

# Physiological Markers for Alzheimer's Disease

*Martin Kurtev*

---

Alzheimer's disease is the most common cause of intellectual decline associated with aging. This disorder involves the deterioration of mental functions resulting from changes in brain tissue, such as the shrinkage of certain brain structures. There is no known definitive cure for Alzheimer's disease, and treatment is mostly aimed at relief of symptoms. The high emotional and medical costs of caring for a patient with Alzheimer's, along with the prevalence of this disease, make its early detection extremely important. Early detection helps the patient and his/her family adjust to living with the disease and plan for future treatment. Current studies have shown that there are subtle physiological clues that might signal the beginning of Alzheimer's disease. Olfactory deficits and certain defects in the skin cells of Alzheimer's patients are considered two of the strongest indicators of the onset of the disease and may prove to be effective diagnostic tools in the near future.

Diagnosing Alzheimer's disease still poses a serious challenge to the medical profession, and it may take several years of testing before doctors can reach a decision on a patient's condition. A clinical evaluation of Alzheimer's disease must exclude all other neurological, psychiatric, and medical disorders that may be causing the mental decline<sup>1</sup>. The current procedure for detecting the onset of Alzheimer's disease begins with a detailed assessment of the patient's and his/her family's medical history. Physical examinations and laboratory tests are performed periodically for several months or even years. Brain scans using new imaging techniques, such as computed tomography (CT) scans and magnetic resonance imaging (MRI), are used to rule out other forms of dementia like tumors and strokes. The patient also undergoes neuropsychological testing in which he/she completes memory, language, arithmetic, and other exercises related to brain functioning. The definitive diagnosis of Alzheimer's disease, however, is only possible during an autopsy when the characteristic neural plaques and fibrillary tangles can be detected. The possible alternative solution to the current diagnostic problems is the presence of a biological marker, like an abnormal protein or tissue, that is external to the brain. These new tests offer hope for not only an early, fast, and easy detection of the disease, but also for finding an actual cure.

A recent study published in the *American Journal of Psychiatry* discussed the possibility of detecting the development of Alzheimer's disease through the use of an olfactory test<sup>2</sup>. The study was based on the observation that patients with Alzheimer's disease have consistently demonstrated olfactory identification deficits in relation to a control group. Dr. D. P. Devanand and colleagues at Columbia University gave a multiple-choice aroma test to 90 patients who were suffering from memory problems and mild cognitive impairments. The patients were asked to identify 40 different smells, such as those of peanuts and menthol. A follow-up study monitored 77 of the patients. Forty-seven of these patients had low olfaction scores, and 19 of them (40%) developed Alzheimer's disease. No patients of the 30 with high olfaction scores developed the disease. The percentage of people who performed poorly on the test and developed Alzheimer's is significantly higher than the occurrence of the ailment in the general population, which is one out of 10 people (10%) over 65 years of age.<sup>3</sup>

During the follow-up study, one of the challenges Devanand's team faced was conclusively diagnosing participants with Alzheimer's disease. The researchers diagnosed patients for dementia on the basis of DSM-IV criteria. The diagnosis of possible or probable Alzheimer's disease was made on the basis of criteria from the National Institute of Neurological and Communicative Disorders and Stroke (NINDS) and the Alzheimer's Disease and Related Disorders Association. Making a diagnosis based on the established guidelines, however, does not guarantee with certainty that any of the participants will actually develop Alzheimer's disease.

In their attempt to better correlate the olfaction scores with the development of the disease, the researchers divided the patients into two categories—those who were aware of their olfactory deficit and those who were not. They discovered that the participants who were not aware of their olfactory deficiency were more likely to develop Alzheimer's disease than the participants who were aware of their olfactory shortcomings. Of the 47 people with olfactory deficits, 37 were not aware that they had any problems, and 16 of these patients (43%) developed Alzheimer's. More importantly, low olfaction scores accompanied by subjective reports of no problems smelling were present in 16 of the total 19 (84%) patients

who met the criteria for Alzheimer's disease in the follow-up study. These data and statistical analyses showed that low olfaction scores and being unaware of olfaction deficits are strong indicators of the onset of Alzheimer's disease. The researchers also used two other statistical indicators, the Cox proportional hazards model and the Mini-Mental State score, to show that low olfaction plus lack of awareness was a significant predictor of Alzheimer's disease.

The correlation between being unaware of olfactory problems and the development of Alzheimer's disease is important because it identifies a possible area of brain research that may bring us closer to a cure. Even though the sense of smell often declines with age, the loss of normal olfaction may also result from the shrinking of certain brain areas due to Alzheimer's disease. Obviously, a poor sense of smell by itself is not a predictor of the illness, but experiments have shown that it might be related to the disease. Devanand's team proposed that awareness of losing the sense of smell may be localized at the medial-temporal lobe structures, which are known to be affected in early Alzheimer's disease and are associated with olfactory detection deficits. This could explain why low olfaction scores, accompanied by a lack of awareness of the olfactory deficits, strongly predicted Alzheimer's disease.

