NEUROLOGICAL SIGN

Why bother testing the sense of smell?

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When was the last time you asked a patient about their sense of smell? When did you last perform any test of smell identification? Probably never is the answer to both questions. And if you ever did, I expect it was an afterthought and you had to send the clinic nurse scurrying off for an orange or some coffee grains, or worse still you dug out those prehistoric smell bottles that are more appropriate for reviving the dead than assessing the rhinencephalon (the smell brain). Ammonia is useful for cleaning metal. Tinct. asafoetida – the smell of flatus – is an important ingredient of one of the Pentagon’s most repugnant smells ‘US Government Standard Bathroom Malodor’, which causes volunteers to scream and curse within a few seconds. Exposure is perhaps best avoided. People can smell cloves from these bottles in the car park let alone in the clinic.

What every neurologist needs to know is how to do a rapid screen of olfaction, perhaps followed by a more detailed analysis; which patient merits assessment; and what it means if there is an abnormality.

ESSENTIAL BACKGROUND INFORMATION

Patients may not recognize there is a problem with their sense of smell unless it is essential for their work or hobbies, e.g. a chef or wine taster. Hence they must be questioned specifically about it. Even when asked, a significant percentage (around 40%) of patients will be unaware of any problem, especially if there is cognitive impairment, the defect is unilateral, the anosmia is long-standing, or if it came on gradually. When anosmia is present, the patient often confuses it with loss of taste, stating that food tastes bland, but only rarely are the two modalities impaired simultaneously.

The history should be directed particularly to exclude local nasal or sinus disease. It is helpful to know the time of onset of the smell problem and whether it dated to any possible cause, such as an upper respiratory tract infection, nasal or sinus disease, head/nasal/neck trauma, work in a dusty environment, nasal or sinus surgery. If smell loss arises because air is unable to reach the olfactory neuroepithelium, it is called conductive. If the loss varies and
there are periods of normality then it is probably conductive in origin because of fluctuation in nasal congestion, etc. A constant defect is more likely to be perceptive, i.e. of neurological origin.

HOW TO DO A BEDSIDE SCREEN OF THE SMELL SENSE
Two major nerves have branches in the nose - the olfactory and trigeminal. It is particularly easy to stimulate both of them simultaneously and produce wholly misleading findings. We do not test pupils with a search-light, and likewise the nose - it needs the same delicate assessment of its components. Irritant odours like onion or ammonia stimulate the trigeminal nerve and are completely unsuitable, even for suspected malingerers.

The first thing to do then is to get hold of those old quasi-chemistry sets masquerading as smell test kits and throw them into the nearest waste bin. If you are really desperate, in the middle of a ward round for example, use the following emergency odourants (and obviously away from the patient’s line of vision.)

- chocolate – always on someone’s locker and little affected by age
- any fruit such as orange peel, a bottle of orange squash, or banana
- liquorice allsorts – popular sweets with the elderly – and once more liquorice smell resists ageing
- a jar of coffee
- mint sweets

It is not necessary to test each nostril individually, but the nostrils should be tested to ensure that at least one is open. The patients should be asked if they can smell anything at all and then if they can name the smell. The first question addresses olfactory perception, which is a mainly peripheral process, the identification part is cognitive and thus more central. This is of relevance because in the early phase of Alzheimer’s disease, for example, perception is preserved but identification is poor due to cognitive impairment.

For more detailed analysis, one of the scratch and sniff kits is best – abbreviated to UPSIT - the University of Pennsylvania Smell Identification Test (Fig. 1). For each odour, the subject makes a forced choice from four alternatives. In the full version there are 40 odours, and normative values are available for about 2000 Americans standardized for age and sex. But outside America it is preferable to establish local control scores. In general, healthy people under 60 years old should score at least 30/40, whilst anosmics will attain an average of 10 ± 5. Malingers score 0–5 as they intentionally de-select the correct answer.

The UPSIT is a reliable procedure and useful for both routine clinical and medicolegal cases. However, non-Americans may have difficulty with some of the forced choices, e.g. skunk, pumpkin pie, root beer. To avoid this problem there is an international version that has just 12 odourants. While this is adequate for routine clinical purposes it is insufficiently sensitive for research. (UPSI tests available from Sensonics Inc. PO Box 112, Haddon Heights,
The complexity and expense of the apparatus make olfactory evoked potential testing just a research procedure at present.

For absolute minimum screening the Q-SIT is available, also scratch and sniff but relying on just three common odours (chocolate, banana and smoke). If any one of these three is not identified by a forced choice from four alternatives then there is a significant problem with olfaction. It is definitely better than no test at all, being rather similar to testing visual acuity with newspaper headlines.

