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Blood-Based Biomarkers

Cerebrospinal fluid and serum MHPG improve Alzheimer's disease versus dementia with Lewy bodies differential diagnosis

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Abstract

Introduction: Given the challenges concerning the differential diagnosis of dementia, we investigated the possible added value of monoaminergic compounds to the standard cerebrospinal fluid (CSF) Alzheimer's disease (AD) biomarkers. Particularly, regarding the AD versus dementia with Lewy bodies (DLB) comparison, monoamines or their metabolites might have added discriminative value as there is a more severe neuropathological burden in the locus coeruleus of DLB patients, the principal site of noradrenaline synthesis.

Methods: We applied enzyme-linked immunosorbent assay (ELISA) to analyze CSF amyloid β peptide of 42 amino acids, total tau, and tau phosphorylated at threonine 181, in patients with AD, frontotemporal dementia, DLB/Parkinson's disease dementia, and controls. Reversed-phase high-performance liquid chromatography with electrochemical detection was implemented to study monoamine and metabolite levels in CSF and serum. Stepwise forward conditional logistic regression and receiver operating characteristic (ROC) curve analyses were performed to assess the diagnostic accuracy of these newly fitted models containing the most discriminative indicators of disease status.

Results: Most significant differences in CSF and serum were confined to the noradrenergic system. More specifically, CSF 3-methoxy-4-hydroxyphenylglycol (MHPG) levels were higher, whereas serum MHPG levels were lower, in DLB patients compared with all other groups. Addition of CSF and serum MHPG levels to the CSF AD biomarker panel significantly increased diagnostic accuracy between DLB/Parkinson's disease dementia and AD. Interestingly, a model only including CSF and serum MHPG without the classic AD biomarker panel reached similar area under the curve values.

Discussion: We hypothesize that varying degrees of neuronal loss in the locus coeruleus of DLB/Parkinson's disease dementia versus AD patients result in differentially altered MHPG levels, making this metabolite a valuable biomarker.

Keywords: MHPG; Biomarkers; Alzheimer's disease; Dementia with Lewy bodies; Monoamines; Diagnostic accuracy; RP-HPLC-ECD

1. Introduction

Alzheimer's disease (AD) and associated neurodegenerative brain disorders remain an important health-care burden [1]. Recent findings from the Alzheimer's Association indicate that in 2015, 46.8 million people suffered from dementia

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worldwide, while this number is expected to increase in the next couple of decades [2], giving rise to even higher health strategies. Early detection of this neurocognitive disorder, combined with treatment strategies in the initial stages of the disease could aid in its reduction [3,4].

Although current cerebrospinal fluid (CSF) biomarkers for AD diagnosis (amyloid β [$A\beta_{1-42}$], total tau (T-tau), and tau phosphorylated at threonine 181 [$P\text{-}tau_{181P}$]), as comprised in the International Working Group-2 criteria [5], are widely used in clinical research, they still bring about several challenges. As such, they lack specificity to accurately discriminate between AD and dementia with Lewy bodies (DLB), which is especially complicated by the presence of AD co-pathology in patients with DLB [6]. Thus, apart from shared clinical symptoms, some dementia types can also share a common etiology. Because overlapping concentrations exist in CSF T-tau and $P\text{-}tau_{181P}$ between AD, frontotemporal dementia (FTD), DLB, and vascular AD [7], current diagnostics often require additional imaging investigations for differential dementia diagnosis. Another pitfall associated with CSF biomarkers is that their diagnostic performance decreases with age [8]. Given the aforementioned complications and the practical difficulties associated with CSF sampling, the search for efficient blood biomarkers is imperative [9,10]. Nevertheless, variability of the distinct blood constituents involves supplementary challenges concerning reproducibility of biomarker analysis. In addition, questions arise about the applicability of blood biomarkers as the blood compartment is not in direct contact with the central nervous system and might therefore inaccurately reflect changes in disease progression [10]. Moreover, it was shown that plasma and CSF $A\beta_{1-42}$ levels did not correlate in either patients with AD, non-AD, mild cognitive impairment, and control subjects (CONTR) [11]. Although a recently published article provided the first evidence for plasma neurofilament light as a potential blood biomarker for AD [12], such a blood biomarker for discrimination between AD and non-AD cases, to the best of our knowledge, has not been identified nor validated yet.

