Brain Imaging: Exciting Applications for AD

It is currently very difficult to detect AD in its early stages. In her presentation at the 12th Congress of the IPA, Dr. Agneta Nordberg demonstrated how current imaging techniques can be used to detect AD early.

One of the problems with the management of AD is that by the time the disease is identified, the disease process is already well underway, explained Agneta Nordberg, Professor of Clinical Neurosciences at the Karolinska Institute in Stockholm. She used the model shown in Figure 1 to illustrate her point. Patients in the earliest stages of the disease may present with mild cognitive impairment (MCI) but, by the time cognitive symptoms are noticeable enough for a diagnosis of AD, the disease may already have been active for three or more years.1 Patients may even progress further along the disease course by the time they are diagnosed.

While not all patients with MCI will go on to develop clinical AD, she explained, MCI represents prodromal, or early AD for many patients.

Dr. Nordberg presented statistics from an American epidemiologic study2 showing that many prevalent cases of AD (approximately half) fall into the mild category (usually defined as a mini-mental state examination [MMSE] of at least 18 out of 30), approximately one third are classified as moderate (MMSE 10 to 17 out of 30) and approximately one fifth as severe (MMSE 9 or lower; Figure 2).

Because of the difficulty identifying patients with prodromal AD, it is not currently known what percentage of the total AD population these patients would represent if they were included in such an analysis.

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2 American Epidemiologic Study.
However, as Dr. Nordberg discussed, there is reason to be optimistic about early identification. Led by researchers like Dr. Nordberg herself, medical science has identified several brain abnormalities that are present in patients with AD—even in its earlier stages—that are detectable by current brain imaging techniques.

AD, she explained, has long been associated with the presence of amyloid plaques in the brain. In fact, it was Alois Alzheimer himself who described these plaques in a post-mortem evaluation of one of his patients, Auguste D. The actual compound found in plaques, Dr. Nordberg described, is beta-amyloid. She discussed how the gradual accumulation of this compound has been found to be a key characteristic of AD, as outlined by Braak and Braak in 1991. This accumulation and proliferation is illustrated in Figure 3.

Modern science has developed methods of identifying this and other substances implicated in AD: positron emission transaxial tomography (PET), single photon emission computerized tomography (SPECT) and magnetic resonance imaging (MRI) have all been used to document amyloid depositions in AD patients.

As Dr. Nordberg discussed, genetic science has identified several mutations that cause AD through abnormalities in the processing of the amyloid precursor protein (APP). By examining early changes in these patients, researchers have identified several early warning signs for impending AD.

Dr. Nordberg and colleagues examined patients who carry a specific genetic mutation known to cause AD. By using PET scanning, the group was able to discern significant changes in brain glucose metabolism 10 to 15 years before the estimated onset of disease. Furthermore, Dr. Nordberg presented serial PET scans in a patient with a particular genetic abnormality causing AD—one set of scans from a period in which there were no symptoms and another set of scans 40 months later, when this patient had developed cognitive symptoms of AD (Figure 4). The blue sections are the areas with impaired glucose metabolism. While these deficits were most pronounced in the second set of scans, they were already clearly present in the earlier scans during the asymptomatic period. Dr. Nordberg also showed images from other researchers, who found that changes in glucose metabolism that match the brain areas affected in patients with clinical AD have been detected in patients with MCI who carry the ApoE E4 allele. These early deficits in glucose metabolism, she explained, highlight the importance of detecting AD at an early, pre-symptomatic stage.

Another focus of brain-imaging research is the investigation of the binding of amyloid itself, once restricted to autopsy investigations. One of the most exciting developments in this field, Dr. Nordberg explained, has been the validation of a tracing compound for use in PET scanning. This compound, known as Pittsburgh Compound-B (PIB), has been found to provide quantitative information on amyl-
When tested in AD patients compared to controls, the compound was found to have marked retention in cortical areas known to be associated with large amounts of amyloid deposit (Figure 5).

Dr. Nordberg also showed how researchers using PET scanning techniques are able to measure the activity of important brain enzymes in AD (e.g., acetylcholinesterase [AChE]). In the context of the most common current treatment strategies for AD, which address cholinergic deficits in AD, these PET studies are particularly enlightening.

A 2000 study, for example, showed that levels of AChE, as measured by PET, correlate with MMSE scores in patients with AD. She also indicated that, while AChE levels decrease over the course of disease, there can still be significant benefit derived from inhibiting whatever AChE remains.
Dr. Nordberg also explained that PET scanning is able to detect the effects of cholinesterase inhibitors using novel markers. She described how AD is associated with a consistent loss of nicotinic AChE receptors (nAChRs),9 which are detectable early in the course of the disease by PET. Cholinesterase-inhibitor therapy, she explained, has been shown to improve nAChRs in PET studies.10 This goes beyond the explanation that cholinesterase inhibition simply increases available acetylcholine in the brain.

There are also other possible mechanisms of benefit for these agents, Dr. Nordberg explained. In an animal study, donepezil was shown to protect cortical neurons against neurotoxicity and prevent apoptotic neuronal death.11 Other investigators have shown that donepezil has beneficial effects on the processing and trafficking of key proteins involved in the disease process (e.g., APP).12,13 Anti-inflammatory processes, she concluded, may also be part of the cholinesterase inhibitors’ therapeutic effects.

Dr. Nordberg concluded by summarizing the key points of her presentation. She explained that the ability to detect changes consistent with AD before the development of symptomatic disease represents an important breakthrough in the overall management of AD. Identifying patients before symptoms begin, she said, represents an opportunity to distinguish between patients most at risk of progressing to AD and those who likely will not. This, in turn, can provide the rationale for initiating therapy at an early stage to delay or perhaps prevent the emergence of symptoms. Dr. Nordberg said she looks forward to future research in this area. “If patients with MCI show amyloid deposition at that stage, that will be very important,” she said. “We should be able to start therapy as early as possible.”

Dr. Nordberg’s presentation not only showed how the emerging understanding of the biology of AD presents many opportunities for the development of novel AD therapies, it also showed that today’s therapies (e.g., cholinesterase inhibitors) have the ability to positively impact AD through a variety of mechanisms, which have significance from the earliest stages of the disease.

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