APOE genotype
A risk factor for adverse effects from anti-amyloid therapy in Alzheimer's disease

By Dr Jacqueline Gosink

The apolipoprotein E (*APOE*) genotype influences the development of Alzheimer's disease and has recently been found to be a risk factor for side effects from new disease-modifying therapies. Carriers of the *APOE* ε4 allele have the highest risk, especially if they are homozygous. *APOE* genotyping is therefore increasingly relevant for risk assessment prior to the use of anti-amyloid drugs.

Alzheimer's disease

Alzheimer's disease is the most common age-related cause of dementia and is a major global health concern. The number of cases is rising rapidly and is projected to continue growing over the coming decades, causing a massive societal and economic burden. Most cases of Alzheimer's disease are late onset, occurring in people over 65. The prevalence doubles with about every five years of age, from just over 1% in the age group 65–69 to more than 25% in those over 90 years old [1]. Early-onset Alzheimer's disease, which can occur in people in their 40s or 50s, is much rarer, constituting about 5% of Alzheimer's cases. The main pathologic feature of Alzheimer's disease is aggregation of amyloid-beta in the brain which drives the rest of the disease process, such as the neurofibrillary tau tangles that result from an imbalance between amyloid-beta production and clearance [2]. In the last few years, novel disease-modifying drugs that clear the toxic amyloid deposits have appeared on the market. However, in some individuals they induce severe side effects that are linked to the *APOE* genotype.

Apolipoprotein E

Apolipoprotein E (Apo-E) is a lipid transporter that delivers cholesterol and phospholipids throughout the body. Apo-E plays a role in Alzheimer's disease by interacting with amyloid-beta and regulating its aggregation and clearance. Apo-E also contributes to Alzheimer's pathogenesis via various other amyloid-beta-related and -independent pathways: for example, by modulating brain synaptic plasticity, glucose metabolism, neuronal signalling, oxidative stress, neuroinflammation, mitochondrial function and cholesterol transportation [3].

APOE alleles

There are three clinically relevant *APOE* alleles, which are denoted ε2, ε3 and ε4. Depending on the allele, three different isoforms of the Apo-E protein are produced, which differ in the amino acids at positions 112 and 158. E2 contains cysteine at both positions, E3 contains cysteine and arginine respectively, and E4 contains arginine at both positions.

Variant ε3 is the most frequent of the three alleles. ε3/ε3 is considered the normal genotype and is carried, for example, by 63% of the population. The ε4 allele is associated with an increased risk of developing Alzheimer's disease. This variant occurs at frequencies of 21% for the heterozygous ε3/ε4 form, 2% for the combination ε2/ε4, and 2% for the homozygous ε4/ε4 form. The ε2 allele, on the other hand, is neuroprotective for Alzheimer's disease. Eleven percent of the population carry the heterozygous ε2/ε3 form and 1% the homozygous ε2/ε2 form [4].

The ε4 allele is found around three times more frequently in Alzheimer's disease patients than in the cognitively normal

