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A 10-Item Smell Identification Scale Related to Risk for Alzheimer's Disease

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University of Pennsylvania Smell Identification Test data from control subjects (n = 63), patients with mild cognitive impairment (n = 147), and patients with Alzheimer's disease (n = 100) were analyzed to derive an optimal subset of items related to risk for Alzheimer's disease (ie, healthy through mild cognitive impairment to early and moderate disease stages). The derived 10-item scale performed comparably with the University of Pennsylvania Smell Identification Test in classifying subjects, and it strongly predicted conversion to Alzheimer's disease on follow-up evaluation in patients with mild cognitive impairment. Independent replication is needed to validate these findings.

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Early in the course of Alzheimer's disease (AD), neurofibrillary tangles appear in olfactory-related brain regions (eg, anterior olfactory nucleus and entorhinal cortex).[1] Olfactory deficits, which have been observed consistently in AD,[2] occur early,[3,4] are predictive of a future diagnosis of AD,[5,6] and increase with disease severity.[7,8]

The University of Pennsylvania Smell Identification Test (UPSIT)[9] is widely used in research to assess odor identification deficits,[2,10] but it is less widely used in clinical practice, partly because administration takes 10

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to 15 minutes. The Brief Smell Identification Test [B-SIT], composed of 12 UPSIT items, was developed as a rapid cross-cultural screen for detecting olfactory deficits.[11] To improve the clinical utility of the UPSIT for specific diseases, attempts have been made by several research groups to identify those items that best distinguish diagnostic groups such as patients with Parkinson's disease (PD)[12,13] or AD[14,15] from control subjects. The aim of this study was to identify an optimal subset of UPSIT items related to risk for AD with the goal of improving clinical applicability.

Subjects and Methods

Data from 310 subjects participating in separate studies at three medical centers were analyzed. MCI patients (n = 147) and healthy control subjects (n = 63) were recruited at the New York State Psychiatric Institute and Columbia University Medical Center.[6,16] AD patients participated at Mount Sinai Medical Center (n = 56),[8] or in a study jointly performed at Jefferson Medical College and the Smell and Taste Center of the University of Pennsylvania (n = 44).[4] Detailed inclusion/exclusion criteria for the respective studies have been described.[4,6,8,16]

Control subjects were recruited by advertisement and evaluated annually.[6,16] MCI patients presented with memory complaints to a Memory Disorders Center and were evaluated at 6-month intervals in a longitudinal study of early diagnostic markers of AD. Expert clinical raters, blind to UPSIT scores, made a consensus research diagnosis at each visit[6,16] based on Diagnostic and Statistical Manual, Fourth Edition, Criteria, and National Institute of Neurological and Communication Disorders-Alzheimer's Disease and Related Disorders Association criteria.[17] Patients with AD met criteria for a clinical diagnosis of probable AD[17].

Statistical Analysis

Initially, 290 of the 310 subjects were ranked according to risk for AD: (1) "healthy" control subjects (n = 63); (2)

"low-risk" MCI patients, with at least 2 years of follow-up, who had not converted to AD within that period (n = 96); (3) "high-risk" MCI patients who converted to AD within 2 years of follow-up (n = 31); and (4) AD patients (n = 100). Cochran-Armitage linear trend tests were applied to UPSIT data with the goal of identifying items that showed a decreasing trend in the proportion of correct smell identifications across these ordinal groups (multiple test adjusted $p < 0.20$). UPSIT items that did not show a decreasing trend were excluded from subsequent analyses.

The remaining items were submitted to logistic regression (LR) analysis using a stepwise selection procedure. Dichotomous predictors (ie, correct vs incorrect on each UPSIT item) and a binary outcome variable (ie, control subjects plus MCI nonconverters at 2 years vs MCI converters within 2 years plus AD patients) were used. Only items that were related ($p < 0.10$) to the outcome after adjusting for all other items were retained. A second LR analysis using a likelihood score–based selection procedure[18] also was applied for statistical validation. Item subsets ranging in size from one item to a set containing all items and Akaike Information Criterion[19] were used to select the final set of items related to risk for AD. To further evaluate variability in item selection, the same procedures that were used to derive the 10-item scale (Cochran-Armitage tests and stepwise LR) were applied to 100 bootstrapping samples obtained by random sampling with replacement from the original sample (n = 290).