**SPECIAL TESTS**

**Olfactory evoked potentials (OEP)**

A difficulty with the UPSIT, and threshold tests, is that they are all subjective and evaluate cognitive function to varying degree as well as smell. For more objective testing, evoked potentials can be used (Fig. 2). Selected odours are embedded in a fast flowing air stream that enters the nostril by way of a short piece of Teflon tubing. By introducing a short odour pulse (i.e. 200 milliseconds), an evoked potential is obtained from the vertex after an interval of approximately 600 milliseconds. It is objective and less dependent on cognitive factors and this in principle makes it more valuable than identification or threshold tests. It is a useful, and perhaps the only reliable, method for detecting malingerers, a point of considerable relevance to medico-legal practice.

Several major neurological disorders have been studied by olfactory evoked potentials and the most marked abnormalities occur in idiopathic Parkinson’s disease (Fig. 3). Unfortunately the complexity and expense of the apparatus make olfactory evoked potential testing just a research procedure at present.

**Computed tomographic (CT) scanning**

CT is the most useful and cost-effective technique for evaluating sinonasal tract inflammatory disorders. Coronal scans are particularly valuable in assessing paranasal anatomy – all of little interest to the jobbing neurologist.

**Magnetic resonance imaging (MRI)**

MRI excels in defining soft tissues but it shows bony structures less well than CT and tends to over-emphasize mucosal disease, which is not a problem for the neurologist. MRI is the technique of choice for assessing the olfactory bulbs, olfactory tracts, and intracranial causes of chemosensory dysfunction (Fig. 4). It is also the preferred technique for imaging the skull base for invasion by sinonasal tumours.
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MAJOR NEUROLOGICAL CAUSES OF OLFACTORY LOSS

Head injury

Head injury causes both peripheral and central disturbances of the sense of smell, peripheral being more common. The main sites of damage are the sinonasal tract, cribriform plate entry zone, and inferior frontal lobe or temporal poles from contusion or haemorrhage. In the primarily neurological sphere, head injury is the most common cause of anosmia and usually attributed to shearing of olfactory nerve fibres as they emerge from the cribriform plate to enter the bulb, but lesions of the central pathways are also recognized. To produce post-traumatic anosmia the skull usually has to be fractured. However, even a gentle blow to the head, or acceleration forces, e.g. whiplash injury, may on rare occasion be sufficient to cause anosmia, a point of considerable relevance in medicolegal practice. According to traditional wisdom anosmia is more likely to occur if the front or back or the head is struck rather than the sides, because the opportunity for shearing forces on the frontal lobes is greater.

Recovery from post-traumatic anosmia is poor (Doty et al. 1997): of 66 patients who could be retested, 36% improved slightly, 45% were unchanged and 18% actually worsened. Only three patients recovered from initial anosmia.
One reason for failed recovery may be scar tissue in the cribiform plate, which acts as a barrier to regenerating neurons. Another reason might be traumatic lesions in the frontal or temporal zones causing central anosmia and consequently less opportunity for recovery.

All patients who have sustained any head injury should be asked about and tested for smell disorder. Apart from the obvious career impact in wine tasters, etc., an elderly person with anosmia is particularly vulnerable to common hazards such as food poisoning, burns, etc. (they may not perceive the odour of smoke until too late).

**Parkinson’s disease**

Many clinicians have noted anecdotally that olfactory loss may precede the motor symptoms of Parkinson’s disease by several years, but only recently has some concrete evidence been provided in support of this notion, as described below.

Most olfactory studies have used clinical diagnostic criteria and none have correlated changes in life with those found post mortem. Given this limitation, in broad terms around 80% of patients with Parkinson’s disease have some form of olfactory defect. Studies of olfactory evoked responses confirm this, with absence or significant increase in latency of the cortical response (Fig. 3).

It has been suggested that the olfactory system is the site of initial damage in Parkinson’s disease and that the motor component is but a late manifestation of what is basically a primary olfactory disorder. This viewpoint has now received strong support from pathological studies by Braak and colleagues (Braak et al. 2003) (Fig. 5).

In essence they argued that patients dying from non-neurological causes, who showed brain deposits of α-synuclein (the hallmark of Parkinson’s disease), were in the preclinical phase of disease. Thus it was observed that the earliest abnormalities were in the olfactory bulb and dorsal motor nuclei of cranial nerves IX and X in the medulla, followed by the pontine tegmentum, midbrain, and basal forebrain until they reached the cerebral cortex. Clearly this opens the way for ‘premotor’ testing in subjects at risk, especially in a subject with unexplained anosmia who might be destined to suffer Parkinson’s disease several years later (see below). If a good neuroprotective agent could be found, then the hyposmic phase would be the time to give it. As well as Parkinson’s disease, smell sense is severely impaired in Lewy body disease, which would not surprise those who consider this a malignant form of Parkinson’s disease. There are mild abnormalities of smell sense in multiple system atrophy, but relative normality in progressive supranuclear palsy, and vascular parkinsonism.

