display cerebellar symptoms only when exposed to small amounts of alcohol [5].

5. Are there common risk factors or clinical features?

Interestingly, some risk factors or clinical features are shared among several neurodegenerative conditions. For example, a history of head trauma has been implicated in some studies on amyotrophic lateral sclerosis, Parkinson disease or the age of onset in essential tremor [6,7]. Hyposmia is found in many neurodegenerative conditions, i.e. in PD, AD, FTD, and less pronounced in PSP or MSA. Depression is common to many chronic neurodegenerative diseases, with evidence of premotor mood disorder e.g. in Parkinson disease [7]. In many of these diseases (PD, MSA, PSP, FRDA, RLS, ET), prevalences of depression between 30 and 50% have been observed, with lower prevalences of 10–20% in ALS and SCA.

6. Common pathophysiological themes

On a cellular level, some common pathophysiological themes have emerged. Protein misfolding and aggregation, dysregulation