

# Interview

## Imaging in Alzheimer's Disease



### Professor Nordberg speaks to Cara Sutton, Commissioning Editor

Professor Nordberg completed her predoctoral training at Uppsala University, Uppsala, Sweden, and then commenced a post-doctoral position in the Department of Pharmacology, Uppsala University, where she was appointed Associate Professor in 1979 and Senior Lecturer in 1982. In 1984 she obtained her license to practice medicine and in 1992 became a specialist in geriatric medicine. In 1992 she was also appointed as a professor at Karolinska Institutet, Stockholm, Sweden. Professor Nordberg has trained 21 PhD students to their thesis and hosted 22 foreign post-docs in her laboratory. She is presently supervisor of five PhD students and four post-docs. Professor Nordberg has been awarded numerous awards including The Luigi Amaducci award in Alzheimer's disease in 2001, the Lifetime Achievement Award at the ICAD conference in 2002, Imaging award of Alzheimer association in 2004, and the Alois Alzheimer award in 2006, and has published more than 390 scientific publications and reviews. She is also the Vice-Chairmen of the Wennergren Society and a member of the Nobel Assembly.



**Agneta Nordberg**

*Karolinska Institutet, Department of Neurobiology, Care Sciences & Society, Alzheimer Neurobiology Center, Karolinska University Hospital Huddinge, Department of Geriatric Medicine, Novum, 141 86 Stockholm, Sweden  
Agneta.k.nordberg@ki.se*

■ **Your background is in pharmacology, what made you decide to move into medicine?**

My PhD research was on pharmacology and dealt with the turnover of the neurotransmitter acetylcholine in the mouse brain. Once I had finished my medical studies I became a specialist in geriatric medicine. My research now has a translational approach and ranges from basic experimental research in cell lines, human embryonic stem cells and transgenic animal models to clinical imaging and drug trials in Alzheimer's patients.

■ **When did you first become interested in Alzheimer's disease?**

The Nobel laureate in medicine, Professor Arvid Carlsson, initiated work on Alzheimer's disease in Sweden with studies of neurotransmitter and enzymes in postmortem brain tissue from Alzheimer's patients. There were 17 different laboratories involved in the research and my laboratory was responsible for the analysis of activity of the enzyme choline acetyltransferase, which is markedly reduced in activity in the brains of Alzheimer's patients.

I found it fascinating that there were changes in the brain of Alzheimer's patients and I felt we had to image these changes within living patients, rather than in dead

tissues. As a clinician, I am aware that a patient can be diagnosed with a disease 20 years before they die from that disease and imaging the tissue once the patient is dead is like studying a desert; almost everything has disappeared.

However, when you image someone who is in the very early stages of disease progression, who has only recently been diagnosed, most of the brain function is quite normal. Imaging in living patients has been a step forward since pathological processes can be detected very early in progression of the disease.

■ **Your research group performed the first PET scan of an amyloid plaque in a living patient: what led to this groundbreaking study?**

The main histopathological features of Alzheimer's disease are the amyloid plaques and the neurofibrillary tangles. The detection of plaques was also the reason why autopsy studies were performed since this was the final confirmation of that the patient had Alzheimer's disease.

We had been discussing in the group whether we could image this plaque and if it was possible to study the plaque in the living patient. At this time Professor Bengt Långström, who was the head of the PET center in Uppsala and also an organic chemist, had met Willam Klunk



and Chester Mattis, who was based at the University of Pittsburgh, at a conference and discussed the possibility of using some of the compounds they had been studying in test tubes. Klunk came to Sweden and we discussed the PET project planned to be performed in Alzheimer's patients. When the studies started one of the compounds they had developed was chosen to inject into the patient to see if it could be taken up by the brain. At the Uppsala PET center the compound was named PIB.

The patient we selected was young, she was 56 years old, and had volunteered for the study. She had been diagnosed a couple of years previously and was at an early stage of the disease. The patient received an intravenous injection of PIB. Once it was injected it was quite clear that the compound stayed in the brain much longer than in the healthy control and we saw a lot of binding in the brain. It was clear we were visualizing the amyloid plaque for the first time in a living patient.

