



Olfactory Testing in the Diagnosis of AD and Other Neuro-Degenerative Disorders

Olfactory testing can be a convenient and relatively inexpensive method to gather supporting information for the diagnosis of neuro-degenerative diseases.

By Ronald Devere, MD

In the last 15 years many articles have been published on the subject of olfactory testing and its relationship to many neuro-degenerative disorders. These include cognitive decline in the normal elderly population, prediction of amnesic mild cognitive impairment in the normal elderly population, and prediction of amnesic mild cognitive impairment and the development of Alzheimer's disease. This

also includes the diagnosis of classic Parkinson's disease versus Parkinson's-plus syndromes, such as multiple system atrophy, cortical basal degeneration, progressive supranuclear palsy, and vascular Parkinson's disease. It is also predictive of development of Parkinson's disease and Parkinson's-plus syndromes in people with rapid eye movement sleep behavioral disorder (RBD).

In 2008, I wrote a two-part article in this journal on taste and smell disorders in clinical neurology¹ that discussed diagnosis, treatment, prognosis and morbidity of disorders a neurologist would encounter in clinical practice. However, I did not discuss the value of olfactory testing as a diagnostic tool for certain neurological disorders. Allow me to clarify that I have no business interest and receive no reimbursement from the companies that sell smell-testing products. I am currently on the speakers' panel for Forest Pharmaceuticals (Namenda) and very recently joined the speakers' panel of Accera Pharmaceuticals (Axona).

Two of the most reliable and sensitive olfactory tests are the University of Pennsylvania Smell Identification Test (UPSIT) and the Brief Smell Identification Test (B-SIT). They are used most frequently here and abroad in published studies and in physician offices. They are available in different languages and are culturally sensitive. The UPSIT is most sensitive and is made up of 40 smell samples that are standardized for age and gender. The B-SIT is made up of 12 smell samples and standardized for age only. Both tests consist of pages that have a microcapsule strip containing an odor. The patient being tested scratches the surface of the strip to release the odor and sniffs the page. The patient has to identify the correct smell from four choices; guessing is permitted. The B-SIT is reasonable to start with, but if the score is borderline, then follow-up with the UPSIT is necessary for more detailed olfactory information. Many published papers have used only one or the other exclusively in their studies.

These tests are very easy to administer and are inexpensive to purchase. The B-SIT costs \$14.95 each and the UPSIT is \$28.95 each. The scoring manual and scoring cards are purchased separately, but only need to be purchased one time. They can be purchased from US-based Sensonics (sensonics.com). There is a billing code for doing these tests in the office (92512). I charge \$50 for the smell test whether I use the B-sit or UPSIT. I charge \$50 for taste testing and use the same code. Another test available in Europe called Sniffin Sticks[®] combines odor identification and odor threshold in one test. These sticks are pen-like wands that have the odor embedded in one end. Their advantage is that they can be used repeatedly.

Olfactory Testing and Cognitive Function in the Normal Aging Population

Graves, et al. in 1999² did a two-year study to determine whether olfactory status predicts cognitive decline. Normal elderly people (n=1,836) from a Japanese-American community were given a baseline cognitive screening test and the equivalent of the B-SIT olfactory identification test. Two years later 1,604 of the original 1,836 subjects were re-

screened. In addition, 69 percent of these 1,604 participants also had APOE genetic typing. The study showed that individuals who were anosmic at baseline had twice the risk of cognitive decline over two years compared to individuals with normal smell. If the anosmic group had also an APOE4 allele, the risk of cognitive decline was five times greater than in individuals with a normal smell and no APOE4 allele. Individuals whose smell loss was only very mild to moderate and who had an APOE4 allele had less risk than anosmics but at least two to three times the risk of cognitive decline of the individuals with normal smell.

Swan, et al. in 2002³ studied 359 normal individuals with the B-SIT and a variety of cognitive measures of verbal learning, memory, executive function, and global cognitive function. Impaired olfaction on the B-SIT was related to a greater five-year decline in verbal memory only after baseline adjustments were made for age, education, cognitive performance, gender, and history of a smell disorder. They did not find a correlation with APOE status.

