Pharmacogenomics of Alzheimer’s Disease

Ramón Cacabelos

Professor & Chairman, EuroEspes Biomedical Research Center, Institute for CNS Disorders and Genomic Medicine, EuroEspes Chair of Biotechnology and Genomics, Camilo José Cela University, 15165-Bergondo, Corunna, Spain; President, World Association of Genomic Medicine

The number of people affected by dementia is becoming a public and socioeconomic concern in many countries all over the world, independently from the economic condition of the society in question. The growing of the elderly population is a common phenomenon in both developed and developing countries, bringing about future challenges in terms of health policy and disability rates. In the U.S.A., death rates for the leading causes of death are heart disease (200.2 x 100,000), cancer (180.7 x 100,000), and stroke (43.6 x 100,000), with Alzheimer’s disease (AD), as the fifth leading cause of death in people older than 65 years of age, representing 71,600 deaths/year. Disability caused by senility and dementia affects 9.2 x 1,000 in the population aged 65-74 years, 33.5 x 1,000 in those within the 75-84 range, and 83.4 x 1,000 in the population over 85 years of age [1].

From a medical point of view, the 3 major problems related to dementia are (i) the poor understanding of pathogenic mechanisms leading to premature neuronal death; (ii) the lack of specific biomarkers for an early diagnosis; and (iii) the absence of a curative treatment, the scarcity of therapeutic options, and the doubtful cost-effectiveness of drugs for the treatment of dementia.

Over the past 50 years, different etiological proposals have been posed to explain AD pathogenesis. At present, the two prevalent theories (amyloidopathy, tauopathy) do not explain in full the mechanisms by which neurons prematurely die in AD patients, leading to the phenotypic expression of the disease (e.g. memory deficit, behavioral changes, functional decline). With the incorporation of genomic studies to scrutinize the genetic background of AD, during the past two decades over 1,000 different genes have been screened in the human genome as potential candidates for AD susceptibility, but less than 100 genes have survived replication studies in different cohorts [2]. Likewise, both APP (<1%) and presenilin-1 (PSEN1) and 2 (PSEN2) mutations (<5%) account for a minimum number of declared AD cases. The most significant susceptibility gene for AD is the apolipoprotein-E (APOE) gene. Individuals harboring the APOE-4 allele are more susceptible to neurodegeneration, cerebrovascular disorders, and atherosclerosis than APOE-3 carriers, and a very few cases with an APOE-2 allele might be protected against dementia; however, the number of APOE-4 carriers represents less than 20-30% of the cases; and other susceptibility genes may show SNPs of risk in less than 10% of the cases [2-5]. Consequently, the genomics of AD and dementia-related neurodegeneration still needs further elucidation [6], as well as the cerebrovascular component of AD [7], the impact of exogenous factors and the influence of epigenetic phenomena in AD pathogenesis [2,4,8].

A quite different issue -to move forward in the appropriate management of dementia- is pharmacogenomics. In recent times, significant advances have propelled the introduction of pharmacogenomic approaches in drug development and also in clinical practice to optimize therapeutics [4,8,9-11]. The vast majority of CNS drugs are metabolized via enzymes of the cytochrome P450 family (CYPs). The genes encoding CYP2D6, CYP2C19, CYP2C9, and CYP3A4/5 isoenzymes are highly polymorphic, with great allelic variation in different ethnic groups. In the Western population, only 25% of its members are extensive metabolizer (EM) for the trigenic cluster integrated by CYPs 2D6+2C19+2C9, the most relevant genes (and enzyme products) involved in drug metabolism, together with CYP3A4/5, which participates in the metabolism of over 80% of common drugs. The other 75% of the population is potentially at risk for developing adverse drug events (ADEs) due to defective variants encoding deficient enzymes which give rise to intermediate (IM), poor (PM) or ultra-rapid metabolizers (UM). This population cluster of defective metabolizers requires dose-adjustment to avoid side-effects [8]. However, not only CYPs are important in terms of drug efficacy and safety. In fact, 5 categories of genes are mainly involved in pharmacogenomics: (i) genes associated with disease pathogenesis (e.g. APP, PSEN1, PSEN2, MAPT, APOE)[2,4,6,8,9], (ii) genes associated with the mechanism of action of a particular drug (e.g. receptor genes)[12,13], (iii) genes associated with phase I (CYPs) and phase II reactions (UGTs, SULTs, NATs) [6,14-18], (iv) genes associated with transporters (ABCs, OATs)[19-23], and (v) pleiotropic genes and/or genes associated with concomitant pathologies [24].