■ **How has the imaging of the amyloid plaque impacted our understanding of Alzheimer's disease?**

The first study we carried out was in spring 2002, with 16 Alzheimer's patients and nine healthy controls. This study was published in 2004 [1] and described the high binding of PIB in the brains of the Alzheimer's patients, reflecting the binding to fibrillar  $\beta$ -amyloid.

We were surprised at how much binding occurred in areas of the brain that were not expected to be impaired by the disease; for example, there was a high PIB binding in the frontal cortex. Measuring the function of the brain by measuring the glucose metabolism had shown regional deficits in other regions such as the parietal cortex and we were therefore surprised to discover a somewhat different distribution of the amount of amyloid in the brain.

Next, we imaged patients who had mild cognitive impairment [2]. These patients did not fulfill the criteria of having dementia or Alzheimer's disease, but already exhibited memory problems. When we followed up these patients a couple of years later we found that those who had developed Alzheimer's disease

had shown very high levels of amyloid (high PIB binding) in the brain when they were initially scanned as a patient with mild cognitive impairment. Those patients who had shown low amyloid levels (low PIB binding) had not developed Alzheimer's disease. We therefore demonstrated that, even in patients with mild cognitive impairment and prior to the diagnosis of Alzheimer's disease, elevated levels of amyloid can already be seen in the brain and these patients very likely will progress to Alzheimer's disease.

■ **Is there an accumulation of amyloid in the brain throughout the progression of the disease?**

When we rescanned the initial cohort of patients imaged with PIB again after 2 years [3] we noticed that the levels of amyloid were high, but unchanged. The patients had continued to decline in terms of cognitive performance and they also showed a continuous decline in glucose metabolism in the brain at 2 years follow-up. Nine of the initial 16 patients (some of the others had died and some were unable to participate as they had developed advanced Alzheimer's) were followed-up 5 years after the first scan [4]. We found stable values of amyloid in the brains of these nine patients; again, the levels were high but unchanged, while there was further decrease in cognition and glucose metabolism.

We also investigated some patients who had mild cognitive impairment. These patients were rescanned after 3 years [4] and we observed an increase in the amount of amyloid in the brain. Combining the data from both studies and similar studies performed by other research groups, it appears that amyloid is exhibited in the brain very early in the disease progression and does not continue to accumulate during clinical disease progression [3-5].

We are now investigating subjects who are at high risk of developing Alzheimer's disease since they belong to families with known mutations. Those who carry mutations for the disease may be normal in their cognitive abilities, but may already have amyloid in the brain. These studies will provide further understanding of the time course of amyloid deposition in Alzheimer's disease brains.



■ The individual who first received a PET scan for amyloid plaque imaging was monitored for a number of years. How did the progression of the disease in this individual assist in your understanding of the disease?

The progression of Alzheimer's disease is often different in different patients. Generally in a younger patient, such as this individual, the disease is more aggressive. However, progression can be affected by other factors; for example, if the patient is receiving treatment the progression will be different as the patient is responding to treatment.

However, the progression of the disease in this individual and the group of monitored patients highlighted that patients were developing amyloid early on and when they were followed up at 2 years and then at 5 years there was a very significant decline in cognition function and glucose metabolism, but the amount of amyloid was quite stable.

The results from the first patient specifically allowed us to show how glucose metabolism became more and more impaired following the progression of the disease. We were first able to measure her glucose metabolism when she was 54 and were then able to monitor this for 7 years. This monitoring allowed us to see there was a year-by-year decrease in glucose metabolism [6].

■ Once the individual had passed away your group carried out further analysis of the individual's brain, did this postmortem investigation provide any additional information that could not be obtained from a living patient?

The next of kin gave permission for research studies to be performed on the brain tissue after the patient's death. This made it possible to measure the amount of different forms of amyloid in the autopsy brain tissue and compare it with the earlier PET imaged levels of amyloid in brain with PIB. The autopsy brain studies also revealed how different pathological changes were related to each other and shared significant correlation between the amount of amyloid, the glucose metabolism and the inflammatory process.