That same year, Royal, et al. reported a study of 173 normal elderly who had baseline B-SIT and cognitive testing followed by repeat testing three years later. Twenty-five percent of the participants had total anosmia, and 21 percent had normal smell at baseline. Their studies showed that the individuals with anosmia had more short-term memory loss and overall faster rate of cognitive decline compared to those with normal smell.

Wilson, et al. in 2006⁵ studied 481 normal, older people with baseline B-SIT and various cognitive tests annually for up to three years. After adjustments for age, sex, and education, a B-SIT score 6 out of 12, which is less than the tenth percentile, was associated with lower function of each cognitive domain studied at baseline as compared to a higher B-SIT score of 11 out of 12 or ninetieth percentile. The lower odor score at baseline correlated strongly with twice as rapid decline in perceptual speed and episodic memory. The semantic and working memory, as well as visual spatial ability, were not affected.

The following year, Wilson, et al.,⁶ studied 589 cognitively normal elderly with no smell complaints, administering baseline B-SIT and cognitive tests with a five-year follow-up. They also did yearly cognitive testing. Thirty percent of studied individuals developed amnesic mild cognitive impairment. Those that had a baseline B-SIT score of 8 out of 12 or less (twenty-fifth percentile) had a greater than 50 percent risk of developing amnesic mild cognitive impairment plus a more rapid decline in episodic and semantic memory and perceptual speed compared to a B-SIT score of 11 out of 12 (seventy-fifth percentile).

What does all this information about smell testing and cogni-

tive decline mean for the practicing clinical neurologist? Certainly for research purposes olfactory testing in the normal population may complement other studies, such as amyloid load measurement with Pittsburgh Compound B or other agents, fMRI, and spinal fluid analysis for Beta amyloid and tau ratios, in trying to find the best marker or combination of biomarkers to detect or predict early Alzheimer's and related disorders in the normal population.

However, smell testing has a place in the neurologist's office or clinic, particularly for relatives of known Alzheimer's patients who come for a neurology consultation to determine their own risk of getting the disease. In these cases, a thorough cognitive and neurological examination, with pertinent history about any smell or taste issues, should be discussed. After a discussion with the patient about smell testing and cognitive decline in general, smell testing should be offered to patients who are 60 years of age or older unless there is a preexisting smell and taste complaint or the patient refuses the testing. Patients in general, but especially those who test as mildly to moderately smell impaired, should be counseled about the value of physical exercise and increasing brain activities along with aggressive treatment of high blood pressure, diabetes, and high cholesterol. I encourage my patients to seek further evaluation if they detect any changes in their memory or if others recognize a problem. These patients should be followed every six-months with repeat office cognitive testing and detailed history of Activities of Daily Living from other family members. Even though smell testing in the presence of a positive APOE4 test increases the probability of cognitive decline, I do not believe APOE4 testing is indicated. In my opinion, an abnormal genetic test result is much more likely to create more fear and anxiety in the relatives of patients with Alzheimer's disease than is an abnormal smell test. This test is also expensive and not covered by insurance.

What is the pathological relationship between olfactory impairment and cognitive decline in the normal elderly population? Wilson, et al. in 2007⁷ studied a group of the normal elderly population who agreed to have their smell tested initially and an autopsy of their brain when they died. They enrolled 129 patients in this study with an average follow-up of 1.2 years and an average age at death of 87 years. In 12 percent of these individuals (16) every two-point drop in smell testing score resulted in increased plaques and tangles in the medial temporal lobe. This study strongly suggested that poor smell test scores in the normal elderly population, and who have no smell complaints, are in part due to Alzheimer's disease-like pathology in the entorhinal cortex and hippocampus, which are both important parts of the brain necessary to identify smell.