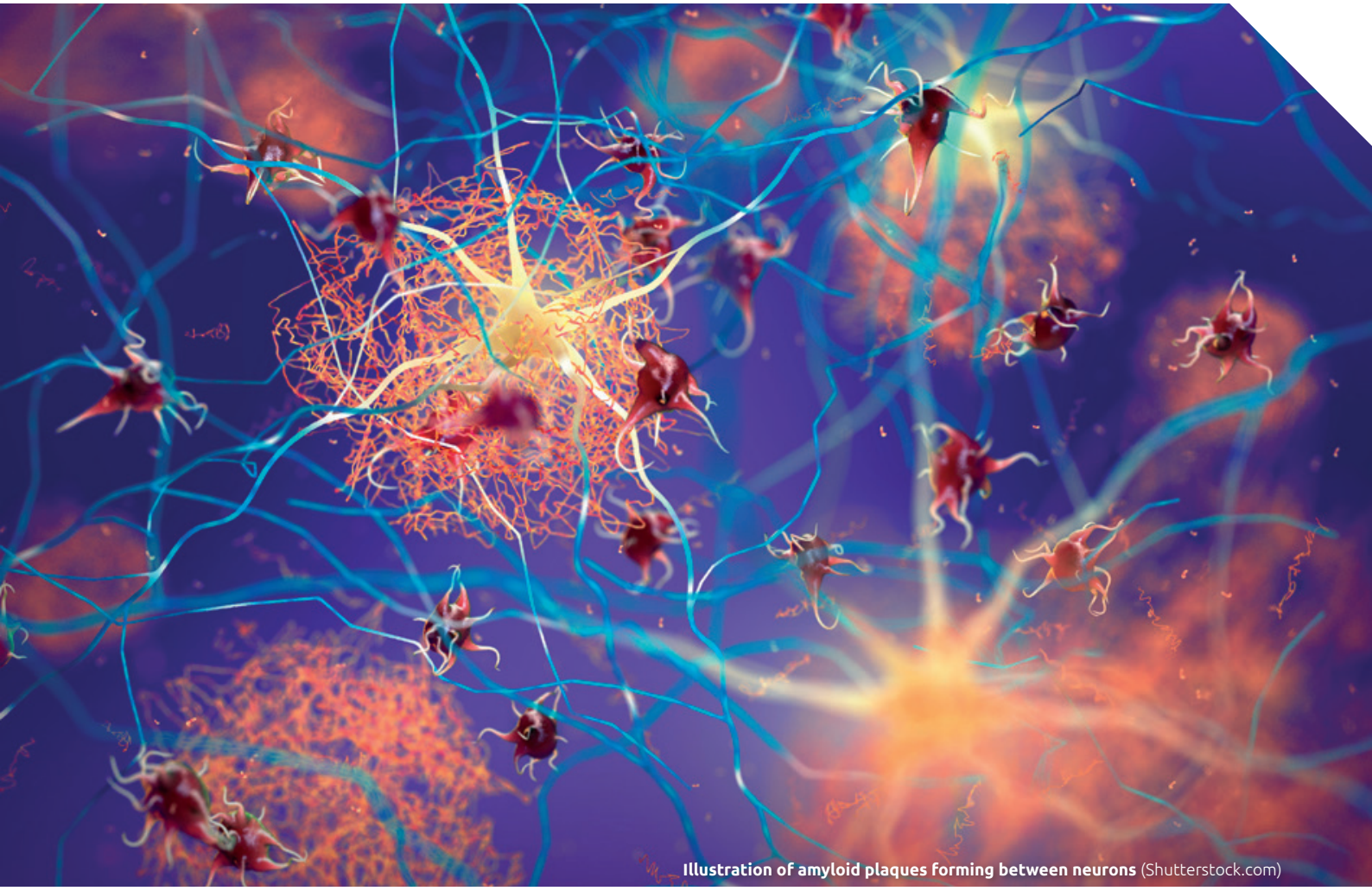

Illustration of amyloid plaques forming between neurons (Shutterstock.com)

population, corresponding to about 38% compared to 14%, respectively [5]. In contrast, the ε2 allele occurs in just 3.9% of Alzheimer's patients compared to 7% of cognitively normal persons. Furthermore, the ε4 gene dosage impacts both the disease risk and the age at which late-onset Alzheimer's disease manifests. The relative risk of developing late-onset Alzheimer's disease with respect to the genotype is in ascending order: ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4 and ε4/ε4. The average age of disease onset amounts to 84 years for non-ε4 carriers, 76 years for heterozygote carriers and 68 years for homozygous carriers [6]. In the early-onset familial form of Alzheimer's disease, numerous mutations in other genes are implicated, including genes for amyloid precursor protein and presenilin 1 and 2.

