International Journal of Basic and Applied Medical Sciences ISSN: 2277-2103 (Online)
An Open Access, Online International Journal Available at http://www.cibtech.org/jms.htm
2014 Vol. 4 (2) May-August, pp. 243-245/Iyer
Review Article

PHARMACOGENOMICS IN ALZHEIMER'S DEMENTIA (AD) - A CASE REPORT AND REVIEW

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ABSTRACT
Alzheimer's dementia is a complex form of brain degeneration with incidences increasing gradually and significantly in the Indian subpopulation. The capital toll and the emotional load it takes on relatives and patients is overwhelming and debilitating. Though the management of such patients has remained fairly similar over the years, the individual variation in genomics puts severe constraints on how each patient reacts to medications, as regards both side effect profiles and efficacies of medications. This case report and review is aimed at discussing the variations in genomics and how it affects the outcome of management in such patients and what interventions are available for testing.

Keywords: *Alzheimer's Dementia, Genomics, Management*

INTRODUCTION
The WHO 2012 Report "*Dementia: a public health priority*" estimates there are 35.6 million people suffering from dementia worldwide. Dementia of the Alzheimer's type is the most frequent cause of dementia. As the world population ages, the frequency is expected to double by 2030 and triple by 2050 (Blennow *et al.,* 2006). The magnitude of the situation will have grave consequences on the healthcare and financial systems of the world. Hence proactive measures in the form of research in pharmacological management and genetics is the best means of formulating acceptable means of managing future comorbidities.

CASES
A 75 year old retired married male with a past medical history of diabetes and hypertension over the past ten years was brought in to the doctor's office by his wife for symptoms of forgetfulness. He described having had such symptoms for a year, gradually progressing to a point when he can no longer manage his accounts, pensions and can no longer take walks unsupervised.
He described having normal sleep, appetite, bowel and bladder functions and no difficulties adjusting to temperatures. His affect seemed normal which validated his description of a normal mood over the past two weeks. He denied mood fluctuations and embarrassing public behaviours like incontinence.

On Examination
He was conscious and cooperative. He displayed appropriate eye contact and social manner without gross gait difficulties or involuntary movements.
Speech**:** was spontaneous without obvious deficits.
Thought**:** Content and form were appropriate.
Mood and Affect: was euthymic and appropriate.
Perception seemed appropriate with no AV hallucinations or delusions or accompanied paranoia.
Cognition**:** As checked using Folstein's MMSE, the score was 24/30 on the initial visit, affected in the areas of Immediate retention and recall and recent memory with fairly intact remote memory. Other aspects of Concentration, Attention, Intelligence and abstract thinking were found fairly intact.
He showed poor insight and impaired test judgment.

Management and Subsequent Follow ups:
A differential diagnosis of Alzheimer's dementia (AD), dementia due to B12 deficiency and hypothyroidism was considered. After CT head studies and laboratory biochemistry work up, we were able to rule out B12 deficiency and hypothyroidism. With a primary diagnosis of AD, the patient was

started on Memantine 5mg PO qHS, Folate and Vitamin supplements and was asked to return on follow up in 8 weeks. He was also set up with an appointment with a psychologist for conscious environmental stimulation and habilitation therapy in conjunction with pharmacological interventions.

With Memantine, he ended up with severe dizziness and nausea, as a result he was prescribed Donepezil 5mg PO qHS with follow up after 8 weeks, as it takes 4-6 weeks for the mechanism of Donepezil to start acting. After 8 weeks, the condition did not seem to respond to treatment. His MMSE score was 22/30 now. Donepezil was increased to 10mg PO qHS, which also, did not seem to improve his subjective symptoms.

A special genomic assay test was done from the patient's buccal swab. The results revealed that he was a CYP 2C19 extensive metabolizer, CYP 3A4 intermediate metabolizer and CYP 2D6 poor metabolizer, which corroborated his decreased responsiveness to medical treatment. In view of the recent developments, he was transitioned to Rivastigmine 3mg PO BID (Sr. Creat in the patient was <50).

Presently, on his latest visit, his MMSE seem unchanged at 22/30 with improvements in subjective social interactions.

DISCUSSION

Exact estimates of the prevalence of dementia depend on the definition and specific threshold used (Priority Medicines for Europe and the World, 2013). The syndrome affects approximately 5%-8% of individuals over age 65, 15%-20% of individuals over age 75, and 25%-50% of individuals over age 85. Alzheimer disease is the most common dementia, accounting for 50%-75% of the total, with a greater proportion in the higher age ranges (Braak and Del, 2012). Vascular dementia is the next most common followed by the remaining types of dementias.