Impaired Smell in Amnesic Mild Cognitive Impairment and Risk of Developing AD

It is well accepted that AMCI in many subjects is the transient status between normal memory and aging and Alzheimer's disease. Each year five to 32 percent of subjects with AMCI developed Alzheimer's disease or other dementias.

Devanand, et al. in 2001⁸ studied 90 patients with AMCI and 45 cognitively normal controls, and followed them at six-month intervals up to two years to see who developed Alzheimer's disease. They all received olfactory testing using the UPSIT test. The mean baseline UPSIT score in the AMCI group was 31 out of 40, versus 35 out of 40 in controls. As usual, age, mini mental testing results, years of education, smoking history, and duration of cognitive impairment were all accounted for. In the 77 AMCI cases, 19 out of 47 who had low olfactory scores (defined as 34 or less), developed Alzheimer's disease versus none of the 30 with high olfactory scores (defined as 35 or greater). Sixteen out of 64 patients who reported no smell problem compared to three out of 13 who reported smell problems developed Alzheimer's.

The study concluded that an olfactory score equal to or less than 34 out of 40 in AMCI cases leads to a 100 percent sensitivity and 46 percent specificity in predicting Alzheimer's disease. However, if the olfactory score is equal to or less than 34 out of 40 and there is a lack of awareness of the olfactory deficit, this leads to 75 percent sensitivity and 64 percent specificity in predicting Alzheimer's disease. An olfactory score of 30 or less out of 40 and lack of awareness of smell deficit leads to 40 percent sensitivity and 82 percent specificity in predicting Alzheimer's disease. The authors discussed that lack of awareness of smell loss can be possibly considered to be anosognosia. The authors state that the parietal lobe is thought to primarily be involved in this phenomenon, but argue that Anton's syndrome, which is lack of awareness of visual field loss due to visual association cortex damage, is very close to the visual cortex. The brain center for awareness of sense of smell has not been well localized but may be in the medial temporal lobe structures that are known to be affected by Alzheimer's disease. This could explain possibly why low olfactory score and lack of awareness of the olfactory deficit in patients with AMCI strongly predict Alzheimer's disease.

Three years later Devanand, et al.,⁹ presented a poster at a clinical psychology meeting. They studied 150 AMCI cases with minimal cognitive deficits. These 150 cases were evaluated every six months as were 62 matched controls. All subjects were followed for 36 months. Thirty-six patients of the caseload converted to probable Alzheimer's. The UPSIT test was administered at baseline to these cases. The baseline

UPSIT score of the AMCI patients was a mean of 31 out of 40, compared to controls whose score was 35 out of 40. The mean UPSIT score in the AMCI patients who converted to Alzheimer's was 26 out of 40 compared to the AMCI non-converters who had a mean score of 31 out of 40. For diagnostic prediction, as in the previous 2001 study, there was a strong sensitivity and specificity for the UPSIT score in the 27 to 32 range.

What is the role of smell testing in helping to determine which patients with AMCI will develop Alzheimer's disease? Over the last 10 years many published papers have discussed various biomarkers and their roles in predicting Alzheimer's disease from AMCI. These biomarkers have included cerebral spinal fluid beta amyloid/tau ratios, imaging that includes volumetric MRI of the hippocampus, PET and SPECT brain scans, and a battery of neuropsychological testing. Fleisher, et al. in 2008¹⁰ showed that ventricular and hippocampal volumes on the MRI alone in 129 amnesic mild cognitive cases was 60 percent predictive of future Alzheimer's disease. This prediction increased to 78 percent when strong clinical variables were added, such as impairment in the delayed word list and recall score of delayed paragraph recall and the score on the Alzheimer's disease assessment cognitive subscale.

Ewers, et al. in 2007¹¹ studied the cerebral spinal fluid phosphorylated tau in a multi-center study as a predictor of AMCI conversion to Alzheimer's. The sensitivity of the test ranged from 65 to 100 percent and specificity from 67 to 78 percent among different centers.

