Parkinsonism and Related Disorders 65 (2019) 1–2

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

Multiple system atrophy – Are cerebrospinal fluid cytokines reliable potential diagnostic marker?

The lack of a reliable marker that might help clinicians diagnose multiple system atrophy (MSA) early and distinguish it from other α-synucleinopathies, especially Parkinson's disease (PD), resulted in a much-needed search for diagnostic and prognostic biomarkers. Body fluids, including blood plasma and cerebrospinal fluid (CSF), are the main focus regarding biomarker search, given that they are easily accessible. The attention has turned to α-synuclein (AS) levels in plasma and CSF, however with no conclusive outcome. CSF levels of AS are diminished in PD compared to controls and Alzheimer's disease (AD) [1], yet no differentiation between PD and other synucleinopathies is possible to date [2]. Furthermore, the light chain of neurofilament (NfL), a marker of neurodegenerative processes and coenzyme Q10 levels in CSF and peripheral blood were examined. NfL was significantly increased in MSA compared to PD in blood and CSF samples [3–5], whereas coenzyme Q10 was significantly reduced in MSA compared to PD and control CSF [6]. Both markers show potential as probable diagnostic markers, however further validation studies have to be performed to confirm their sensitivity as diagnostic tool. Moreover, various studies investigating inflammatory markers in peripheral blood and CSF were conducted, given that α-synucleinopathies show prominent inflammation. A significant increase of pro-inflammatory and microglial-related cytokines in MSA compared to PD was reported in two separate studies using CSF samples, including C reactive protein (CRP) [7,8], tumor necrosis factor α (TNF-α), Interleukin-1β (IL-1β), and Il-6 [8] as well as Chitinase-3-like protein 1 (CHI3-L1, YKL-40) [7]. In the current issue of Parkinsonism & Related Disorders, Compta and colleagues present the measurement of 38 cytokine levels in CSF of MSA patients compared to PD patients and controls [9]. The sample size of MSA patients is high compared to other studies and MSA-P (parkinsonian variant of MSA) and MSA-C (cerebellar variant of MSA) were separately examined. Furthermore, the number of cytokines measured was comparatively high. Yet, CRP and YKL-40 levels in CSF have not been investigated in the current study. In future investigations, it might be of interest if the MSA patient cohort of this study shows a similar increase of CRP and YKL-40 amount compared to PD patients as shown in the aforementioned studies [7,8]. Another strength of the study is clearly the exclusion of patients treated with non-steroidal anti-inflammatory drugs (NSAIDs), which was not executed in other studies, though the treatment with NSAIDs could interfere with the release of cytokines into CSF or peripheral blood. Three cytokines were significantly elevated in MSA compared to PD CSF (monocyte chemotactic protein 3 (MCP-3), macrophage derived chemokine (MDC) and IL-12p40); MCP-3 and MDC showed the highest levels in MSA, also when comparing MSA-P to PD and therefore may be useful as MSA-P predictors [9]. Since there is often a misdiagnosis of early MSA-P as PD, a marker to distinguish these two disorders at an early time-point would be an enormous help for clinical diagnosis. However, validation studies with a larger cohort of patients would be necessary to confirm MCP-3 and MDC as markers for MSA-P.

Interestingly, in the current study IL-6 levels were not elevated at all, although it is a cytokine released by activated microglia and astroglia and has already been shown to be increased in MSA patients in various studies [8,10]. Furthermore, one would assume that TNF-α is an important cytokine that might be elevated in MSA. In the study of Compta, TNF-α levels were significantly elevated, but only comparing MSA with PD and controls pooled together, whereas in a different study it was shown that TNF-α levels are significantly higher in MSA versus PD CSF [8,9].

How do these differences regarding cytokine levels in CSF samples between studies occur? One major problem regarding measurements of biomarkers in CSF or peripheral blood might be the choice of the assay. A variety of tests for cytokine/chemokine measurement have been employed including multiplex bead assays from different companies or ELISA. Every assay works a little bit different, uses different incubation times or has variable sensitivity. Furthermore, exclusion criteria of patients for every study in different centers are diverse; e.g. patients treated with NSAIDs are excluded in one study and accepted in another. Differences in collection of peripheral blood and CSF samples may also contribute to variable study results. One center collects CSF after overnight fasting, the other center after non-fasting, followed by the usage of different centrifugation protocols and so on. Therefore, these methodological issues call for a multi-center study including a large cohort of MSA, PD and control patients, unifying the recruitment of patients (same exclusion criteria for every center), the sample collection procedure and the assay used to analyze cytokine levels in the CSF of patients.

