ALZHEIMER'S DISEASE: ASSOCIATION STUDY BETWEEN RESPONSE TO CHOLINESTERASE INHIBITORS AND CANDIDATE GENES IN A SARDINIAN SAMPLE

Squassina Alessio[1], Congiu Donatella[1], Manconi Francesca[1], Putzu Paolo F[2], Chillotti Caterina[1], Del Zompo Maria[1], Piccardi Mariapaola[1]

[1]Unit of Clinical Pharmacology, Department of Neurosciences ''B. B. Brodie'', University of Cagliari, [2]Division of Geriatrics, Local Health Agency 8, Cagliari, Italy

Background: Alzheimer's disease (AD) is characterized by an extensive loss of cholinergic neurons, and their cortical projections, from the basal forebrain area. The resulting reduction in cholinergic activity is associated with decreased levels of the neurotransmitter acetylcholine (ACh), decreased activity of acetylcholinesterase (AChE), choline acetyltransferase (ChAT), and increased butyrylcholinesterase (BChE) activity.
Cholinesterase inhibitors currently represent the most established treatment strategy in AD. The inhibitors of AChE are particularly effective in the treatment of cognitive changes associated with Alzheimer's disease. However, AChE inhibitors are not effective in all AD patients. Differences in response might be attributable to the alleles of genes involved in drug mechanism of action.
We designed a case-control study to evaluate the association of some candidate genes, APOE, BCHE, ACHE and CHAT with the response to AChE inhibitors in a Sardinian sample of AD patients.
Methods: AD patients (n = 158), all of Sardinian ancestry (parents, grandparents and great-grandparents), were recruited from the Division of Geriatrics, Local Health Agency 8, and the Unit of Clinical Pharmacology, Department of Neurosciences, University of Cagliari. Patients were diagnosed according to DSM-IV, and NINCDS-ADRDA criteria for possible or probable AD. Cognitive screening was performed by means of Mini-Mental State Examination (MMSE). Patients were randomized to receive either donepezil or rivastigmine. The outcome measure used in this study was the ADAS-cog and MMSE. Safety and tolerability assessments included adverse events and measurement of vital signs.
All patients gave informed consent for participation in the study.
SNP analysis was performed by PCR/RFLP or an ABI Prism 7900HT instrument using Assays-On-Demand reagents from Applied Biosystems, Inc.
Results: Of the 158 patients enrolled in the study, 103 patients constituted the valuable population. No significant differences in allele, genotype or haplotype frequencies were observed between responders and non-responders.
Conclusion: These results suggest that APOE, AChE, ChAT and BChE polymorphisms do not constitute a major genetic risk factor for drug response in a Sardinian population.