The previous year, Hansson, et al.,¹² studied 137 patients with mild cognitive impairment and studied the cerebral spinal fluid for beta amyloid 42, total tau, and phosphorylated tau, and followed these cases for four to six years. Forty-two percent of the cases developed Alzheimer's disease, 15 percent developed other dementias, and 41 percent remained cognitively stable. The combination of the cerebral spinal fluid T-tau and AB42 at baseline yielded 95 percent sensitivity and 83 percent specificity for detection of incipient Alzheimer's in those cases with AMCI. Adding phosphorylated tau to T-tau and AB42 did not add any further specificity.

Yuan, et al. in 2008¹³ reviewed the literature on SPECT, PET, and MR imaging for prediction of converting AMCI to Alzheimer's disease. The authors found four eligible studies with 1,112 patients. The FDG-PET performed a bit better than SPECT and structural MR imaging in predicting a conversion of AMCI to Alzheimer's disease. The specificity of FDG-PET was 86 percent, SPECT was 75 percent, and structural MR imaging was 76 percent. Talbert, et al. in 2006¹⁴ studied 108 patients with AMCI. They found that the best prediction of the neuropsychological testing that would lead amnesic mild cognitive impairment to convert to

dementia was the score from the immediate to delayed recall on the selective reminding test and the score on The Wechsler Adult Intelligence Scale-Revised Digital Symbol Test. The combined accuracy of these two measures for conversion of AMCI to Alzheimer's disease within three years was 86 percent. As you can see from these studies, no one test predicts beyond 86 percent specificity which patients with AMCI will develop Alzheimer's.

How does this play out in clinical neurology practice and where does smell testing fit in? Many suspected AMCI cases in practice will likely be sent for neuropsychological evaluation and MRI of the brain. If neuropsychological testing shows verbal memory storage disturbance and abnormalities in psychomotor speed and executive function impairment, the predictive accuracy of developing Alzheimer's disease within three years is 86 percent. If you order an MRI with special requests for hippocampal, entorhinal cortex and ventricular volumes, and it is appropriately done by your radiologist and found to be abnormal, this will lead to a 60 percent specificity by itself of developing Alzheimer's disease. However, combined with the cognitive testing results, this can increase to an 80 percent prediction when the neuropsychological data is included. You could order further studies to provide more information about your AMCI patient's risk of developing Alzheimer's. These possibilities include PET and SPECT scans and CSF analysis for abeta amyloid and tau, but from the practical standpoint all of these tests are very expensive. Medicare does not cover these spinal fluid studies, and if your patient has an HMO, it will also not likely pay for the PET scan or the spinal fluid studies. In the best studies, analysis of spinal fluid for beta amyloid and tau give an 80 percent prediction of who will develop Alzheimer's, and PET and SPECT scans give an 86 percent and 76 percent, respectively, on prediction. However, none offer greater than 86 percent prediction. The UPSIT smell test, which costs \$28.95, has a specificity of 64 percent if the smell test score is less than 34 and there is lack of smell awareness. This specificity increases to 82 percent if the olfactory score is 30 or less and there is lack of smell awareness.

Aricept (donepezil, Eisai/Pfizer) has shown limited success in the ability to help slow the conversion of AMCI to Alzheimer's, though other acetylcholinesterase inhibitors have not.¹⁵ This limited Aricept success was diminished further in a recent article by Doody, et al. in 2009.¹⁶

Lu, et al. in 2009¹⁷ reported that patients with AMCI and a Becker depression score of greater than 10 predicted AMCI conversion to Alzheimer's disease. Treatment with Aricept delayed progression to Alzheimer's disease in the AMCI depressed cohort. The authors argue that depression and AMCI really represent Alzheimer's disease, and hence, the

Aricept benefit. Smell testing would be of interest in these cases, because a normal smell test would be an unusual finding if these patients already have Alzheimer's disease. If smell testing were abnormal and the patients were unaware of it, that would further reassure that those with AMCI and depression are even more likely on their way to developing Alzheimer's disease.