In conclusion, the study by Compta and colleagues highlights that cytokine levels in CSF might be an interesting diagnostic tool to distinguish between MSA and PD [9]. CSF is easily accessible and might tell us at least partly what is going on in patients with PD or atypical parkinsonism. However, the detection of a reliable diagnostic or prognostic cytokine marker needs further investigation and validation until it can be used in clinical routine.

References

[1] L. Gao, H. Tang, K. Nie, L. Wang, J. Zhao, R. Gan, et al., Cerebrospinal fluid alpha-synuclein as a biomarker for Parkinson's disease diagnosis: a systematic review and meta-analysis, Int. J. Neurosci. 125 (2015) 645–654.

[2] M.B. Aerts, R.A. Esselink, W.F. Abdo, B.R. Bloem, M.M. Verbeek, CSF α-synuclein does not differentiate between parkinsonian disorders, Neurobiol. Aging 33 (2012) 430.e1-430.e3.

[3] T.M. Marques, A. van Rumund, P. Oeckl, H.B. Kuiperij, R.A.J. Esselink, B.R. Bloem, et al., Serum NFL discriminates Parkinson disease from atypical parkinsonisms, Neurology 92 (2019) e1479–e1486.

[4] O. Hansson, S. Janelidze, S. Hall, N. Magdalinou, A.J. Lees, U. Andreasson, et al.,

https://doi.org/10.1016/j.parkreldis.2019.09.019
Received 10 September 2019; Received in revised form 14 September 2019; Accepted 16 September 2019

Blood-based NfL: a biomarker for differential diagnosis of parkinsonian disorder, Neurology 88 (2017) 930–937.
[5] X. Hu, Y. Yang, D. Gong, Cerebrospinal fluid levels of neurofilament light chain in multiple system atrophy relative to Parkinson's disease: a meta-analysis, Neurol. Sci. 38 (2017) 407–414.
[6] Y. Compta, D.M. Giraldo, E. Muñoz, F. Antonelli, M. Fernández, P. Bravo, et al., Cerebrospinal fluid levels of coenzyme Q10 are reduced in multiple system atrophy, Park. Relat. Disord. 46 (2018) 16–23.
[7] S. Hall, S. Janelidze, Y. Surova, H. Widner, H. Zetterberg, O. Hansson, Cerebrospinal fluid concentrations of inflammatory markers in Parkinson's disease and atypical parkinsonian disorders, Sci. Rep. 8 (2018) 13276.
[8] C. Starhof, K. Winge, N.H.H. Heegaard, K. Skogstrand, S. Friis, A. Hejl, Cerebrospinal fluid pro-inflammatory cytokines differentiate parkinsonian syndromes, J. Neuroinflammation 15 (2018) 305.
[9] Y. Compta, S.P. Dias, D.M. Giraldo, A. Perez-Soriano, E. Munoz, J. Saura, et al., Cerebrospinal fluid cytokines in multiple system atrophy: a cross-sectional Catalan MSA registry study, Park. Relat. Disord. (2019), https://doi.org/10.1016/j.parkreldis.2019.05.040 [Epub ahead of Print].
[10] E. Kaufman, S. Hall, Y. Surova, H. Widner, O. Hansson, D. Lindqvist, Proinflammatory cytokines are elevated in serum of patients with multiple system atrophy, PLoS One 8 (2013) e62354.

Lisa Fellner*, Gregor K. Wenning
Division of Neurobiology, Department of Neurology, Medical University of Innsbruck, Innrain 66, 6020 Innsbruck, Austria
E-mail addresses: lisa.fellner@i-med.ac.at (L. Fellner), gregor.wenning@i-med.ac.at (G.K. Wenning).

* Corresponding author.