The apolipoprotein E (ApoE) ε4 allele is the largest known genetic risk factor for late-onset sporadic Alzheimer’s dementia (AD). Populations for therapeutic or prevention studies usually are stratified by age, sex, cognitive performance and ApoE genotype. In order to provide an estimate of the ApoE genotype distribution for screening purposes, we studied subjects with subjective memory impairment (SMI) who underwent further cognitive assessment.

Introduction

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Methods

In an ongoing screening project, we determined ApoE genotype in subjects with SMI. They had to have noticed a decline in memory during the last five years and had to be concerned about it. Cognitive performance was assessed by means of a standardized neuropsychological test battery including the ADAS-cog and the computer-assisted Memory and Attention Test (MAT). A two test-1.5 SD criterion was applied for a diagnosis of cognitive impairment. Activities of daily living were assessed by means of a structured interview and the DAD scale. In case of a diagnosis of dementia, further clinical, neuropsychological and neuroradiological examinations were initiated.

The Memory and Attention Test (MAT)

The MAT allows the differentiated and standardized assessment of seven cognitive domains:
- working memory for verbal, figural and episodic material
- short-term memory for verbal, figural and episodic material
- selective attention

The test adapts to the individual level of performance of the subjects. Thus, subjects with a good performance can be tested up to their limits, whereas subjects with a poor performance don’t end frustrated through a large number of tasks they cannot master.

Results

The assessments were carried out in 123 subjects with SMI at ages between 46 and 90 years (mean ± SD: 67.0 ± 9 years). In 70 (56.9 %) of them no cognitive impairment was found, in 31 (25.2 %) a mild cognitive impairment (MCI) and in 20 (16.3 %) a diagnosis of AD was ascertained. Other types of dementia were diagnosed in two patients, who will not be further considered in the following.

Apo E genotypes and cognitive status

Performance in the MAT selective attention task was highly correlated with age for all ApoE groups (r=-0.430; p<0.01). When comparing this correlation for ApoE ε3/ε3 and ApoE ε3/ε4 subjects, we found a stronger age-related decline in the ApoE ε3/ε4 subjects. Individual values and regression lines are shown in the following diagram.

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ApoE genotype has an effect on the age-related decline of selective attention

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Disclosure

This study was sponsored by Novartis GmbH, Nürnberg.
Brevican is an important component of specialized extracellular matrix structures involved in the stabilization of synapses, regulating outgrowth of neurites and maintaining neuroplasticity. Brevican has been detected in amyloid plaques and neurofibrillary tangles in postmortem AD brains and the protein has been suggested to increase the formation of Aβ. The objective of this study was to investigate whether a fragment of brevican (frag-brevican) could serve as serological biomarker of AD diagnosis.

Methods: A highly sensitive ELISA specifically detecting frag-brevican was developed. The specificity and reactivity of the assay were characterized in human serum and the technical performance of the assay was evaluated. To assess that frag-brevican reflects a neurophysiological process, a tissue profile of brevican was made using different rat tissue extracts. Well-characterized serum samples from patients with AD and mild cognitive impairment (MCI) (n=36), other dementias (n=42) and controls (n=51) were used to investigate the clinical potential of frag-brevican. Results: The ELISA assay specifically detected frag-brevican and was technically robust. The tissue profile showed that brevican was exclusively expressed in the brain with the strongest presence in the hippocampus and frontal cortex. This is an important finding, since hippocampus is involved in the early changes of AD. Brevican was present as large bands >150 kDa and as a band around 52 kDa. The latter correlates with an ADAMTS4 cleavage product of brevican, while the large bands reflect its glycosylated forms. The serum levels of frag-brevican were significantly elevated in AD/MCI patients when compared to other dementias (p=0.0003) and controls (p=0.043).

P2-28: APOLIPOPROTEIN E GENOTYPE IN SUBJECTS WITH SUBJECTIVE MEMORY IMPAIRMENT ASSESSED FOR OBJECTIVE COGNITIVE IMPAIRMENT. GEORG ADLER, BINDER J, YVONNE LEMBACH (Institut fuer Studien zur Psychiatrischen Gesundheit (ISPG), Mannheim, Germany)

Background: The apolipoprotein E (ApoE) epsilon4 allele is the largest known genetic risk factor for late-onset sporadic Alzheimer’s dementia (AD). Populations for therapeutic or prevention studies usually are stratified by age, sex, cognitive performance and ApoE genotype. In order to provide an estimate of the ApoE genotype distribution for screening purposes, we studied subjects with subjective memory impairment (SMI) who underwent further cognitive assessment. Methods: In an ongoing screening project, we determined ApoE genotype in subjects with SMI. They had to have noticed a decline in memory during the last five years and had to be concerned about it. Cognitive performance was assessed by means of a standardized neuropsychological test battery including the ADAS-cog and the computer-assisted Memory and Attention Test (MAT).