The ability of the 10-item scale in classifying subjects was compared with that of the UPSIT and B-SIT by calculating receiver-operating characteristic curves for each scale. A nonparametric test[20] was used to assess the difference in areas under the curves (AUCs). Corresponding sensitivities and specificities for the full range of possible scores were calculated. Survival analyses were conducted on an expanded sample of MCI patients (n = 147) to examine the effect of the UPSIT, B-SIT, and 10-item scale scores on conversion to AD (mean follow-up, 42 months). This expanded sample included 20 additional MCI patients with less than 2 years of follow-up.

Table 1. Summary of Demographic and Clinical Variables and Smell Identification Scores for Healthy Elderly Subjects and MCI and AD Patients (n = 310)

Demographic Variable	Healthy Elderly (n = 63), Mean (SD)	MCI Patients (n = 147), Mean (SD)	AD Patients (n = 100), Mean (SD)	p^a	MCI Nonconverters (n = 109), Mean (SD)	MCI Converters (n = 38), Mean (SD)	p^b
Age (yr)	65.71 (9.38)	67.43 (9.85)	71.72 (9.54)	<0.001	65.59 (9.99)	72.71 (7.28)	<0.001
Education (yr)	16.68 (2.60)	14.96 (4.29)	13.09 (4.35)	<0.001	15.27 (4.19)	14.08 (4.49)	0.142
Sex (% female)	54.0	55.1	63.8	0.33	54.1	57.9	.417
Folstein MMSE score	29.37 (0.768)	27.28 (3.23)	19.96 (5.96)	<0.001	27.68 (3.43)	26.13 (2.21)	0.01
UPSIT score	34.86 (4.18)	31.22 (6.45)	23.72 (6.48)	<0.001	33.02 (4.68)	26.05 (7.96)	<0.001
B-SIT score	10.60 (1.53)	9.56 (2.21)	7.04 (2.62)	<0.001	10.12 (1.70)	7.95 (2.67)	<0.001
10-item Scale score	8.98 (1.24)	8.26 (1.66)	5.48 (1.71)	<0.001	8.75 (1.23)	6.84 (1.90)	<0.001

[a]One-way analysis of variance or Fisher's exact test (sex) were conducted to compare healthy elderly, MCI patients, and AD patients.
[b]t tests or Fisher's exact test (sex) were conducted to compare nonconverters vs converters to AD on follow-up evaluation.

MCI = mild cognitive impairment; SD = standard deviation; AD = Alzheimer's disease; MMSE = 30-item Mini-Mental State Examination; UPSIT = University of Pennsylvania Smell Identification Test; B-SIT = Brief Smell Identification Test.

Table 2. Percentage Correct Smell Identifications across Four Ordinal Groups Increasing in Risk of AD and Corresponding Raw and Adjusted (multiple test adjusted p value >0.20) Cochran-Armitage Linear Trend Test p Values

