

SHORT REPORT

Smell testing: an additional tool for identification of adult Refsum's disease

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Background: Adult Refsum's disease (ARD) is characterised by the presence of retinitis pigmentosa, ataxia, deafness, sensory neuropathy, and bony changes. The diagnosis is confirmed by the presence of phytanic acidemia. Although reduced smell function has been described in ARD, its value in the diagnosis of the condition has not been fully evaluated.

Objective: To investigate the prevalence and degree of olfactory dysfunction in patients with ARD.

Method: The olfactory function of 16 patients with ARD was assessed using the quantitative University of Pennsylvania Smell Identification Test (UPSIT).

Results: All patients had complete anosmia or grossly impaired smell function with a mean UPSIT score of 14.7 (SD 4.7) (normal >34) despite having been treated with an appropriate diet for a median of 15 years (range 1–25).

Conclusions: Identification of ARD patients can be facilitated by using the UPSIT in combination with the presence of retinitis pigmentosa, even if they have no neurological or bony features. Phytanic acid screening should be performed in any patient manifesting these two signs.

In 1945, Sigvald Refsum described a disease in two families that he termed heredoataxia hemeralopica polyneuritiformis, whose symptoms and signs included night blindness, retinitis pigmentosa, concentric visual field loss (hemeralopia), polyneuropathy, and ataxia.¹ The illness is now known as heredopathia atactica polyneuritiformis (Online Mendelian Inheritance in Man (OMIM) 266510) or adult Refsum's disease (ARD).² In 1946, Refsum described the patients in detail in a monograph.³ Microsmia (hyposmia) was mentioned in three of the five cases, but this feature was not thought to be a part of ARD.⁴ In 1963, Klenk and Kahlke showed that patients with ARD had raised plasma levels of phytanic acid.⁵ The pathophysiology of smell loss in ARD is uncertain but may be related to central sensory neurone toxicity analogous to that found in photoreceptors and to a lesser extent in auditory neurones. Phytanic acid levels are usually measured in cases of retinitis pigmentosa with associated polyneuropathy or short metacarpals.⁶ These latter two signs are not universally present. Microsmia has been previously recognised as part of ARD and its prevalence has been assessed in a cohort of patients.^{7–8} However, the utility of microsmia as a clinical diagnostic criterion for ARD, assessed precisely using modern objective techniques, is unknown. This study aimed to define the utility of a simple, but comprehensive, card based smell test in screening for olfactory dysfunction in Refsum's disease.

METHODS

Patients with previously diagnosed ARD, identified by the presence of retinitis pigmentosa,⁹ neurophysiological or

radiological signs of ARD,¹⁰ and raised plasma phytanic acid (reference limit <30 µmol/l) prior to initiation of dietary therapy, were evaluated.

All the patients had been treated since their presentation with a low phytanic acid diet.¹¹ They had had their sensation of smell tested on first presentation to the Refsum's Clinic using a four bottle (peppermint, eucalyptus, lavender, wintergreen) test. Formal neurological 10+ odour panel tests or butanol appreciation had not been performed on presentation as many patients had presented more than 15 years ago, and such tests were not available at the time. Bony changes were assessed visually and on foot and hand radiographs.⁶ Phytanic and pristanic acid levels in plasma were measured by standard gas chromatographic techniques.¹²

Smell function at the current visit was assessed by using the University of Pennsylvania Smell Identification Test (UPSIT) (Sensonics Inc., Haddon Heights, NJ), a standardised micro-encapsulated 40 odourant test.¹³ The test was applied over a period of 15–20 minutes each in an outpatient clinic to all patients with ARD by one of the investigators (FBG). For each odour the subject had to choose one of four possible answers.

Perfect smell sensation on this test gives a score of 40 (normal range: males 35–40; females 34–40); complete anosmia a score of about 10 out of 40 (6–18) achieved by chance on guessing. Scores of 19–25 are classified as severe microsmia; 26–30 as moderate microsmia; 31–34 as mild microsmia; and 35–40 as normal smell appreciation.¹⁴ The test has been validated and the manual gives a standardised operating procedure.¹⁴ The reference values have been derived from recorded reference ranges for the UPSIT test based on American males and age adjusted where necessary.

Statistical analysis was performed using GBStat 7.0 (Dynamic Microsystems, Silver Springs, MD). Observed smell test scores were compared with the published reference group ranges. Smell test scores were correlated by univariate linear regression with age at certification of blindness or deafness, age, weight, and log transformed current and initial phytanic acid levels. A least squares multiple linear regression analysis including all the variables cited was done to ascertain whether the smell test results correlated with any of these clinical or biochemical parameters.

RESULTS

The patients included 10 men and six women. Two patients, both women, were aged >65 years. The 16 patients had been on treatment for a median of 15 years (range 1–25) and in five (31%) phytanic acid levels had fallen to within the normal range (<30 µmol/l). Seven patients (44%) had bone

Abbreviations: AMAC, α -methyl acyl-CoA racemase deficiency; ARD, adult Refsum's disease; UPSIT, University of Pennsylvania Smell Identification Test

abnormalities and thirteen (81%) reported ataxia at some time.

On questioning, all patients complained of poor appreciation of smell, but some could not remember normal smell appreciation at any stage in their lives and this made it difficult for them to appreciate what anosmia or hyposmia was. Ten patients (63%), when questioned on presentation, had reported poor appreciation of smell and demonstrated anosmia on the four bottle smell test. Some patients reported an improvement in smell sensation with dietary treatment but none achieved normal smell appreciation even if phytanic acid levels had returned to normal.