Although impaired smell identification is not specific for Parkinson’s disease this information can aid diagnosis. If a patient is suspected to have the disease and on testing is found to have normal age-related smell sense then the diagnosis should be reviewed. Normal olfaction may be found in tremor dominant parkinsonism. If the provisional diagnosis is benign essential tremor, which is occasionally confused with Parkinson’s disease, smell tests should be normal, thus significant olfactory loss would also merit diagnostic review.

Spinocerebellar ataxias may simulate tremulous parkinsonism. In spinocerebellar ataxia type 3 (SCA 3; Machado–Joseph syndrome) smell sense is usually normal but there is mild impairment in SCA 2. Clearly smell test in this context would not be so helpful.

**Familial and presymptomatic Parkinson’s disease**

In the Michigan study of familial Parkinsonism, UPSIT-40 was applied to six kindreds of which three had typical Parkinson’s disease and three had a ‘parkinsonism-plus’ syndrome. In the typical families, there were four apparently healthy individuals at 50% risk of whom three were microsmic. In the parkinsonism-plus families there were eight at risk and two had an abnormal UPSIT score. It is not known whether these subjects at risk will develop clinical parkinsonism. In PARK 2, which is a dominant form of parkinsonism, smell sense is relatively preserved whilst in PARK 1 most subjects are hyposmic.

Others have given a test battery to first-degree relatives of Parkinson’s disease patients with measurement of motor function, olfaction (UPST-40) and mood. There were significant differences in first-degree relatives (both sons and daughters), particularly where the affected parent was the father. Another group evaluated asymptomatic but hyposmic relatives of patients with Parkinson’s disease. Dopamine transporter binding was abnormal in 4/25 hyposmic relatives, two of whom subse-
It has been suggested that hyposmia is an early and consistent change in Alzheimer’s disease.

Finally, Ross et al. (2005) applied the international UPSIT-12 test in 2263 healthy elderly men aged 71–95 years participating in the Honolulu-Asia Ageing Study. They were followed up for seven years and during this period 19 men developed Parkinson’s disease. After adjustment for confounders the relative odds for Parkinson’s disease in the lowest tertile of the UPSIT-12 score was 4.3 (95% CI 1.1–16.1; P = 0.02). This is the first prospective study to show the predictive value of smell testing in an apparently healthy aged population.

CONCLUSIONS

- After taste, smell testing is probably the most neglected of all neurological examinations.
- It is worth testing smell – especially when diagnosing a movement disorder and after head injury, whether the skull is fractured or not.
- The scratch and sniff test is probably the most informative screening procedure, but at least 12 odours need to be examined for a reliable result, and for recent research work the UPSIT-40 is essential. For rapid outpatient screening the Q-SIT (http://www.q-sit.com) is a reasonable compromise, and in emergencies the bedside locker tests are better than nothing at all.
- In the absence of local nasal disease or head injury, anosmia in an otherwise healthy middle-aged patient needs to be taken seriously; it may be the forerunner of Parkinson’s or Alzheimer’s disease.
- Now is the time for a complete reappraisal of the role of smell testing in your neurological practice.

Alzheimer’s disease
Numerous psychophysical studies of olfaction in presumed Alzheimer’s disease have shown abnormalities and, in some, correlation of dementia severity with anosmia. The majority have used clinical criteria for diagnosis of Alzheimer’s and rarely have autopsy data been available. With this caveat, severe abnormalities have been documented in most reports for smell identification, recognition and threshold detection. It has been suggested that hyposmia is an early and consistent change in Alzheimer’s disease. Indeed some studies imply that raised olfactory threshold may be the first change before cognitive impairment sets in. This concept has been given strongest support in a well-designed prospective population-based study by Graves et al. (1999). They tested 1836 healthy people at baseline with the international UPSIT-12 test and a cognitive screening procedure. Hyposmia, and particularly anosmia, was significantly associated with cognitive failure on retesting 2 years later.

Miscellaneous causes of reduced smell sense
- Most patients with Refsum’s disease are anosmic. Thus the combination of retinitis pigmentosa and anosmia makes Refsum’s disease the most likely cause.
- The cardinal signs of superficial siderosis are ataxia, deafness and myelopathy often on a background of prior bleeding episodes. Anosmia is a frequent (and overlooked) sign in this syndrome.
- Some people are born without a sense of smell (congenital anosmia) and in males, where this is accompanied by hypogonadism, the likely diagnosis is Kallmann’s syndrome – an X-linked recessive disorder.
- Rarely anosmia may be a feature of paraneoplastic disorder or lymphoma.

COMPETING INTERESTS
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