UPSIT Item No.	Odorant Name	Healthy Elderly (n = 63)	MCI "Low-Risk" Patients (n = 96)	MCI "High-Risk" Patients (n = 31)	AD Patients (n = 100)	Raw (p)	Multiple Test Adjusted (p)[a]	Frequency (%) in 100 Bootstrapping Samples (n = 290 each)	No. of Negative[b] Regression Coefficients in the 100 Final Item Subsets
1	Pizza	91	81	61	61	<0.0001	<0.0001	5	3
3	**Menthol**	92	85	84	48	<0.0001	<0.0001	62	62
4	Cherry	98	88	81	59	<0.0001	<0.0001	11	10
5	Motor oil	91	90	77	64	<0.0001	<0.0001	31	0
6	Mint	95	87	74	55	<0.0001	<0.0001	21	15
7	*Banana*	94	82	68	58	<0.0001	<0.0001	15	1
8	**Clove**	94	94	65	59	<0.0001	<0.0001	88	88
9	**Leather**	97	93	77	50	<0.0001	<0.0001	94	94
11	*Onion*	89	82	68	56	<0.0001	<0.0001	19	19
13	Licorice	97	91	84	61	<0.0001	<0.0001	14	14
16	*Gasoline*	95	92	81	67	<0.0001	<0.0001	21	6
17	**Strawberry**	92	84	61	56	<0.0001	<0.0001	61	60
20	Gingerbread	84	70	55	49	<0.0001	<0.0001	12	8
21	**Lilac**	94	94	81	62	<0.0001	<0.0001	69	69
24	Root beer	95	91	74	68	<0.0001	<0.0001	34	33
26	***Pineapple***	90	85	74	55	<0.0001	<0.0001	58	58
29	Wintergreen	92	83	71	52	<0.0001	<0.0001	13	11
30	Watermelon	87	85	71	61	<0.0001	<0.0001	31	31
31	*Paint thinner*	95	92	81	60	<0.0001	<0.0001	33	33
33	***Smoke***	92	83	52	55	<0.0001	<0.0001	66	65
34	Pine	92	88	77	58	<0.0001	<0.0001	21	19
35	Grape	97	91	68	59	<0.0001	<0.0001	39	39
37	***Soap***	89	94	71	56	<0.0001	<0.0001	76	76
38	**Natural gas**	87	93	68	58	<0.0001	<0.0001	51	51
39	*Rose*	91	85	61	55	<0.0001	<0.0001	14	6
40	Peanut	98	94	81	68	<0.0001	<0.0001	32	32
2	Bubble gum	86	83	55	60	<0.0001	<0.0001	26	26
25	Dill pickle	94	76	68	62	<0.0001	<0.0001	42	0
19	*Chocolate*	89	85	74	64	<0.0001	0.0003	18	16
23	Peach	81	84	74	61	0.0002	0.0057	7	3
22	*Turpentine*	83	80	58	62	0.0003	0.0089	9	6
36	***Lemon***	71	68	55	49	0.0006	0.0174	49	49
18	Cedar	84	79	74	63	0.0007	0.0192	14	1
10	Coconut	79	79	45	64	0.0024	0.0655	5	2
15	*Cinnamon*	83	80	61	67	0.0042	0.1068	6	1
14	Cheddar cheese	64	57	26	53	0.0553	0.6938	7	7
27	Lime	76	62	58	62	0.0737	0.7757	0	—
32	Grass	67	77	42	64	0.0955	0.8473	1	1
28	Orange	79	67	61	75	0.4558	0.9998	1	0
12	Fruit punch	43	38	29	56	0.9800	1.000	0	—

Bolded odorants comprise the 10-item scale. Italicized and underlined items occur in the B-SIT. The four bolded, italicized and underlined items occur in both the B-SIT and the 10-item scale.

[a]Items are ranked according to multiple test adjusted p values. Note: The bottom five items did not show a decreasing trend across groups ($p > 0.20$).

[b]Logistic regression (Beta) coefficients for the UPSIT items in the final selected item subsets indicate the magnitude and direction of the relationship between the given item and the binary outcome (controls plus MCI nonconverters vs MCI converters plus AD patients) after adjusting for all other items in the item subset. Negative regression coefficients (frequency are listed in the table for each UPSIT item) indicated that an incorrect response on the given item after adjusting for the other items in the subset is associated with the classification of "MCI converter plus AD patient" and a correct response with the classification of "Control plus MCI nonconverter."

AD = Alzheimers disease; UPSIT = University of Pennsyluania Smell Identification Test; MCI = mild cognitive impairment.

Results

Demographic and clinical variables and olfactory scores for the control subjects and MCI and AD patients are summarized in Table 1. Cochran-Armitage linear trend tests demonstrated that five UPSIT items did not show a decreasing trend across the ordinal groups (Table 2). These five items were excluded from further analyses.

Both LR selection procedures (stepwise and likelihood score based/Akaike Information Criterion)

yielded the same 10 items (see Table 2). A list of selection frequencies across 100 bootstrapping samples showed that the originally selected 10 items were also the most frequently selected across the 100 final item subsets (see Table 2). Also, across the final item subsets, regression coefficients consistently indicated that an incorrect response for the 10 items, after adjusting for any of the other items in the subset, was associated with being classified as an MCI converter or AD patient (see Table 2). For the 290 subjects (using the same binary outcome), receiver-operating characteristic curve analyses showed that the AUC for the 10-item scale was greater than for the UPSIT (AUC: 0.908, standard error [SE] = 0.018 vs 0.882, SE = 0.020, respectively, $p = 0.048$) and B-SIT (0.841, SE = 0.023, $p < 0.001$). A similar AUC pattern was observed when the sample was restricted to 127 MCI subjects, classified as converters within 2 years of follow-up versus nonconverters at 2 years (10-item: 0.816, SE = 0.042; UPSIT: 0.789, SE = 0.044; B-SIT: 0.756, SE = 0.050). Sensitivities and specificities for a range of possible scores on each scale are shown in Table 3.

