Biomarkers of neurodegeneration – not only Alzheimer’s disease and not only cerebrospinal fluid: a guest-editor’s introduction

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The current special issue of the *Journal of Neural Transmission* features 15 papers dealing with the biomarkers of neurodegenerative disorders, and as stated in the title they are neither restricted to one particular disease nor to the given type of diagnostic material.

The cerebrospinal fluid (CSF) biomarkers of Alzheimer’s disease (AD) have evolved over the last three decades from an interesting but peculiar finding without practical meaning, to one of the central diagnostic tools, and this is a very interesting evolution. The first evidence that there is something going on came, at least to my best knowledge, from Delaney, who 30 years ago reported ten AD patients with decreased CSF aluminum concentrations (Delaney 1979). Of course, by far it was not enough to make any clinical use, and the first McKhann criteria (McKhann et al. 1984) spoke no single word about the biomarkers in the CSF. Only with the first papers by Blennow, in the early 1990s, the avalanche started; interestingly enough, however, neither amyloid β ($A\beta$) nor Tau but monoamine metabolites and neuron specific enolase were the first serious biomarker candidates (Blennow et al. 1992, 1994). The consensus report of 1998 defined the criteria a candidate biomarker should fulfill to be accepted for diagnostic purposes (The Working Group on: “Molecular and Biochemical Markers of Alzheimer’s Disease” 1998) and interestingly these criteria, published 15 years ago, remain valid until today. Meanwhile, dozens of expert groups worldwide have struggled to find new

biomarkers or to optimize the existing ones. Their efforts are also reflected in the papers published in this issue of the JNT, and they eventually brought about significant change in the approach to the diagnostic utility of the CSF biomarkers: The new McKhann recommendation (McKhann et al. 2011) includes the application of the CSF biomarkers, and moreover, in his comments (McKhann 2011), Dr. McKhann states, “*The most novel aspect of the 3 sets of recommendations is the application of biomarkers, which are measures of a biological fluid or imaging findings that systematically relate to the presence and progression of the underlying disease process*”, continuing with the explanation that the CSF alterations: decreased $A\beta$ and increased Tau (along with its phosphorylated form) do reflect pathology of AD: accumulation of amyloid β in plaques and neuronal injury, respectively.

Similarly, the research criteria published by Dubois et al. (2007) focussed on the role of the CSF biomarkers, defining them as one of the supportive features for probable AD, and also German diagnostic and treatment guideline recommends CSF biomarkers as a routine diagnostic tool (2009). Finally, a recently published expert consensus describes procedures for the proper collection and preanalytical sample handling (Vanderstichele et al. 2012); moreover, with the growing number of centers performing CSF analyses as a routine diagnostic tool, first international multicenter projects had to start to control and improve inter-laboratory variation of the results (Lewczuk et al. 2006a; Mattsson et al. 2011).

Perhaps one issue accentuated by Dubois et al. is particularly worth a short discussion, as it excellently stresses the value of the CSF biomarkers in AD: cognitively normal people having CSF alterations typical for AD are defined as “asymptomatic at risk for AD”. This reflects the most important feature of the CSF biomarkers—their alterations

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can be observed years (or perhaps decades) before the onset of the clinical symptoms, making neurochemical dementia diagnostics (NDD) an excellent tool for the early diagnosis (Hansson et al. 2006; Lewczuk and Kornhuber 2011). Should we find one day a drug stopping the disease progression that we could moreover use in prophylaxis of this devastating disorder, the early diagnosis offered by the CSF biomarkers would become one of the most important diagnostic tools in the current medicine.

Irrespectively of the fact that the available CSF biomarkers are good enough to be applied for diagnostic purposes, we want to have even better tools. As stated above, many research groups worldwide work to test, validate, and optimize new biomarker candidates. In the current issue of the JNT we find excellent contributions reporting in details their methodology and the results, but perhaps it makes sense to discuss briefly general strategy of how to validate novel candidates [for the more detailed discussion, see (Lewczuk and Kornhuber 2011)]. First of all, no golden standard of AD diagnosis exists. Finding plaques and tangles on the neuropathologic examination must be viewed critically: (a) neither plaques nor tangles are pathognomonic for AD and (b) the time frame between the diagnostic LP and the neuropathologic confirmation of the diagnosis is very long, sometimes extending 10 years. Therefore, it is unlikely to find biomarkers (or their constellations) with absolute sensitivity and specificity because an error is already made at the stage of categorizing subjects into “Patients” and “Controls”. Moreover, the pre-clinical phase in neurodegeneration disorders lasts sometimes 20 years. This means that it is very probable that some “healthy individuals” are indeed subjects whose pathobiochemical mechanisms are already running, although neither subjective nor objective cognitive dysfunctions are observed. A good strategy to avoid the error of including ill subjects into the “Control” group is to observe them for a certain time period. This strategy is actually successfully applied by many centers, even if its drawback is much longer observation times and the reduction of the number of study patients due to fall-outs. Furthermore, the biomarkers already known (for example, A β peptides) are quite sensitive to preanalytical handling (Zimmermann et al. 2011) and that there is actually no good reason to believe that the new biomarkers we are searching for will be more robust. Therefore, a trivial statement gets extremely important here that only well characterized, prospectively collected samples can be used for novel biomarkers development. This holds true particularly for multicenter studies (Lewczuk et al. 2006b).

In our center, patients are categorized into “AD” (including “MCI of AD type”) or “Control” groups only when their clinical/neuropsychologic diagnoses, supported by the corresponding results of neuroimaging, stay in

accordance with the NDD findings. Such groups of “AD supported by positive NDD” and “Controls supported by negative NDD” are further confirmed by the higher percentage of APOE ϵ 4-allele carriers in the AD group, so we apply a kind of 3-dimensional stratification strategy: clinical, neurochemical, and genetic. For example, material from patients clinically diagnosed as having AD but without clear alterations in the CSF is not used for biomarker discovery experiments. This strategy, successfully applied in recently published studies (Lewczuk et al. 2008, 2010) has one serious drawback, and we are aware of it: it assumes, perhaps falsely, that all AD subjects have alterations in the CSF and that “Controls” do not.

As stated in the first lines of this introduction, neither neurodegeneration is restricted only to Alzheimer’s disease nor does clinical neurochemistry utilize exclusively CSF; excellent contributions published in this issue deal also with biomarkers (or candidates) for Parkinson’s disease, amyotrophic lateral sclerosis or dementia with Lewy bodies; approaches to use plasma as an easier-available source for potential biomarkers, as well as genetic risk factors are covered by outstanding publications too.

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