Those of you who still wish to use Aricept in AMCI cases can use smell testing to help decide who has higher risk of converting to Alzheimer's disease. In my practice I still use Aricept in these cases since I believe the benefit, no matter how small, is worth it. Axona[®], a new medical food product approved by the FDA for Alzheimer's, has an unique action of providing ketones to the brain, another source of energy for cell metabolism.¹⁸ It has been shown in AMCI and Alzheimer's disease that glucose utilization in the brain is impaired. There have been no studies on AMCI and the use of Axona. I am prescribing this product for AMCI, but only in cases with higher risk of developing Alzheimer's disease. I determine the high-risk AMCI patients with neuropsychological testing, MRI for hippocampal volumes, and smell testing. I follow these patients very closely with three-month follow-up that includes in-office cognitive testing and ADL assessments by the caregivers. If any new product comes down the pipeline shown to be of some benefit in delaying or preventing AMCI conversion to Alzheimer's disease, the higher risk AMCI population will be ready to try these new treatments.

Many of the AMCI trials with failed or poor outcome over the last five years or more in relationship to conversion to Alzheimer's disease have not identified the highest risk cases that are more likely to convert to Alzheimer's. That is why the yearly conversion rate of MCI to Alzheimer's disease has varied so widely from five to 32 percent. I believe that neurologists in private practice should do the best they can at the lowest cost to try to identify the AMCI patients with the highest risks of developing Alzheimer's disease. Combining neuropsychological testing, MRI volumes of hippocampus (if available in your practice area), and smell testing are the most cost-effective predictive tests for the development of Alzheimer's disease from AMCI.

Also remember that smell testing, unlike all of the other tests, gives us information about the patient's smell capability regardless of whether the smell loss is due to central or peripheral olfactory pathology. Many of these patients have a safety risk because of impaired ability to smell smoke and natural gas and spoiled food. Many elderly patients live alone or with a spouse who has smell loss, whether age-induced or dementia related. Counseling patients and caregivers about installing a smoke and gas alarm and dating foods left over

in the refrigerator is important for both quality of life and safety. Also if any of the AMCI patients have a taste disorder or decreased appetite and weight loss, it may well be due to impaired smell resulting in inability to recognize flavor of foods. Suggested treatments for this problem are mentioned in the taste and smell article I wrote for this journal in 2008.¹

Smell Testing In the Diagnosis of PD and Related Disorders

Ansare, et al. in 1975¹⁹ were the first to describe smell loss in Parkinson's disease. This did not correlate with medication, smoking, disease severity, motor or cognitive function, or disease duration. Doty, et al. in 1988²⁰ corroborated these findings. Deeb, et al. in 2006²¹ reported a correlation between UPSIT scores and motor scores in early Parkinson's disease. The summary of all olfactory studies that have been done in Parkinson's disease shows that 90 percent of Parkinson's patients have smell impairment in their disease course, and as a pre-motor finding. Most importantly, these patients are unaware of the smell impairment.^{22, 23}

One of the largest studies done on asymptomatic smell loss and PD was by Ross, et al. in 2008.²⁴ They did smell testing (B-SIT) in 2,267 healthy Japanese-American males, ages 71 to 95. After eight years of follow-up, 35 developed Parkinson's disease after 2.7 years. The odds for developing Parkinson's disease in the lowest B-SIT score was 4.3 times that associated with the higher score. Of the 35 who developed Parkinson's disease and died, a brain autopsy was done to check for Lewy bodies in the substantia nigra and locus ceruleus. Those who had the lowest B-SIT score were more likely to have Lewy body changes in those areas of the brain. They concluded from their study that those who developed Parkinson's disease had the low smell loss scores, and they developed Parkinson's disease in the first four years of the study. Among those that developed Parkinson's disease after four years, there was no correlation with smell loss scores. Their conclusion was that olfactory loss predates Parkinson's disease by four years.

