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Evaluating combinations of diagnostic tests to discriminate different dementia types

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Abstract

Introduction: We studied, using a data-driven approach, how different combinations of diagnostic tests contribute to the differential diagnosis of dementia.

Methods: In this multicenter study, we included 356 patients with Alzheimer's disease, 87 frontotemporal dementia, 61 dementia with Lewy bodies, 38 vascular dementia, and 302 controls. We used a classifier to assess accuracy for individual performance and combinations of cognitive tests, cerebrospinal fluid biomarkers, and automated magnetic resonance imaging features for pairwise differentiation between dementia types.

Results: Cognitive tests had good performance in separating any type of dementia from controls. Cerebrospinal fluid optimally contributed to identifying Alzheimer's disease, whereas magnetic resonance imaging features aided in separating vascular dementia, dementia with Lewy bodies, and frontotemporal dementia. Combining diagnostic tests increased the accuracy, with balanced accuracies ranging from 78% to 97%.

Discussion: Different diagnostic tests have their distinct roles in differential diagnostics of dementias. Our results indicate that combining different diagnostic tests may increase the accuracy further.

Keywords: Differential diagnosis; Biomarkers; Diagnostic test assessment; Clinical decision support system; CSF; MRI; Alzheimer's disease; Frontotemporal dementia; Dementia with Lewy bodies; Vascular dementia

1. Background

Dementia affects an increasing number of people worldwide [1]. Alzheimer's disease (AD) is the most frequent cause of dementia accounting for 50%–70% of dementia

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cases [2]. Other common causes of dementia include vascular dementia (VaD), dementia with Lewy bodies (DLB), and frontotemporal dementia (FTD) [3–6]. To ensure appropriate pharmacological treatment, counseling, and inclusion in clinical trials, early and precise diagnosis of the underlying disease causing dementia is important.

Cognitive profiles differ between dementia types showing primarily memory impairment in AD, visuospatial and executive dysfunction in DLB, delayed cognitive processing in VaD, and mainly language, executive, and behavioral dysfunction in FTD, although considerable overlap exists [7,8]. Progress in biomarker development has provided new disease insights and improved accuracy of dementia diagnosis. This has led to an increasing role of biomarkers, such as those obtained from cerebrospinal fluid (CSF) measures and structural magnetic resonance imaging (MRI), in diagnostic criteria and guidelines [3–6]. CSF biomarkers can provide evidence for the presence of β amyloid 1–42 ($A\beta_{42}$) accumulation and downstream neuronal dementia in AD (tau and tau phosphorylated at threonine 181 [p-tau]), whereas isolated elevation of tau may also be seen in FTD, and intermediate concentrations of CSF biomarkers often occur in DLB and VaD [9,10]. On structural MRI, typical abnormalities for different causes of dementia have been described, such as hippocampal and parietal atrophy in AD, frontal-temporal atrophy in FTD, and profound white matter hyperintensities (WMHs) in VaD, whereas DLB presents with unspecific mild generalized atrophy [11–13].

Despite these advances, differential diagnosis of dementia in terms of accurately identifying the underlying etiology remains challenging. First, biomarkers for other types of dementia are less developed than those for AD; and second, there is often overlap in underlying pathology and clinical presentation as most patients do not present in an archetypical fashion [9,11]. In addition, diagnostic guidelines remain relatively general and address one disease only. In reality, a clinician is often faced with a complex differential diagnostic task of simultaneously evaluating a range of potential diagnoses and combining data from multiple tests and biomarkers. More knowledge on performance and value of biomarkers in the differential diagnosis of dementia is therefore needed.

Combination of diagnostic tests, such as MRI and CSF, has been studied for AD and progression, but not previously for differential diagnosis in a multicenter cohort [14,15]. We used a classifier based on the Disease State Index (DSI) [16] in a large cohort from four European memory clinics to differentiate between controls and patients with AD, FTD, DLB, and VaD. We used a data-driven approach to explore the diagnostic accuracy of commonly used clinical diagnostic tests, including cognitive tests, CSF biomarkers, and automated MRI features. Furthermore, we evaluated performance of all diagnostic tests combined and which combinations of tests were optimal for each pairwise comparison of diagnoses.

2. Methods

2.1. Subjects

We included 844 subjects, which were pooled from four different memory clinic-based cohorts: 543 subjects from the Amsterdam Dementia Cohort at the VU Medical Center Amsterdam [17,18], 112 subjects from the Danish Dementia Research Center at Copenhagen University Hospital, Rigshospitalet, 139 subjects from the Department of Gerontology and Geriatrics of the University of Perugia, "S. Maria della Misericordia" Hospital of Perugia, and 50 subjects from the Department of Neurology from the University of Eastern Finland. Data from Rigshospitalet, University of Perugia, University of Eastern Finland, and 44 subjects from VU Medical Center had been collected as part of the PredictND study [19]. The remainder of VUmc subjects was included from Amsterdam Dementia Cohort. The pooled cohort consisted of subjects with the following diagnosis: 326 AD, 87 FTD, 61 DLB, 38 VaD, and 302 controls with subjective cognitive decline (SCD) (Table 1). Subjects were eligible for inclusion if brain MRI was available.

All subjects had received a standardized workup, including medical history, physical, neurological and neuropsychological assessment, MRI, laboratory tests, and a subset examination of CSF. Individuals were diagnosed as SCD when the cognitive complaints could not be confirmed by cognitive testing and criteria for mild cognitive impairment or dementia were not met. The diagnoses were established based on the following diagnostic criteria: the criteria of the NIA-AA for AD dementia [3], the Rascovsky and Gorno-Tempini criteria for FTD [5,20], the NINDS-AIREN criteria for VaD [4], and the McKeith criteria for DLB [6,21]. All patients had provided written informed consent for their data to be used for research purposes.

2.2. Clinical assessment

2.2.1. Neuropsychology

We used the Mini–Mental State Examination for global cognitive functioning [22]. For memory, the Consortium to Establish a Registry for Alzheimer's Disease word list memory test and the Rey Auditory Verbal Learning Task were included [23,24]. To measure mental speed and executive functioning, we used Trail Making Tests A and B (TMT-A and TMT-B, respectively) [25]. Language and executive functioning were tested by category fluency (animals) [26]. Missing data ranged from n = 1 (Mini–Mental State Examination) to n = 31 (4%) (memory). To pool the different memory tests, we standardized Rey Auditory Verbal Learning Task and Consortium to Establish a Registry for Alzheimer's Disease memory tests per center to z-scores using SCD subjects.

2.2.2. Cerebrospinal fluid biomarkers

CSF $A\beta_{42}$, total tau, and p-tau were measured with commercially available ELISA tests (Innotest, Fujirebio,