Age-stratified Cox proportional hazards models for the 147 MCI patients with variable follow-up times showed that scores from the UPSIT and 10-item scale significantly predicted conversion to AD ($p < 0.0001$), even after adjusting for sex, education, and Mini-Mental State Examination scores. The UPSIT and 10-item scale showed maximum risk ratios (RRs) of 4.30 (score ≤ 32; 95% confidence interval [CI], 1.81–10.26; $p = 0.001$) and 5.03 (score ≤ 7; 95%

CI, 2.46–10.28; $p < 0.0001$), respectively. Controlling for the same covariates reduced the RRs (UPSIT RR: 2.52; 95% CI, 0.99–6.42; $p = 0.053$; 10-item RR: 3.94; 95% CI, 1.79–8.67; $p < 0.001$). B-SIT scores adjusted for the same covariates also were associated with conversion to AD ($p = 0.059$; a cutoff score ≤8 yielded a maximum RR of 2.21; 95% CI, 1.05–4.67; $p = 0.037$).

Discussion

Analyses yielded a 10-item scale that performed comparably with the UPSIT with indications of superiority to the B-SIT in classifying subjects with increasing risk for AD. In an expanded sample of MCI patients with variable follow-up times, the 10-item scale and UPSIT predicted conversion to AD after adjusting for clinical and demographic covariates. Importantly, with the data from 290 subjects, two different statistical selection procedures identified the same 10 items. The same 10 items were also the most frequently selected items in 100 bootstrapping samples. An incorrect response on these 10 items was consistently associated with risk for AD. These findings suggest that the 10 identified items represent an optimal subset related to risk for AD. The greater risk associated with certain UPSIT items may be explained by AD-related pathology in olfactory-related brain areas that may differentially impact the neural circuitry mediating odor processing.

It should be noted that, in a previous study by our group,[6] with smaller sample size (77 MCI patients of which 19 converted to AD on follow-up) and shorter follow-up (mean duration of follow-up was 20

Table 3. Sensitivity and Specificity Values for the 40-Item UPSIT, 12-Item B-SIT, and 10-Item Scale When Classifying AD Patients and MCI Converters within 2 Years of Follow-up vs MCI Nonconverters at 2 Years of Follow-up plus Controls (n = 290) and When Restricting the Sample to 31 MCI Patients Who Converted to AD within 2 Years of Follow-up vs 96 MCI Patients Who Had Not Converted to AD within 2 Years (n = 127)

Score	n = 290		n = 127	
	Sensitivity (≤ cutoff score)	Specificity (> cutoff score)	Sensitivity (≤ cutoff score)	Specificity (> cutoff score)
UPSIT cutoff scores				
29	77.10	84.28	58.06	80.21
30	82.44	81.13	61.29	77.08
31	87.79	76.73	70.97	73.96
32	91.60	69.18	83.87	62.50
33	93.13	64.15	87.10	56.25
10-item scale cutoff scores				
6	63.36	93.08	45.16	92.71
7	83.21	89.31	58.06	87.50
8	94.66	67.92	83.87	65.63
9	97.71	38.36	96.77	34.38
B-SIT cutoff scores				
7	47.33	88.68	41.94	88.54
8	65.65	79.25	54.84	86.46
9	78.63	54.72	67.74	75.00
10	90.08	27.04	80.65	48.96

months), low olfaction in patients with lack of awareness of olfactory deficits was a better predictor of conversion to AD than low olfaction scores alone. With increased power in this study's cohort of 147 MCI patients (of which 38 converted to AD) and with longer follow-up (mean duration of follow-up was 42 months), low olfaction scores alone, after adjusting for demographic and clinical variables, strongly predicted outcome.

For olfactory tests to be clinically useful for early detection, they must be sensitive to early pathological and functional changes, significantly add to the predictive accuracy of known demographic and clinical risk factors, and be brief. The proposed 10-item scale meets these criteria and can be self-administered by patients in 5 minutes with minimal supervision. Scoring is objective and can be performed rapidly by a trained person. The practitioner needs only to review and interpret the results in the context of a clinical workup. Pending independent replication, the 10-item scale's potential diagnostic and predictive utility make a strong case for including it as part of a standard clinical workup for patients at risk for AD.