Ponson, et al. 2004²⁵ studied smell in 361 asymptomatic relatives of Parkinson's disease patients. Forty relatives were found to be hyposmic within two years of follow-up. Ten percent of these hyposmic relatives developed Parkinson's disease; 12 percent of this group had detectible pre-symptomatic abnormality on their DAT SPECT scan measuring dopamine content in the brain. None of the relatives with normal smell tests showed any DAT SPECT scan abnormalities.

From the clinical neurology practice standpoint there is not much reason to do smell testing in relatives of Parkinson's disease patients. Even though there seems to be

some value, currently little is known about how to delay PD. One can still argue for smell testing because if the smell is significantly impaired and the person is asymptomatic, counseling about safety issues as mentioned previously may be worth the \$28.95 cost of the smell test.

As previously stated, more than 90 percent of classic Parkinson's disease patients have moderately impaired smell on testing and are usually unaware of it. The American Academy of Neurology in 2006²⁶ after a carefully detailed review of the literature to date concluded that if a patient with suspected Parkinson's disease scores 25 out of 40 or less on the UPSIT, this strongly supports the diagnosis of classic Parkinson's disease with a 77 percent sensitivity and 85 percent specificity. If the UPSIT score is 26 out of 40 or greater, one should doubt the diagnosis of classic Parkinson's disease and consider one of the Parkinson's-plus disorders.

Over the years many experts in movement disorders have stated that about 20 percent of the time the diagnosis of Parkinson's disease in clinical practice will be incorrect because many of these cases will turn out to be one of the Parkinson plus disorders. Smell testing could reduce this diagnostic dilemma.

Smell Testing In Parkinson's-Plus Syndromes

Progressive Supranuclear Palsy (PSP). Tsuboi, et al. in 2003²⁷ studied 27 patients and looked at their olfactory bulbs at the time of death. They did not find any tau amyloid or alpha synuclein pathology in any of the cases. The UPSIT scores in all of these cases were normal to low normal. Doty in 1993²⁸ found no difference in UPSIT scores between patients with PSP and controls. There are some PSP patients who have looked very similar to classic Parkinson's disease patients with asymmetrical tremor and a temporary response to L-dopa. These cases also have been found to have normal to mildly decreased UPSIT scores. Doty in 2009²⁹ stated in his book "this may possibly be the reason why some classic Parkinson's disease cases have been reported to have normal olfactory function."

Multiple System Atrophy (MSA). Wennington, et al. in 2003³⁰ studied UPSIT scores of 29 patients with MSA. The mean UPSIT was 27 out of 40 compared with controls at 34 out of 40. There were no differences between the Parkinson and cerebellar types of MSA in this study. All the published studies suggest mild to moderate smell loss in MSA, but the deficit is significantly less than Parkinson's disease.

Corticobasal Degeneration (CBD). This is a tau storage disorder involving the frontal parietal cortex and basal ganglia. Tsuboi, et al. in 2003²⁷ studied the olfactory bulbs of 93 patients after death and found only three CBD cases. All three had normal pathological findings. In 1995,

Wennington³¹ studied seven patients with suspected CBD. The UPSIT score was a mean low normal of 27 out of 40, which was the same as controls.

Vascular Parkinson's Disease (VPD). Many neurologists are familiar with cases of widespread vascular disease involving the basal ganglia and clinically look like underlying Parkinson's disease. In gradual onset, these vascular cases can be very hard to separate from classic Parkinson's disease. Patients who develop Parkinson's disease shortly after a stroke, which can occur unilaterally or bilaterally and have MRI vascular changes in the basal ganglia are more likely to be diagnosed as vascular Parkinson's disease. L-dopa scanning can easily determine if these are classic or vascular Parkinson's disease, because dopamine levels in the brain are usually normal in the vascular patients but not in the classic Parkinson's disease. Katzenschlager, et al. in 2004³² studied the UPSIT scores in 14 vascular Parkinson's patients, 18 with classic Parkinson's disease, and 27 normal controls. The median UPSIT score was 26 out of 40 for the vascular Parkinson's cases, 17 out of 40 for classic Parkinson's disease, and the normals were 26 out of 40. This study strongly suggested that UPSIT testing is usually normal in vascular Parkinson's disease as compared to classic Parkinson's disease and can help in sorting out the differential diagnosis.

