MEETING REPORT

World Alzheimer Congress 2000

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Introduction

In July 2000 a unique conference was held in Washington, DC. The World Alzheimer Congress involved both scientific and layperson-caregiver organizations. The 7th International Conference on Alzheimer's Disease and Related Disorders was held from July 9 to 13, a continuing medical education endeavour titled "Bridging the Gap" was held on July 14 and 15, and "Creative Care" was held from July 15 to 18. The congress combined the 22nd conference of the Alzheimer Society of Canada, the 9th national Alzheimer's Disease Education conference and the 16th Alzheimer's Disease international conference. This communication reports some of the exciting new data presented in the scientific sessions.

Of particular note are the differences between this conference and the 6th International Conference on Alzheimer's Disease and Related Disorders, held in Amsterdam in 1998. Of the 17 plenary sessions in Amsterdam, 4 were predominantly clinical, 3 discussed the apolipoprotein E or other genes, 2 each for neuropathology and amyloid's association with Alzheimer's disease, and 1 each on prions, neuroimaging, epidemiology, the inflammatory hypothesis, the function of the presenilin protein and a new theory of Alzheimer's disease as a disease of neuronal metabolism. Hot topics in Amsterdam included defining diseases such as Lewy-body dementia, vascular cognitive impairment and frontal lobe dementia; the relative importance of tau and amyloid in the development of Alzheimer's disease; and a search for genetic factors in Alzheimer's disease.

Plenary and scientific sessions

The Washington meeting showcased the impressive progress in this field since the Amsterdam meeting. The first plenary session, chaired by Robert Katzman, presented an overview of the epidemiology of Alzheimer's disease. A particular area of emphasis, now that we have a fair understanding of its epidemiology in the developed world (of which our own Canadian Study of Health and Aging is a prominent example) is the epidemiology of Alzheimer's disease in the developing world, and comparing emigrants and their descendants to those who stayed at home. For example, the apolipoprotein E4 allele is very common in Africans but seems not to be a risk for Alzheimer's disease in this population.

The second plenary session, by Ronald Petersen, presented data on mild cognitive impairment. This condition, defined as significant memory impairment without the other impairments necessary for the diagnosis of dementia, has a high rate of conversion to Alzheimer's disease in short-term follow-up. Studies are underway to see if progression of this impairment can be halted with agents such as vitamin E or acetylcholinesterase inhibitors. Laura Fratiglioni later presented a session on predicting who will subsequently have dementia.

Not surprisingly, a lot of data was presented on the treatment of the dementias. Most of this centred on the acetylcholinesterase inhibitors such as donepezil, rivastigmine and galantamine. Many groups presented the positive effects of these agents on behaviour, function and health care costs. Serge Gauthier and Howard Feldman presented data from a trial of

donepezil in severe Alzheimer's disease and reported that it is just as effective in advanced dementia as in early dementia. Ezio Giacobini has found that cholinergic stimulation, predominantly muscarinic, promotes the secretion of soluble (or good) amyloid rather than the insoluble or disease-promoting form. Agents from other classes are in development, and both memantine (an *N*-methyl-D-aspartate antagonist) and AIT-082 (an agent that enhances neurotrophic factors) seem particularly promising.

Among the most important of the new developments reported in Washington were the data on the presenilins and γ-secretase. It is now understood that the proteins encoded by the presenilin genes are metabolized into a novel enzyme, an intramembrane cleaving protease (I-CLiP). This enzyme is likely γ-secretase, which metabolizes the amyloid precursor protein into the insoluble β-amyloid 42. Although the structure of the enzyme is not understood, inhibitors are in the earliest phases of pharmacologic development. If these agents reach clinical practice they may well prove to be disease-modifying.

Another approach to disease modification (or even prevention) has been the development of a vaccine against β-amyloid. A publication in *Nature* last year[1] reported that mice bred to produce amyloid plaques did not do so if immunized when young against β-amyloid. Immunization of older mice halted the progression of established plaques. Dale Schenk of Elan Pharmaceuticals reported that single doses of the vaccine have been given to humans safely, and repeated dosing was safe in rodents and primates. Clinical efficacy has yet to be established.