All the patients when tested with the UPSIT had deficient smell (table 1). Four had severe microsmia and the rest had complete anosmia. None had scores below 8, which might have occurred if a patient had deliberately attempted to choose the wrong answer. The average score of this population on the smell tests was 14.7 (SD 4.7) points (median 13, range 8–24). No significant difference was found between the sexes (women 14.3 (4.9) *v* men 14.9 (4.9); *p* = 0.84). The patients sampled included one with atypical ARD with only mild phytanic acidemia (34–70 $\mu\text{mol/l}$) but low pristanic acid (0.2 $\mu\text{mol/l}$; normal 3–5 $\mu\text{mol/l}$) and who was found to have anosmia (UPSIT score 8). No significant correlation was found between the UPSIT score and the initial or final phytanic acid level, total phytanic acid exposure (phytanic acid years), age, age of certification of blindness, or weight.

DISCUSSION

ARD is caused by mutations in enzymes and transporters in the peroxisomal α -oxidation pathway. It has a prevalence of approximately 1 in 10^6 in the UK. Lower prevalences of Refsum's disease (<1 in 10^7) reported in other Caucasian populations (for example, USA) imply that differences in clinical assessment strategies, dietary phytanic acid intake, assay availability, and methodology may significantly affect the reliability of phytanic acid screening programmes for ARD.

Three forms of ARD are now recognised: phytanoyl-CoA hydroxylase deficiency (classic adult Refsum's disease)²; peroxin-7 deficiency (a variant of rhizomelic chondrodysplasia punctata)¹⁵; and α -methyl acyl-CoA racemase deficiency (AMACR).² Biochemical tests for ARD are only done at specialist centres and are considered too expensive for routine screening of patients with visual impairment or

retinitis pigmentosa and vague neurological signs. Phytanic acid screening will identify patients in the first two groups but not reliably in AMACR.¹⁶

In the diagnosis of ARD, the identification of short metacarpals, metatarsals, obvious acute neuropathy, or ataxia have been used to guide biochemical test selection. However, radiological and electrophysiological surveys of patients with ARD show that these clinical signs are found in only 20–35% of patients while ataxia is a feature of acute rather than chronic presentation. Only 25% of the patients in this series had bony changes and 69% had ataxia on acute presentation although in 56% radiology identified bony changes and 89% had ataxia at some time during follow up. ARD is a clinical syndrome with a wide spectrum of phenotypic presentations, ranging from early onset retinitis pigmentosa with polyneuropathy and leukodystrophy to adult onset visual loss with retinitis pigmentosa alone.²

The prevalence of microsmia as a clinical sign and symptom in ARD was uncertain.^{2,17} Assessment of smell has either not been done or performed with crude non-quantitative tests. The availability of a simple, stable, scratch card based 40 odour test system has many potential advantages for diagnosis.¹³ It is simple, safe, and stable, and can be performed by non-clinical staff. The UPSIT has been used successfully in patients with anosmia due to neurodegenerative disease,¹⁸ Kallmann's syndrome, and Usher's syndrome.¹⁹ This study assessed the utility of the UPSIT test in patients with ARD and showed that all patients demonstrated moderate microsmia with a smell test score of 14.7 (4.7) (normal >30), despite having been treated with a low phytanic acid diet for a median of 15 years. Thus, smell loss is a constant feature of ARD. A bioinformatics search of the OMIM website (<http://www.ncbi.nlm.nih.gov>) revealed that the combination of retinitis pigmentosa and anosmia was more specific for ARD (3/5 conditions) than the combination of retinitis pigmentosa and metacarpal/metatarsal abnormality (2/5).

In the assessment of the condition a substantial degree of underdiagnosis is likely to result from the use of either neurological or bony signs in combination with the presence of retinitis pigmentosa as a basis for further investigation by the measurement of phytanic acid. The use of UPSIT smell testing in patients with retinitis pigmentosa will result in an increase in the diagnostic yield for phytanic acid testing as microsmia is a universal feature of ARD.

Table 1 Clinical characteristics and smell test results of 16 patients with adult Refsum's disease

Patient	Age (years)	Year of presentation	Microsmia	Bone changes	Ataxia	Phytanic acid ($\mu\text{mol/l}$)		Smell test (/40)
						Peak	Current	
1	72	1989	+	–	+	650	10	12
2	18	1998	+	+	+	1252	530	23
3	41	1984	+	+	+	1070	217	24
4	36	2001	+	+	+	143	136	11
5	50	1987	+	+	+	530	123	23
6	41	1987	+	+	–	1987	160	16
7	56	1970	+	–	+	2810	10	11
8	44	1986	+	–	+	999	23	11
9	49	1986	+	–	+	568	136	15
10	45	1986	+	–	+	1013	232	14
11	41	1986	+	–	+	1313	344	13
12	31	1990	+	–	+	2684	166	12
13	61	1987	+	–	+	1048	10	15
14	18	1997	+	+	–	49	5	8
15	75	1956	+	–	+	1172	41	12
16	30	2001	+	+	–	608	342	15

In conclusion, the present study has shown that smell testing using the card based UPSIT system, which can be performed in 15–20 minutes will identify all patients with classic ARD as having moderate to severe microsmia. We would recommend that if routine phytanic acid and peroxisomal profile screening of patients with retinitis pigmentosa is not possible, patients with a probability of having ARD, who require formal biochemical assessment, should be identified by card based smell testing.

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