Tremor. In 1992 Busenbark, et al.,²² studied smell function in 15 subjects with essential tremor, and all were normal. Many other authors have verified this data. In 2008, Shah³² found that 64 patients who had tremor-dominant Parkinson's disease have very abnormal scores on the UPSIT test. Doty and Hawks, in *Neurology of Olfaction* state, "in practical terms the expectation of normal olfactory function in essential tremor whether familial or not, can be used diagnostically. If a patient with suspected essential tremor has abnormal olfactory scores then the diagnosis of essential tremor merits a review. If the patient is thought to have tremor-dominant Parkinson's disease then olfactory testing should be abnormal."²⁹

REM Sleep Behavioral Disorder (RBD) and Olfactory Testing

RBD is an uncommon disorder with an estimated prevalence of 0.4 percent in the elderly population. It is characterized by a loss of the normal muscle atonia that accompanies REM sleep. This leads to excessive motor activity, such as punching, kicking, and crying out in association with dream content. RBD is strongly associated with the synucleopathies with alpha synuclein deposition in the brain and brain stem, especially the pontine tegmentum.³⁴ Postuma, et al. in 2009³⁴ followed 93 patients with the diagnosis of idiopathic RBD for five to 12 years. Over this follow-up period, 26 out of 93

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patients (28 percent) developed a neurodegenerative disorder. Fourteen out of 26 (54 percent) developed Parkinson's disease, seven out of 26 (27 percent) developed Lewy Body disease, four out of 26 (16 percent) developed Alzheimer's disease, and one out of 26 (three percent) developed MSA. They noticed that the five-year risk of development of these neurodegenerative disorders was 17.7 percent, the 10-year risk was 40 percent, and the 12-year risk 52.4 percent. Interestingly, the frequency of RBD in Parkinson's disease is 35-60 percent of patients, 60-80 percent for Lewy body dementia, and 80-95 percent in MSA.³⁴

Postuma, et al.³⁶ studied 25 patients with idiopathic RBD and 25 controls through

- 1.) olfactory testing using the B-SIT,
- 2.) testing color vision,
- 3.) quantitative motor testing, and
- 4.) autonomic function.

Seventeen out of 23 RBD patients had impaired color vision versus eight of 22 controls. Fourteen out of 25 with RBD scored 6 out of 12 on B-SIT (less than twenty-fifth percentile) versus two out of 25 controls. The United Parkinson's Disease rating scale score (motor score) was six for RBD patients and three for controls, which is a very mild difference. However, a motor test called the timed alternate TAP test was much different for patients with RBD and controls. The RBD patients scored 176 TAPS; controls scored 202. (The alternate tap test consisted of how many taps the index finger of each hand separately can tap two flat objects 20cm apart in two trials of one minute for each hand. The RBD patients had 176 total taps, the normals had greater than 200 total taps.) Autonomic dysfunction evaluation, which included symptoms of constipation, erectile dysfunction, urinary symptoms, and orthostatic hypotension, was much more common in RBD patients than in controls. There was a strong correlation between olfactory, color vision, and motor scores, but not so with autonomic dysfunction in the RBD patients compared to controls. Based on this information, the authors believe that RBD can be divided into two subsets: One group that scores normally on multiple domain testing (olfaction, color vision, and motor scores) and another group that has abnormalities in all these domains. The latter group has an alpha synucleopathy, and the former group a probably different disorder. This appears to be a very strong possibility because Postuma et al.,³⁴ noted that only 28 percent of their RBD patients developed a neurodegenerative disorder over a 12-year period. We do not know what the final outcome is for the remaining 72 percent of these RBD patients. Hopefully, this group will be reported in the future.