AD and other forms of dementia are typical paradigms of polypharmacy administration. AD patients receive 6-10 different drugs per day, including anti-dementia drugs (donepezil, rivastigmine, galantamine, memantine), psychotropics (antidepressants, neuroleptics, anxiolytics), antiparkinsonians, anticonvulsants, and many other pharmacological categories of drugs currently used in elderly patients (e.g. anti-hypertensive drugs, diuretics, cardiotonics, statins, anti-histaminics, NSAIDs, etc). According to the U.S. Department of Health and Human Services, adults of 65 years of age and over reporting prescription drug use in the past month were 1.9% in the period 1988-1994 and over 35% in 2003-2006 [1]. Despite the reliability of these epidemiological data, the overuse of pharmaceuticals in the elderly population seems to be a harsh reality. Antidepressant prescribing significantly increased from 21.9% in 1996 to 47.5% in 12,556 US nursing home residents [25]. The use of psychotropic drugs in institutionalized patients ranges from 60-80% in different countries [26]. There is no major clinical benefit when a cholinesterase inhibitor is associated with an antidepressant in either cognitive improvement or emotional stability [27]; and the administration of neuroleptics to treat behavioral disturbances in patients with dementia is an issue fraught with safety concerns [28]. In ambulatory settings in the UK, people with...
dementia are currently prescribed an antipsychotic drug (17.7%), an antidepressant (28.7%) and a hypnotic/anxiolytic (16.7%). Compared to the general elderly population, antipsychotic prescribing is 17.4%, antidepressant prescribing 2.7 and hypnotic/anxiolytic prescribing 2.2 times more likely in people with dementia [29].

Assuming that genetic factors (pharmacogenomics) account for 60-90% variability in the pharmacokinetics and pharmacodynamics of current drugs, it is likely that in more than half of our patients – treated by trial-and-error, without any pharmacogenetic prediction– we can cause more harm than benefit. Therefore, top priorities in AD research and clinical management should emphasize the following items: (i) the convenience of promoting large-scale genome-wide studies for a better understanding of the genetic component of AD; (ii) the need to differentiate endogenous factors from exogenous factors in the pathogenesis of AD; (iii) the evidence that –even in a precarious condition regarding the present knowledge on AD genomics– the therapeutic response to conventional drugs in patients with dementia is genotype-specific, with APOE-ε4 carriers behaving as poor responders [30,31]; (iv) the evidence that polymorphic variants in CYP genes influence the efficacy and safety of cholinesterase inhibitors (this is particularly important in CYP2D6 PMs and UMs, who exhibit a poorer response to donepezil as compared to EMs and IMs) [30,31]; (v) the utility of pharmacogenomics to predict ADRs [32]; (vi) the suggestion that the use of pharmacogenomic approaches to AD treatment may become a cost-effective strategy to optimize our limited therapeutic resources [33]; and (vii) the recommendation to educate physicians and health professionals in the appropriate use of pharmacogenomic procedures [34]. To this end, the World Guide for Drug Use and Pharmacogenomics, and the EuroPharmaGenics (EPG) Database, have been created with over 1,200 drugs, about 500 prevalent genes involved in drug efficacy and safety issues, and more than 20,000 references, to help physicians in their effort to personalize pharmacological treatments in the clinical setting [35].

References

