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Prevalence of Wild-Type Butyrylcholinesterase Genotype in Patients with Alzheimer's Dementia

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Abstract

Approximately, two-thirds patients with Alzheimer's disease (AD) are reported to have homozygous wild-type butyrylcholinesterase (BuChE) gene expression. It is associated with a higher rate of hydrolysis of acetylcholine, which ultimately leads to increase in the levels of BuChE in advanced stages of the disease. Rivastigmine, a dual inhibitor of acetylcholinesterase (AChE) and BuChE, might be of additional benefit in patients with AD with wild-type BuChE allele.

Keywords

Butyrylcholinesterase, Alzheimer's Disease, Genotype

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder with progressive decline in cognitive function, and accounts for 50% - 60% of all dementia cases [1]. The pathological hallmarks of AD are formation of amyloid plaques by oligomerization of beta-amyloid (Aβ) proteins and neurofibrillary tangles (aggregation of tau proteins) [2]. Cholinergic and glutamatergic neurotransmission plays an important role in learning and memory, and current evidence suggests that interference of Aβ proteins with these pathways may account for neurochemical deficits in AD [1] [3] [4]. With the progression of AD, acetylcholinesterase (AChE) activity decreases and butyrylcholinesterase (BuChE) activity increases or remains unchanged in certain regions of the brain. Low levels of BuChE in the cerebrospinal fluid have been associated with increased levels of BuChE/AChE/Aβ complexes either surrounding or trapped in the plaques, thereby leading to neuritic tissue degeneration which ultimately

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leads to greater cognitive decline in the later stages of the disease [5]-[7]. This is predominantly observed in patients with AD with homozygous wild-type BuChE gene expression (approximately two-third of patients with AD), which has a higher hydrolysis rate than the BuChE K-variant (most common polymorphism of BuChE) [6] [7]. BuChE activity is reported to be higher in men than women suffering from AD [7]. These changes in BuChE activity and BuChE gene expression during the course of AD present a strong possibility that these patients might benefit from the inhibition of BuChE [1].

Current treatment options for AD offer only symptomatic benefit and include cholinesterase inhibitors, such as rivastigmine, donepezil, and galantamine, or N-methyl D-aspartate receptor antagonists such as memantine. Rivastigmine inhibits both AChE and BuChE with equal potency, whereas donepezil and galantamine primarily target AChE [1]-[5].

Many studies have been conducted to establish the relationship between BuChE genotype and risk of developing AD and rate of the disease progression [6] [8]-[16]. However, robust evidence is lacking in the clinical practice to understand the effect of wild-type BuChE allele in patients with AD. The main objective of our study was to assess the BuChE genotype in a non-selected population of patients with AD who had deteriorating symptomatology in the last 6 months and were not treated with rivastigmine. Findings from our study are expected to add to the limited knowledge presently available about the role of wild-type BuChE allele in AD population.

2. Methods

BuChE genotype and Alzheimer's dementia

In this multi-center outpatient study, the BuChE genotype was examined in patients with mild-to-moderate-AD exhibiting progressive dementia, either untreated for dementia or treated with donepezil, galantamine or memantine. Demographic characteristics of the study population were recorded. Severity of the disease was estimated using Mini Mental State Examination scores (MMSE; a 30-point questionnaire widely used for estimating the severity of cognitive impairment) and Global Deterioration Scale (GDS; a 7-point rating scale for estimating the magnitude of cognitive and functional capacity) [17] [18]. Inferential statistical examination of relationships between the BuChE genotype and disease severity (for MMSE and GDS) was performed using the Chi-square test.

3. Results

A total of 152 patients between the ages 57 - 100 years with MMSE scores 5 - 26 and GDS scores 1 - 7 were included in this study. A majority of the subjects were women (61.2%) and most of them were treated with donepezil (40.8%), memantine (26.3%) or galantamine (15.8%) and 26 (17.1%) patients did not undergo anti-dementia drug treatment (**Table 1**). Among these, 146 (96.1%) patients carried the wild-type BuChE allele

Table 1. Baseline characteristics of the study population.

Total number of patients, n	152
Sex, n (%)	
Male	59
Female	93
Age, years (mean ± SD)	79.0 ± 7.3
Age, years (range)	57 - 100
MMSE score, range (mean ± SD)	5 - 26 (18.0 ± 5.7)
GDS score, range (mean ± SD)	1 - 7 (4.1 ± 1.4)
Treatment, n (%)	
Donepezil	62 (40.8)
Memantine	40 (26.3)
Galantamine	24 (15.8)
No anti-dementia drug treatment	26 (17.1)

GDS, Global Deterioration Scale; MMSE, Mini Mental State Examination; SD, Standard Deviation.

with 107 (70.4%) patients being homozygous and 39 (25.7%) patients being heterozygous for the gene. The remaining six (3.9%) patients were homozygous for the K allele, which is associated with lower levels of circulating BuChE molecules. To study any relationship between the BuChE genotype and disease severity, patients were separated into two groups each, based on the MMSE and GDS scores (MMSE 0 - 15 [n = 47] and MMSE 16 - 30 [n = 105] and GDS 1 - 4 [n = 81] and GDS 1 - 7 [n = 71]) and BuChE genotype was then analyzed. There were no significant differences in the MMSE or GDS scores among different BuChE genotype groups ($p > 0.05$ for all groups).

4. Discussion

Patients with AD, experiencing deteriorating symptomatology in the last 6 months and who were either untreated or were being treated with a selective AChE inhibitor were included in the present study. Findings from this study indicated that most patients with AD carried the wild-type BuChE. It is predominant in the amyloid plaques and tangles in the form of BuChE protein and is associated with greater cognitive decline, unlike the BuChE-K allele, which is associated with lower expression of enzyme and hence, less rapid cognitive decline in patients with AD [7].

In an open-label study of 171 Italian patients with AD, no relationship between BuChE genotype and response to rivastigmine, donepezil, or galantamine was reported. However, a limited number of DNA samples from the small sample size and a restricted population pool made it difficult to generalize these results [8]. In a retrospective exploratory analysis from a randomized, placebo-controlled study conducted in 1018 patients with mild cognitive impairment, functional decline in female patients with the BuChE wild-type genotype was significantly reduced by rivastigmine unlike male patients or in patients with the K-allele [19]. Results from retrospective analysis of a 2-year double-blind, parallel group study showed a significant benefit in wild-type BuChE carriers, with less functional decline over 2 years, after treatment with rivastigmine compared with donepezil [20]. Similar favorable responses to rivastigmine were observed in a secondary subgroup analysis of another study [21]. When patients in the ADENA database (pooled data from four 26-week, randomized, double-blind trials of rivastigmine capsules in patients with mild-to moderate AD) were grouped by BuChE genotype, patients with wild-type BuChE showed a significant response to rivastigmine compared with placebo (Novartis, data on file). Furthermore, a number of open-label studies indicated that patients experiencing a lack/loss of efficacy or intolerance, with donepezil or galantamine (selective AChE inhibitor) demonstrated improved/stabilized symptoms or improved tolerability after switching to rivastigmine (a dual AChE and BuChE inhibitor) [22].

Although this study is limited by a small sample size, findings from our study support previous studies; suggesting the presence of wild-type BuChE allele, resulting in an increased expression of BuChE in the majority of patients with AD. These patients may benefit from switching to rivastigmine, the dual inhibitor of AChE and BuChE. These results also offer the possibility of a rationalized pharmacogenetic approach towards treating and managing AD. Larger studies are warranted to better characterize the relationship between BuChE genotype and treatment response in patients with AD.

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Conflict of Interest

None.

Disclosures

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