The study has several limitations. First, although differences between the odors identified here and those identified in previous reports involving AD[14,15] or PD,[12,13] or both, can be accounted for to some degree by methodological differences (eg, sample size, patient groups, statistical approaches), the lack of consistency in optimal odors identified across studies emphasizes the need for independent replication. Second, the sample used for the item reduction analyses overlapped with the sample used to evaluate the predictive utility of the scale (ie, 127 of the 147 subjects with variable follow-up were included in both sets of analyses). This limitation further emphasizes the need for replication and validation. Specificity against other disorders such as PD also needs to be established, with neuropathological confirmation if possible. Finally, future cross-cultural validation studies will be needed to ascertain the discriminative and predictive potential of the 10-item scale outside of North America.

In conclusion, if the proposed scale's predictive accuracy for conversion from MCI to AD is replicated and is comparable or superior to other early markers, it may in combination with other diagnostic tests help to improve early detection of AD.

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Mental Retardation and Ataxia Due to Normotriglyceridemic Hypobetalipoproteinemia

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A 12-year-old boy with mental retardation, obesity, ataxia, and visual impairment was shown to have normal fasting plasma triglyceride but low cholesterol and vitamin E levels. Investigations indicated that he was compound heterozygous for two mutations in the apolipoprotein B gene (*APOB*), resulting in a failure to express apolipoprotein B-100, yet retain apolipoprotein B-48 production. The proband therefore was able to form chylomicrons, but not a low-density lipoprotein capable of receptor-mediated endocytosis. This resulted in chronic vitamin E deficiency. We suggest the term *normotriglyceridemic hypobetalipoproteinemia* for this easily recognizable condition.

The apolipoprotein B gene (*APOB*) encodes two proteins: apolipoprotein B-48 (ApoB-48) and ApoB-100. ApoB-48 is formed in the intestine and is essential for the formation and recognition of dietary-derived chylomicrons.[1,2] In contrast, ApoB-100 is found in the very low-density (VLDLs) and low-density lipoproteins (LDLs) of hepatic origin, and is involved in the endogenous transport of triglycerides, cholesterol, and fat-soluble vitamins. The smaller ApoB-48 polypeptide re-

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sults from a tissue-specific, posttranscriptional, single-nucleotide substitution in the intestinal APOB messenger RNA that changes a glutamine codon into a stop codon at residue 2153.[3] The resulting polypeptide chain contains 2,152 amino acids (264kDa), which is 48% (hence the name ApoB-48) of the apparent molecular mass (M_r) of the 4,536 (549kDa) ApoB-100 protein. A number of abnormally truncated ApoB proteins have been described, usually in the heterozygous state, and by convention these are referred to by this percentile system, reflecting their apparent M_r in relation to ApoB-100.[2]

Truncations shorter than ApoB-27 are not expressed in lipoproteins, whereas those less than ApoB-75 show little expression in LDLs.[4–8] Consequently, severe homozygous mutations in the N-terminal third of *APOB* result in the virtual absence of both ApoB-48 and ApoB-100 and their corresponding lipoproteins, and thus low levels of triglycerides, cholesterol, and the fat-soluble vitamins. This condition is known as hypobetalipoproteinemia and is characterized clinically by severe failure to thrive, steatorrhea, and eventually both central and peripheral neurological abnormalities.[2]

In marked contrast to hypobetalipoproteinemia, Malloy and colleagues[9] described a patient with relatively normal concentrations of triglyceride, chylomicron, and ApoB-48 but absent or low concentrations of cholesterol, ApoB-100, and fat-soluble vitamins. Clinically, the patient had obesity and mental retardation with evidence of nerve conduction defects. This condition was called normotriglyceridemic abetalipoproteinemia, and later it was shown that it was caused by a homozygous mutation at codon 2252 in *APOB* that resulted in an ApoB-50 protein in addition to a normal ApoB-48 protein.[10] There have been two other reports of patients with similar biochemistry.[11,12] In the first case, only clinical data from infancy were reported, whereas the second article documented a family with a probable heterozygous condition and much milder clinical features. No molecular analysis was reported in the either article.

We report a patient with strikingly similar clinical and biochemical features to the original case that Malloy and colleagues[9] presented, but with slightly different molecular cause in that the patient was a compound heterozygote for a null allele and a novel ApoB variant, ApoB-66. This second case confirms the condition as a distinct clinical entity, although the term *normotriglyceridemic hypobetalipoproteinemia* is preferred to normotriglyceridemic abetalipoproteinemia.

Patient and Methods

Case Report

The patient, a New Zealand Maori boy, presented at aged 1 year with developmental delay. At aged 2 years, he began having generalized seizures that responded well to carbamaz-