We also measured inflammatory changes and observed that there was a very good correlation between activated astrocytes, measured with GFAP at autopsy and amyloid [6]. It appears that there are probably different types of inflammatory changes early and late in the course of the disease: this will stimulate further investigation.

We also made the interesting observation that the inflammatory process affects nicotinic receptors; these receptors are known to be decreased in Alzheimer's disease and are responsible for cognitive performance. We thus observed that regions with high amyloid load showed greater loss of nicotinic receptors [6]. This new observation may be of importance for the development of anti-amyloid drugs.

These types of studies are very important in order to compare *in vivo* imaging while the patient is alive and the changes in the brain of the patient after death and evaluate the clinical significance of molecular imaging.

■ Your work on amyloid plaque imaging has highlighted a number of neurological changes that occur in patients suffering from Alzheimer's disease. Of these changes, which do you feel are the most interesting & important?

It is important to further understand the time course of the deposition of different forms of amyloid in the brain, which allows us to predict those who are at risk of developing Alzheimer's disease. If a patient with memory problems show high levels of amyloid in the brain this indicates that they have a high risk of developing Alzheimer's disease in the future.

It is important to understand the inflammatory changes in the brain, and the next step, at least for us, is to understand the time course of inflammatory changes in comparison to amyloid development.

We have recently performed PET studies with <sup>11</sup>C-deprenyl in patients with Alzheimer's disease as mild cognitive impairment and healthy controls in order to measure astrocytosis. We can conclude that there are high levels of astrocytes in the brains of patients with mild cognitive impairment [CARTER *ET AL.*, MANUSCRIPT



SUBMITTED]. The results may even indicate that astrocytosis is occurring before amyloid levels increase. These results may also provide us with the opportunity to understand the relationship between amyloid deposition and nicotinic receptors.

New diagnostic criteria have been presented both in Europe and US and the earliest biomarkers to be used for detection of Alzheimer's disease have been suggested to be amyloid imaging and cerebrospinal fluid biomarkers. I am pleased that our observations have rapidly been incorporated into clinical practice.

■ **Your research has made it possible to detect Alzheimer's disease at an earlier stage; how do you envisage this will improve the therapeutic outcome of the disease?** There is presently a large amount of discussion regarding the failures in development of new strategies to tackle Alzheimer's disease. One explanation may be that expectations are too high; a second explanation might be that the treatment starts too late in the course of the disease. When patients have memory impairment changes that have been occurring in the brain for a while, it might be difficult to restore the brain and stop these processes.

Therefore, if biomarkers can be used to detect groups of patients that are at high risk of developing Alzheimer's disease, those patients could be selected and effectively treated. This would have a great impact on disease development and the efficacy of drug therapy.

### Financial & competing interests disclosure

*The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*

*No writing assistance was utilized in the production of this manuscript.*

### References

- 1 Klunk WE, Engler H, Nordberg A *et al.* Imaging brain amyloid in Alzheimer's disease using the novel PET tracer, PIB. *Ann. Neurol.* 55, 306–319 (2004).
- 2 Forsberg A, Engler H, Almkvist O *et al.* PET imaging of amyloid deposition in patients with mild cognitive impairment. *Neurobiol. Aging* 29, 1456–1465 (2008).
- 3 Engler H, Forsberg A, Almkvist O *et al.* Two-year follow-up for amyloid deposition in patients with Alzheimer's disease. *Brain* 129, 2856–2866 (2006).
- 4 Kadir A, Almkvist O, Forsberg A *et al.* Dynamic changes in PET amyloid and FDG imaging at different stages of Alzheimer's disease. *Neurobiol. Aging*. DOI:10.1016/j.neurobiolaging.2010.06.015 (2010) (Epub ahead of print).
- 5 Nordberg A, Rinne J, Kadir A, Långström B. The use of PET in Alzheimer's disease. *Nature Rev. Neurol.* 6, 78–87 (2010).
- 6 Kadir A, Marutle A, Gonzalez D *et al.* Positron emission tomography imaging and clinical progression in relation to pathology in the first Pittsburgh Compound B positron emission tomography patient with Alzheimer's disease. *Brain* 134, 301–317 (2011).