In the study done by Mathuranath (2012) among the 1066 eligible participants who were cognitively normal at baseline, 104 developed dementia (98 with AD) over a follow-up period of 8.1 years. The incidence rates per 1000 person-years for AD was 11.67 (95% CI: 10.9-12.4) for those aged ≥55 years and higher for those aged ≥65 years (15.54, 95% CI: 14.6-16.5). In those aged ≥65 years, the world age standardized incidence rate was 21.61 per 100,000, and standardized against the age distribution for the year 2000 U.S. Census, the age-adjusted incidence rate was 9.19 (95% CI: 9.03-9.35) per 1000 person-years. Incidence rate of AD increased significantly and proportionately with increasing age (Mathuranath, 2012).

Primary pathogenic events underlying the dementia process include genetic factors in which more than 200 different genes distributed across the human genome are involved, accompanied by progressive cerebrovascular dysfunction and diverse environmental factors. Mutations in genes directly associated with the amyloid cascade (APP, PS1, PS2) are only present in less than 5% of the AD population; however, the presence of the APOE-4 allele in the apolipoprotein E (APOE) gene represents a major risk factor for more than 40% of patients with dementia (Cacabelos, 2008). There also seems to be direct correlation between APOE-4 and CYP enzymes. APOE-4 is associated with abnormal liver function due to cholesterol deposition which decreases the elaboration of CYP enzymes subsequently.

The *CYP2D6* locus is highly polymorphic with the worst responders in all genomic clusters being patients with 441122+ genotype, indicating the powerful, deleterious effect of the APOE-4/4 genotype on therapeutics in networking activity with other AD-related genes. Cholinesterase inhibitors of current use in AD are metabolized via CYP-related enzymes. These drugs can interact with many other drugs which are substrates, inhibitors or inducers of the cytochrome P-450 system; this interaction elicits liver toxicity and other adverse drug reactions. CYP2D6-related enzymes are involved in the metabolism of more than 20% of CNS drugs. The distribution of the CYP2D6 genotypes differentiates four major categories of CYP2D6-related metabolyzer types:

(a) Extensive Metabolizers (EM)(*1/*1, *1/*10)(51.61%);

(b) Intermediate Metabolizers (IM) (*1/*3, *1/*4, *1/*5, *1/*6, *1/*7, *10/*10, *4/*10, *6/*10, *7/*10) (32.26%);

(c) Poor Metabolizers (PM) (*4/*4, *5/*5) (9.03%); and

(d) Ultra-rapid Metabolizers (UM) (*1xN/*1, *1xN/*4, Dupl) (7.10%).

PMs and UMs tend to show higher transaminase activity than EMs and IMs. EMs and IMs are the best responders, and PMs and UMs are the worst responders to pharmacological treatments in AD. It seems very plausible that the pharmacogenetic response in AD depends upon the interaction of genes involved in drug metabolism and genes associated with AD pathogenesis (Cacabelos, 2008).

Most individuals (>80%) are EMs; however, remarkable interethnic differences exist in the frequency of the PM and UM phenotypes among different societies all over the world (Cacabelos and Takeda, 2006; Ozawa *et al.,* 2004; Sachse *et al.,* 1997). On average, approximately 6.28% of the world population belongs to the PM category. Europeans (7.86%), Polynesians (7.27%), and Africans (6.73%) exhibit the highest rate of PMs, whereas Orientals (0.94%) show the lowest rate. The frequency of PMs among Middle Eastern populations, Asians, and Americans is in the range of 2-3%. *CYP2D6* gene duplications are relatively infrequent among Northern Europeans, but in East Africa the frequency of alleles with duplication of *CYP2D6* is as high as 29% (Weinshilboum and Wang, 2006).

In our patient, Rivastigmine seemed to be an appropriate option as it is extensively metabolized by the kidneys and thus, bypasses the need for CYP enzymes.

Conclusion

The main problem we face today in modern day neuropsychiatry is the lack of definitive tests to prove conclusively what we discover in history and examination. The central theme of this discussion is to understand how important pharmacogenomics is in the management of a patient with dementia. Hopefully, with recent advancements, these bioassay tests would be developed in inexpensive strip tests so there be quick evaluation and assessment which will influence the mode of management for such patients.

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