

Cerebrospinal Fluid Biomarkers in Neurodegenerative Movement Disorders Parkinsonian Disorders and Huntington's Disease

Akademisk avhandling

som för avläggning av medicine doktorexamen vid Sahlgrenska akademien vid Göteborgs universitet kommer att offentlig försvaras i föreläsningssal Ivan Östlund, Institutionen för neurovetenskap och fysiologi, sektionen för farmakologi, torsdagen den 23 maj 2013, kl 13.00

av

Radu Constantinescu

Fakultetsopponent

Prof. Dr. Günther Deuschl

Christian-Albrechts Universität zu Kiel, Tyskland

The thesis is based on the following studies, referred to in the text by their Roman numerals.

- I. Constantinescu R, Rosengren L, Johnels B, Zetterberg H, Holmberg B. Consecutive analyses of cerebrospinal fluid axonal and glial markers in Parkinson's disease and atypical Parkinsonian disorders. *Parkinsonism Relat Disord.* 2010 Feb;16(2):142-5.
- II. Constantinescu R, Holmberg B, Rosengren L, Corneliussen O, Johnels B, Zetterberg H. Light subunit of neurofilament triplet protein in the cerebrospinal fluid after subthalamic nucleus stimulation for Parkinson's disease. *Acta Neurol Scand.* 2011 Sep;124(3):206-10.
- III. Constantinescu R, Andreasson U, Li S, Podust VN, Mattsson N, Anckarsäter R, Anckarsäter H, Rosengren L, Holmberg B, Blennow K, Wikkelso C, Rüetschi U, Zetterberg H. Proteomic profiling of cerebrospinal fluid in parkinsonian disorders. *Parkinsonism Relat Disord.* 2010 Sep;16(8):545-9.
- IV. Constantinescu R, Andreasson U, Holmberg B, Zetterberg H. Serum and cerebrospinal fluid urate levels in synucleinopathies versus tauopathies. *Acta Neurol Scand.* 2013 Feb;127(2):e8-12.
- V. Constantinescu R, Romer M, Oakes D, Rosengren L, Kiebertz K. Levels of the light subunit of neurofilament triplet protein in cerebrospinal fluid in Huntington's disease. *Parkinsonism Relat Disord.* 2009 Mar;15(3):245-8.
- VI. Constantinescu R, Romer M, Zetterberg H, Rosengren L, Kiebertz K. Increased levels of total tau protein in the cerebrospinal fluid in Huntington's disease. *Parkinsonism Relat Disord.* 2011 Nov;17(9):714-5.



UNIVERSITY OF GOTHENBURG

Cerebrospinal Fluid Biomarkers in Neurodegenerative Movement Disorders

Parkinsonian Disorders and Huntington's Disease

Radu Constantinescu

Department of Neurology, Institute of Neuroscience and Physiology
Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden

ABSTRACT

Background: Parkinson's disease (PD) and atypical parkinsonian disorders (APD) [multiple system atrophy (MSA), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD)] are a large group of idiopathic neurological diseases, together affecting millions of patients worldwide. Huntington's disease (HD) is a rare autosomal dominant neurological disorder with an overall prevalence of about 6/100000. Common to these neurodegenerative movement disorders are combinations of motor, behavioral, psychiatric, cognitive and autonomic symptoms causing much suffering, disability, increased morbidity and mortality. There are no known causal or disease modifying treatments. One of the main obstacles for developing such treatments is the lack of biomarkers for detecting the onset of disease, for discriminating exact diagnosis at an early stage, and for monitoring disease stages and treatment response.

Aim: This dissertation explores the biomarker potential of compounds found in the cerebrospinal fluid (CSF) and serum from patients with parkinsonian disorders (PD and APD) and HD.

Results: The results of this thesis are gathered into six publications. Increased concentrations of neurofilament light chain (NFL), a marker of axonal degeneration, were confirmed in the CSF of MSA and PSP patients compared with healthy controls and PD patients. This observation was also extended to CBD. CSF NFL levels did not correlate with measures of disease stage and were stable over one year. Thus, NFL may be useful in the differential diagnosis of parkinsonian disorders but not in measuring disease stage or progression. (Paper I)

In advanced PD patients treated with deep-brain stimulation (DBS) of the subthalamic nucleus, CSF NFL concentrations increased immediately after the surgical procedure, as expected, but decreased thereafter and were normalized at one year and later, thus indicating no accelerated neuronal death due to the DBS treatment itself. (Paper II)

Using surface enhanced laser desorption/ionization time-of-flight mass spectrometry (SELDI-TOF MS), a panel of four proteins was identified (ubiquitin, β 2-microglobulin, and 2 secretogranin 1 [chromogranin B] fragments), permitting differentiation of APD patients from PD and healthy controls with a sensitivity of 91% and a specificity of 56%. (Paper III)

In males, serum but not CSF urate levels were increased in tauopathies (PSP and CBD) compared with synucleinopathies (PD and MSA). (Paper IV)

Levels of CSF NFL and total tau protein (another marker of neuronal cell damage) were elevated in HD subjects compared to healthy controls. (Papers V and VI)

Conclusion: Taken together, the findings presented in this dissertation suggest that CSF NFL is a promising biomarker to differentiate APD from idiopathic PD and healthy controls, and patients with HD from healthy controls. More studies are needed to identify biomarker patterns that could differentiate specific diseases within the APD group, PD patients from healthy controls, and for measuring disease stage and progression.

ISBN: 978-91-628-8656-1



UNIVERSITY OF GOTHENBURG