Alzheimer's diagnostics

Early diagnosis of Alzheimer's disease is important for effective therapy management and patient support. Diagnosis of Alzheimer's disease is based on clinical evaluation, imaging methods such as positron emission tomography (PET), and analysis of biomarkers in cerebrospinal fluid (CSF). *APOE* genotyping alone does not play a major role in diagnosis of Alzheimer's disease, as its predictive value is limited. CSF analysis is considered the most sensitive diagnostic method, detecting pathologic changes many years before disease onset [7]. The most important CSF biomarkers are the amyloid-beta 1–42 to 1–40 ratio, phosphorylated tau and total tau. These markers can be measured, for example, by ELISA or chemiluminescence immunoassay (ChLIA). A portfolio of ELISA and ChLIA assays* developed by EUROIMMUN in collaboration with ADx Neurosciences demonstrate robust and highly reproducible measurements. The assays use highly specific monoclonal antibodies for precise detection of each analyte.

A new era of therapy

Although Alzheimer's disease cannot be cured, the last few years have witnessed the introduction of disease-modifying therapies, which can delay disease progression in patients with early-stage Alzheimer's disease [8]. These monoclonal antibody-based treatments reduce amyloid-beta plaques in the brain, slowing cognitive and functional decline. To be effective, anti-amyloid therapies must be implemented in the prodromal stage of mild cognitive impairment.

The first drug on the market, aducanumab (Aduhelm), received FDA approval in 2021 under the accelerated approval pathway. A second drug, lecanemab (Leqembi), received traditional approval in 2023 for treatment of patients in the early stage of Alzheimer's disease with confirmed amyloid pathology as demonstrated by PET or CSF testing. Authorization of lecanemab by the European Medicines Agency (EMA) is expected in spring 2024 [9]. Donanemab is also expected to be approved soon in the USA. Many further promising anti-amyloid drugs are in the pipeline. >>

Side effects of amyloid modification therapies

In some cases, anti-amyloid treatments can induce side effects, including amyloid-related imaging abnormalities (ARIA) with edema and/or effusion (ARIA-E) or hemorrhagic changes (ARIA-H) [2,10]. These are thought to be expressions of increased vascular fragility and leakage of proteinaceous fluid and erythrocytes caused by the antibody treatments. Although mainly asymptomatic, ARIA may cause additional symptoms such as headache, confusion, visual changes, dizziness, nausea, gait difficulty and seizures. In a few cases, the side effects have even been fatal. If ARIA are detected, the treatment is usually suspended until improvement or discontinued completely. The risk of developing ARIA is greater in carriers of the ε4 allele, with homozygous carriers considered at highest risk. The rate of ARIA amounted to 5.4% in ε4 non-carriers, 10.9% in heterozygotes and 32.6% in homozygotes. Rates of symptomatic ARIA were 1.4%, 1.7% and 9.2%, respectively [11].

Significance of *APOE* genotyping

The determination of *APOE* gene variants associated with Alzheimer's disease is increasingly recommended as a screening tool prior to anti-amyloid therapy to assess the risk of negative consequences. Information about the increased risk of ARIA for ε4 carriers compared to other genotypes can be included in patient management decisions. In patients receiving lecanemab, post-treatment monitoring is directed principally at detecting ARIA, and heightened vigilance for ARIA is recommended in ε4 carriers, especially homozygotes [11].

PCR-based genotyping test

A real-time PCR test to determine the *APOE* genotype has been developed by EUROIMMUN. The multiplex EURORealTime *APOE* simultaneously detects the APOE ε2, ε3 and ε4 alleles and deduces the six possible genotypes ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4 and ε4/ε4. Only one reaction is required per patient sample. The test is performed on genomic DNA (gDNA) isolated from EDTA blood samples. The assay processing can be automated on established instruments, and results are evaluated, documented and archived using the EURORealTime Analysis Software. The EURORealTime APOE will be launched soon.*

Conclusion

With the advent of disease-modifying therapies for Alzheimer's disease, the use of *APOE* genotyping has become relevant for supporting patient management. For clinicians treating Alzheimer's patients, *APOE* genotyping will grant additional patient information and will enable a more personalized approach in anti-amyloid treatment.

** Regulatory status, precise intended use and product availability must be verified for the user's individual jurisdiction*

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