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Behavioral correlates of cerebrospinal fluid amino acid and biogenic amine neurotransmitter alterations in dementia

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Abstract

Background: Behavioral and psychological signs and symptoms of dementia (BPSD) are a heterogeneous group of behavioral and psychiatric disturbances occurring in dementia patients of any etiology. Research suggests that altered activities of dopaminergic, serotonergic, (nor)adrenergic, as well as amino acid neurotransmitter systems play a role in the etiopathogenesis of BPSD. In this study we attempted to identify cerebrospinal fluid (CSF) neurochemical correlates of BPSD to provide further insight into its underlying neurochemical pathophysiological mechanisms.

Methods: Patients with probable Alzheimer's disease (AD; $n = 202$), probable AD with cerebrovascular disease ($n = 37$), probable frontotemporal dementia (FTD; $n = 32$), and probable dementia with Lewy bodies (DLB; $n = 26$) underwent behavioral assessment and lumbar puncture. CSF levels of six amino acids and several biogenic amines and metabolites were analyzed using ultraperformance liquid chromatography with fluorescence detection and reversed-phase high-performance liquid chromatography with fluorescence detection.

Results: In the AD patients, CSF homovanillic acid/5-hydroxyindoleacetic acid (HVA/5HIAA) ratios correlated positively with anxieties/phobias, whereas CSF levels of taurine correlated negatively with depression and behavioral disturbances in general. In FTD patients, CSF levels of glutamate correlated negatively with verbally agitated behavior. In DLB patients, CSF levels of HVA correlated negatively with hallucinations.

Conclusions: Several neurotransmitter systems can be linked to one specific behavioral syndrome depending on the dementia subtype. In addition to biogenic amines and metabolites, amino acids seem to play a major role in the neurochemical etiology of BPSD as well.

Keywords: Alzheimer's disease; Dementia; BPSD; Biogenic amines and metabolites; Amino acids; Neurochemistry; Cerebrospinal fluid

1. Introduction

Behavioral and psychological signs and symptoms of dementia (BPSD) are a heterogeneous group of behavioral, psychological, and psychiatric disturbances occurring in 50%–80% of dementia patients of any etiology [1]. These behavioral symptoms are generally categorized into seven main subtypes: paranoid and delusional ideation; hallucinations; activity disturbances; aggressiveness; diurnal rhythm disturbances; affective disturbances; and anxieties/phobias [2]. BPSD often lead to a greater amount of caregiver distress, diminished quality of life for both patient and caregiver, greater cognitive impairment [3], premature institutionalization, frequent (re)hospitalizations, and increased secondary morbidity and mortality [4]. Importantly, BPSD also have a significant and increasing socioeconomic impact [5].

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Research has repeatedly suggested that there is a neurochemical basis underlying BPSD although its pathophysiological mechanisms are still not well understood [6]. Alterations in central noradrenergic [6–9], serotonergic [6,10,11], and dopaminergic [6,9] neurotransmitter systems were found to play a critical role in BPSD manifestation. In particular, the balance between those different neurotransmitter systems seems to be of importance, as it is conceivable, due to the neurochemical complexity and diversity of BPSD, that more than one neurotransmitter system contributes to a particular behavioral syndrome [9]. Studying neurotransmitter systems in isolation cannot fully explain changes in behavior, given that many neurotransmitter systems work in conjunction with each other [6,9]. In spite of this difficulty, the neurochemical mechanisms underlying BPSD are proven to be both BPSD- and dementia-specific [6], so that dementia-specific neurochemical alterations might be found.

Nonetheless, this BPSD-related neurochemical basis needs to be examined further in a broader study population that comprises Alzheimer's disease (AD) as well as non-AD dementia patients, as most BPSD-related neurochemical studies are strictly confined to AD. Moreover, current pharmacological treatment options of BPSD are limited and nonspecific. Besides these alterations in monoaminergic neurotransmission, there is also some evidence suggesting that amino acids play a functional role in the neurochemical pathophysiology of BPSD [12–15]. However, this amino acid–based etiology of BPSD requires even further elucidation.

Therefore, in this study we assessed well-characterized patients with several forms of degenerative and mixed degenerative–vascular dementias to identify neurochemical correlates of BPSD and to increase our insight in its underlying pathophysiological mechanisms.

2. Methods

2.1. Study population

The study population consisted of 297 consecutively hospitalized outpatients who had been recruited at the Memory Clinic of Hospital Network Antwerp (ZNA-Middelheim and Hoge Beuken) for diagnostic work-up of dementia. Diagnoses consisted of: probable AD ($n = 202$); probable AD with cerebrovascular disease (CVD) (AD+CVD; $n = 37$); probable frontotemporal dementia (FTD; $n = 32$); and probable dementia with Lewy bodies (DLB; $n = 26$). Diagnosis of probable AD was made according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [16], although all patients also fulfilled the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) [17]. AD+CVD was diagnosed when patients fulfilled the criteria of probable AD according to the NINCDS-ADRDA criteria and, in addition, displayed CVD on brain computed tomography (CT) and/or magnetic resonance imaging (MRI). However, CT and/or MRI images did not meet the criteria of relevant CVD according to the vascular dementia criteria of the NINCDS–Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINCDS-AIREN) [18], thus excluding multiple large-vessel infarcts, strategically placed infarcts, multiple basal ganglia, and white-matter lacunae or extensive white-matter lesions. All FTD patients fulfilled the core diagnostic features and several supportive diagnostic features of the clinical diagnostic criteria for FTD [19]. Diagnosis of probable DLB was made according to the criteria of McKeith et al [20,21].

All patients were clinically followed up, which added to the certainty of clinical diagnosis. In cases of patient death, an autopsy was performed to allow neuropathological confirmation of clinical diagnosis. So far, 38 of the 297 patients included underwent autopsy, which resulted in a diagnosis of definite AD, FTD, DLB, and AD+CVD in 27, 7, 1, and 3 patient(s), respectively.

The age at dementia onset was estimated by the clinician, based on interviews with the patient's main caregiver.

The local ethics committee approved this study. All patients and their caregivers gave informed consent for participation to the study.

2.2. Behavioral assessment

Behavior was assessed at baseline, covering a period of 2 weeks prior to inclusion and using a battery of behavioral assessment scales, including: the Middelheim Frontality Score (MFS) [22]; Behavioral Pathology in Alzheimer's Disease Rating Scale (Behave-AD) [2]; Cohen–Mansfield Agitation Inventory (CMAI) [23]; and Cornell Scale for Depression in Dementia (CSDD) [24].

The MFS is a validated clinical and behavioral assessment scale that measures frontal lobe features with good inter- and intrarater reliability [22]. Each of the 10 items were given a score of either 0 (absent) or 1 (present), yielding a maximum total score of 10. The Behave-AD is a 25-item scale that measures behavioral symptoms in seven clusters (paranoid and delusional ideation; hallucinations; activity disturbances; aggressiveness; diurnal rhythm disturbances; affective disturbances; and anxieties/phobias) with each item scored on a four-point scale of increasing severity [2]. Besides a total score, a global rating score concerning caregiver burden is provided. The CMAI assesses 29 agitated behaviors on a seven-point scale of increasing severity [23]. CMAI cluster scores include aggressive behavior (cluster 1), physically non-aggressive behavior (cluster 2), and verbally agitated behavior (cluster 3); a total score is calculated as well. The CSDD is a 19-item depression scale that is rated on a three-point score of absent, mild or intermittent, and severe [24].

Information was obtained through interview with the professional and/or main caregiver, interview with the patient, clinical files, and behavioral observation.