Skin is another area in which scientists are looking for possible clues that may indicate the onset of Alzheimer's disease. Scientists at NINDS in Bethesda, Maryland, and the Burke Medical Research Institute at Cornell Medical College in White Plains, New York, have discovered physiological differences in the skin cells of those with Alzheimer's disease, a finding that could lead to a standard battery of skin tests for diagnosing the disease.<sup>1</sup> The diagnostic tests are based on the group's discovery that skin cells in Alzheimer's disease patients have defects that upset the cells' ability to properly regulate critical potassium and calcium ions. The presence of these cell defects in the skin suggests that Alzheimer's disease results from physiological changes throughout the body. Dementia may be the first noticeable effect of these changes as the defects affect cells in the brain.

The principal investigator, Daniel L. Alkon, and his colleagues report that, of the 50 people tested, skin cells from 15 patients clinically

diagnosed with Alzheimer's disease were missing a certain type of microscopic tunnel that governs the flow of potassium in and out of the cells. Nearly all of the age-matched members of the control group, and many of the younger ones, had functional potassium channels of this type. When this test and three others were done together, the results were 100 percent accurate in separating those with clinically diagnosed Alzheimer's disease from those without the disease.

The NINDS scientists made their discoveries through a unique line of scientific reasoning. Most scientists who study Alzheimer's disease concentrate on the fibrillary tangles and amyloid plaques prevalent in the brain tissue of those with the disease. Alkon and his colleagues, on the other hand, are memory researchers—they study how the flow of ions and the interactions of neural signals allow the brain to remember. They originally intended only to study memory loss in Alzheimer's disease, but instead found a clinical test for the disease. Since difficulty in forming memories is one of the earliest and most common effects of Alzheimer's disease, they began with the idea that the common denominator for Alzheimer's disease patients might be a defect in the cellular processes of memory. Alkon theorized that such changes in cell physiology might be present throughout the body.

A disruption in the flow of ions across a cell's membrane can have detrimental effects on the cell's overall function, and the adverse condition is likely to affect different physiological processes. The flow of potassium is especially critical in cells responsible for memory formation. The scientists then continued to find two other defects that affect the cells' supply of calcium, a critical ion for the body. The researchers also detected the same cell defects in nerve cells of the olfactory system,

which is an indicator that the abnormalities are also present in other brain cells.

The discovery must be substantiated by further research and a larger experimental group. Also, it is necessary that the results from any physiological test be confirmed later through an autopsy of the patient to prove with certainty the presence of the disease. The study lends support to the already established notion that Alzheimer's disease is present in different parts of the body, such as the olfactory system. Therefore, developing a simple and easy physiological test to detect the disease may soon become a reality. Such a test would be able to detect the disease in its early stages and therefore allow existing methods of patient care to be applied more effectively. By being aware of the presence of the disease before the symptoms take over the patient's body, the patient and his/her family will be better prepared to deal with the emotional hardships that come with the inevitable loss of memory. The studies do not explicitly state how the findings can be used toward the development of a cure for the disease, but the articles have identified two body systems that are more accessible and easier to manipulate than the brain itself.

The studies discussed here offer hope that physicians will ultimately be able to more accurately and easily predict whether a person is at risk for getting Alzheimer's disease, and further studies will hopefully point scientists toward the underlying cause of this disorder. An early diagnosis based on an olfactory or skin test would not only translate into saving millions of dollars in medical costs, but would also allow the patient and his/her family to make a better decision about the course of treatment. Furthermore, as effective drugs for Alzheimer's are discovered, early detection will be of crucial importance to the patient's successful recovery. ■

## References

1. Etcheberrigaray R, Ito E, Oka K, Tofel-Grehl B, et al. Potassium channel dysfunction in fibroblasts identifies patients with Alzheimer disease. *Proceedings of the National Academy of Sciences*. 1993; 90: 8209–8213.
2. Devanand D P, Michaels-Marston K S, Liu X, et al. Olfactory deficits in patients with mild cognitive impairment predict Alzheimer's disease at follow-up. *American Journal of Psychiatry*. 2000; 157: 1399–1405.
3. Alzheimer's Association. *Alzheimer's Disease Statistics* (1994), Chicago, IL.

# What's missing from MIT's Undergraduate Research Journal?



**YOU ARE.**

NEWS • FEATURES • REPORTS

Submissions due September 2002 • [murj@mit.edu](mailto:murj@mit.edu)