There have been no major developments in the genetics of Alzheimer's disease. Three genes (those encoding the amyloid precursor protein, presenilin 1 and 2) are recognized to cause early-onset familial Alzheimer's disease, but these genes are rarely seen. The E4 allele of apolipoprotein is a known susceptibility gene, and Howard Feldman's group from Vancouver confirmed this finding in the Canadian Study of Health and Aging database. Surprisingly, apolipoprotein E was not related to conversion from cognitive impairment to dementia. Literally dozens of genes have been suggested as other susceptibility genes, but most claims have not been supported by confirmatory studies. Data presented in Washington supports the *α2-macroglobulin* gene as the most likely to be related to Alzheimer's disease.

Judes Poirier's group from Montreal presented exciting data extending the role of apolipoprotein E from a risk factor to a possible therapeutic target. Concentrations of apolipoprotein E are decreased in the brains of patients with Alzheimer's disease, and they showed that several agents (such as probucol) can reverse this situation. Another group, from Eli Lilly, reported that the apolipoprotein E4 allele promotes secretion of β-amyloid while the E3 allele promotes secretion of soluble amyloid, so it seems that any agent that increases cerebral apolipoprotein E levels should be E3-specific.

The symptoms of dementia can be divided into 3 broad categories: cognition, function and behaviour. Most of the therapeutic research to date has concentrated on the cognitive symptoms. Although many different agents are used for the behavioural symptoms, there is little evidence for their use. Gratifyingly, randomized controlled trials are now being published in this area, in both community-dwelling and institutionalized populations. Jeffrey Cummings presented an overview of these studies, concentrating on the published trials with risperidone (which was more effective than placebo, and both as effective and safer than haloperidol in agitated nursing home residents with dementia) and an unpublished trial with olanzapine. Also of great interest is the recent finding that the cholinesterase inhibitors improve behaviour. Being able to treat cognitive and behavioural symptoms with a single agent satisfies the geriatric prescribing principle of parsimony.

At several meetings I have heard off-the-cuff remarks that patients with frontal lobe dementia have severe reactions to neuroleptic agents just as often as those suffering dementia with Lewy bodies; I have seen this clinically but have never seen any proof of this assertion. In a report from the United Kingdom, of 100 patients having frontal lobe dementia, 24 were prescribed neuroleptic agents, and 5 had severe side effects, usually parkinsonism. The authors postulate that this is because of a failure to upregulate striatal D2 receptors.

Ian McKeith presented a characteristically entertaining session on dementia with Lewy bodies. A point of contention in Amsterdam had been just what

was meant by the term "fluctuation" in the criteria for this disease. In Washington he presented data on the performance of attentional tasks by subjects with dementia with Lewy-body disease or Alzheimer's disease. The performance of those with Alzheimer's disease was stable from minute to minute; the performance of those with Lewy-body disease fluctuated greatly. He also presented results of a European randomized controlled trial of the acetylcholinesterase inhibitor rivastigmine in dementia with Lewy bodies. Rivastigmine was shown to have a significant positive effect, predominantly in behaviour as measured by the Neuropsychiatric Inventory.

Prion diseases continue to be of interest, and work presented in the plenary sessions suggest that some day we may find agents able to stop the propagation and neuroinvasion of prions. With respect to prions being both necessary and sufficient as the etiology of the transmissible encephalopathies, the jury is definitely still out.

Of note, given the interest in pesticide use in Canada (for example, Halifax has recently banned the residential use of these agents), investigators from the Maastricht study presented data suggesting that pesticide exposure increases the risk of developing dementia. Subjects with self-reported pesticide exposure had odds of 3.07 of suffering from incident cognitive dysfunction compared with those not exposed.

Upcoming conferences

The 8th International Conference on Alzheimer's Disease and Related Disorders will take place in Stockholm in 2002. It is not unreasonable to assume that by then we will have a much better understanding of the pathophysiology of Alzheimer's disease and access to new therapeutic agents with various mechanisms of actions. Other meetings where much relevant data will be presented are the International Association on Gerontology, which meets in Vancouver in the summer of 2001, and the 10th Congress of the International Psychogeriatrics Association in Nice in the fall of 2001, so keep your passport current!

Reference

1. Schenk D, Barbour R, Dunn W, Gordon G, Grajeda H, Guido T, et al. Immunization with amyloid-beta attenuates Alzheimer-disease-like pathology in the PDAPP mouse. *Nature* 1999;400:173-7.

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