A two test-1.5 SD criterion was applied for a diagnosis of cognitive impairment. Activities of daily living were assessed by means of a structured interview and the DAD scale. In case of a diagnosis of dementia, further clinical, neuropsychological and neuroradiological examinations were initiated. Results: The assessments were carried out in 69 subjects with SMI at ages between 53 and 90 years (mean ± SD: 70.4 ± 9.1 years). In 36 (52 %) of them no cognitive impairment was found, in 18 (26 %) a mild cognitive impairment (MCI) and in 15 (22 %) a diagnosis of AD was ascertained. An ApoE epsilon4 allele was found in 18 of all subjects (26 %), in 3 (8 %) of the subjects with no cognitive impairment, in 9 (50 %) of the subjects with MCI and in 9 (60 %) of the subjects with AD. ApoE epsilon4 frequency was significantly higher in the subjects with MCI or AD compared to those with no cognitive impairment (Chi-square=17.37; p=0.001).

Conclusion: The frequency of the ApoE epsilon4 allele in these unselected subjects with SMI, who came for cognitive assessment, is about twice as high as in the general population. In those subjects with SMI, in whom cognitive assessment and further diagnostics revealed MCI or AD, the ApoE epsilon4 allele was found seven times more often compared to the subjects without objective cognitive impairment. About half of the patients with subjective memory impairment, in whom further examination reveals MCI or AD, had an ApoE epsilon 4 allele.

P2-27: ABETA LEVELS IN THE JAGULAR VEIN AND ABETA Oligomer LEVELS IN CSF CAN BE CHANGED AFTER THE TREATMENT OF IVIG FOR AD. TAKASHI KASAI1, MASAKI KONDO1, RYOTAROU ISHII1, TOSHIKI MIZUNO2, TAKAHIKO TOKUDA3 ((1) Department of Neurology, Kyoto Prefectural University of Medicine, Kyoto, Japan; (2) Department of Molecular Pathobiology of Brain Diseases, Kyoto Prefectural University of Medicine, Kyoto, Japan)

Intravenous immunoglobulin (IVlg) has been a promising candidate as a potential anti-amyloid passive immunotherapy for Alzheimer disease (AD) because it contains anti-amyloid β (Aβ) antibodies. Although several studies with IVlg in mild to moderate AD have been published, changing levels of ‘peripheral sink’ Aβ, or solubilization of aggregated Aβ species induced by immunotherapy, have not been properly investigated. Here, we carried out an open label study of add on therapy with IVlg in five relatively young patients with AD. We collected plasma samples from a peripheral vein (peripheral-plasma) and from the internal jugular vein (jugular-plasma) to estimate directly the levels of peripheral sink Aβ. We also measured high molecular weight (HMW) Aβ oligomers in CSF as a marker to detect disaggregated Aβ species. IVlg infusions were well tolerated in the majority of cases. However, one case had epileptic seizures after IVlg. Levels of HMW CSF Aβ oligomers in all participants were significantly increased after IVlg. Aβ40 and Aβ42 levels in jugular-plasma were continuously or temporarily elevated after treatment in three of five patients who also showed preserved cognitive function, whereas levels of these markers in peripheral-plasma did not correlate with reactivity to the treatment. Other conventional biomarkers including 11C-Pittsburgh compound B retention were not altered after the treatment. These findings imply that HMW Aβ oligomer levels could be a better biomarker to reflect the anti-amyloid effects of IVlg than conventional Aβ species; moreover, Aβ in jugular-plasma seems to be a more direct and precise biomarker to estimate clearance of Aβ from the brain in clinical trials rather than Aβ in peripheral-plasma.

P2-29: A FAST AND COST-EFFECTIVE METHOD FOR APOLIPOPROTEIN E ISOTYPING AS AN ALTERNATIVE TO APOE GENOTYPING FOR PATIENT STRATIFICATION IN CLINICAL TRIALS. MIGUEL CALERO1, OLGA CALERO1, ANDRÉS RODRÍGUEZ-MARTÍN1, LUIS GIL-DE-GÓMEZ1, SERGI GASSÓ2, LUIS GARCÍA-ALBERT1 ((1) Chronic Disease Programme, CIBERNED, and CIEN Foundation-Queen Sofia Foundation, Instituto de Salud Carlos III, Madrid, Spain; (2) Biocross, S.L., Valladolid, Spain; (3) CIBERNED and Chronic Disease Programme, Instituto de Salud Carlos III, Madrid, Spain; (4) Pragmatic Diagnostics S.L., Bellaterra (Cerdanyola del Vallès), Barcelona, Spain; (5) Chronic Disease Programme, Instituto de Salud Carlos III, Madrid, Spain)

Background: Apolipoprotein E (ApoE) is a 34 kDa glycoprotein involved in lipid metabolism. The human APOE gene that encodes this protein is polymorphic and is located on chromosome 19.