It appears that abnormal smell testing, along with color

vision and motor evaluation (the alternate TAP test) in RBD strongly suggests an ongoing future neurodegenerative disorder. No study has reported smell testing alone in RBD, but based on abnormal smell testing in many pre-motor Parkinson's patients, I would strongly suspect that abnormal smell testing alone in RBD cases would be predictive at least of classic Parkinson's or Parkinson's-plus disorders. Further studies will be necessary.

What does this mean for the practicing clinical neurologist? RBD cases that have impaired smell, color vision, and a impaired TAP tests have a very high risk of developing a synucleopathy, and will need to be followed very closely for development of autonomic features like dizziness (postural hypotension), urinary complaints, gait, and balance disorder so that early treatment intervention can be instituted. RBD is a very strong clinical symptom (if determined in history taking) that automatically conjures up a possible neurodegenerative disorder as opposed to patients who come to a neurologist and present with all kinds of non-specific symptoms, such as dizziness or urinary and bowel symptoms, which can be due to so many conditions other than a neurological disorder.

An Important Tool

Standardized olfactory testing has become an important tool in clinical neurology in evaluating symptomatic smell and secondary taste complaints such as can occur in head trauma, post viral infections, side effects of many medications, toxic and metabolic disorders, and uncommon structural lesions of the anterior cranial fossa and medial temporal lobe. Olfactory testing also plays an important role in patients who have diagnosed neurological disorders that impair smell, but the patient is unaware or does not complain of any olfactory symptoms. These olfactory disorders can lead to weight loss, decreased appetite, increased depression, and health and safety issues. These disorders include all the neurodegenerative dementias, such as Alzheimer's disease, Parkinson's dementia, Lewy body dementia, and frontal dementia (the behavioral type). Multiple sclerosis is in this category as well.

This paper has reviewed the benefit of olfactory testing in the following:

- 1.) prediction of potential cognitive decline in the normal elderly,
- 2.) prediction of AMCI in the normal elderly population,
- 3.) conversion of AMCI to Alzheimer's disease,
- 4.) help in the diagnosis of pre-motor Parkinson's disease,
- 5.) establishing the diagnosis of classic Parkinson's disease and helping to separate it from the Parkinson's-plus syndromes, and
- 6.) as part of a test battery to predict which RBD patients will develop a neurodegenerative disorder.

Remember to take a good smell and taste history and be sure there is no possible preexisting impairment of these senses due to other causes such as side effects of medications, previous upper respiratory tract infections, cerebral trauma, thyroid deficiency and poorly controlled diabetes, etc. which can decrease the predictability of an abnormal smell test.

There are two very important advantages of olfactory testing not attributable to any other test. Olfactory testing is very affordable (\$14.95 for the B-SIT or \$28.95 for the UPSIT) and is standardized and reproducible and covered by Medicare and other health insurance. Additionally, mild to moderate olfactory impairment affects the safety and quality of life of many of our patients. These patients need counseling about installing smoke and natural gas alarms, labeling and dating opened foods in the refrigerator, and using proper amounts of perfume and after shave lotion, and being aware of personal hygiene. They can benefit from education about modifying their food preparation to enhance enjoyment of eating.

When neurologists and other physicians report cranial nerve testing in a normal neurological exam, the phrase "cranial nerves II-XII are intact" is frequently used. Being aware of the symptomatic and asymptomatic disorders causing smell and taste impairment and the diagnostic value of smell testing in suspected neurodegenerative and other neurological disorders, hopefully, in the future the standard neurological exam will also include cranial nerve I evaluation and testing more frequently. P N

Ronald Devere, MD is on the speakers' panel for Forest Pharmaceuticals (Namenda) and Accera Pharmaceuticals (Axona). He has no other relevant disclosures. He is Director of the Alzheimer's Disease and Memory Disorders Center, Taste and Smell Disorders Clinic in Austin, TX.

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