Recent studies, however, indicate that monoaminergic neurotransmitter profiles could represent an added value in improving etiological dementia diagnosis [13]. One of the first indications of this hypothesis was provided by Aerts et al., who proved that addition of CSF 3-methoxy-4-hydroxyphenylglycol (MHPG), a main metabolite of the monoamines adrenaline (A) and noradrenaline (NA) that aids in indication of central noradrenergic activity [14], to the classical biomarker profile of AD, could increase both sensitivity and specificity for the discrimination between AD and DLB [15,16]. This hypothesis might be further strengthened by the notion that distinct MHPG levels between AD and DLB patients were observed in eight out of 11 brain regions, with DLB patients demonstrating significantly reduced MHPG levels [13]. Other studies investigating monoamine neurotransmitter levels in brain tissue equally gave rise to the awareness that AD and FTD differ in serotonergic and noradrenergic neurotransmitter content [17,18], while an earlier study reported that CSF MHPG levels were considerably higher in FTD patients than those in AD patients [19]. It was also noted that CSF NA and MHPG levels were increased in patients with advanced AD as compared with subjects suffering from moderate AD or CONTR, suggesting hyperactivity of the noradrenergic system in the end stage of the disease [20]. Furthermore, extensive evidence demonstrates that the locus coeruleus (LC), the main NA-producing nucleus in the brain, is severely affected by Lewy pathology in Parkinson's disease dementia (PDD) [21] and associated with severe cell death which might affect the dopaminergic nigrostriatal pathway through loss of noradrenergic innervation [22–25]. This Lewy pathology in PDD has even been shown to precede the appearance of α-synuclein inclusions and neuronal loss in the dopaminergic substantia nigra [21,26–31], indicating an undeniable role of noradrenergic deficits in PDD. Interestingly, MHPG easily passes the blood–brain [32] and blood-CSF [33] barrier. Taking into account all of the above, it appears that monoaminergic systems are indeed differentially implicated in distinct dementia subtypes and could potentially serve as predictive markers.

Accordingly, this study aimed at identifying predictive monoamine biomarkers in both CSF and serum derived from patients suffering from AD, FTD, DLB/PDD, age-matched CONTR, and young control (Y-CONTR) subjects. We hypothesized that these fluid monoamine markers, especially with regard to MHPG, could add significantly to the classical CSF AD biomarker panel, thus increasing diagnostic accuracy.

2. Materials & methods

2.1. Study population

Paired CSF-serum samples derived from patients with probable AD (n = 52), FTD (n = 59), DLB (n = 39), PDD (n = 14), as well as CONTR (n = 88) and Y-CONTR (n = 32), were selected from the Biobank of the Institute Born-Bunge. All patients included in the AD, FTD, DLB, PDD, and Y-CONTR groups were included in a prospective, longitudinal study on neuropsychiatric symptoms [34] between 2001 and 2011 and originally recruited at the Memory Clinic of the Hospital Network Antwerp Middelheim (ZNA) and Hoge Beuken as part of their diagnostic clinical workup. At inclusion, subjects underwent neuropsychological assessment and behavioral analysis as described earlier [34]. If consented patients died, brain autopsy was performed within 6 hour postmortem. The left hemisphere was frozen at −80°C, whereas the right hemisphere was fixated in paraformaldehyde (12%) for neuropathological examination, which was performed as described earlier [13,17]. None of the age-matched CONTR nor Y-CONTR suffered from neurological disease. In addition, CONTR were excluded in case of psychiatric antecedents or suspicion of central nervous system pathology. Thus, the CONTR group consisted of patients requiring lumbar radiculography as they suffered from