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Letter to the Editor

Olfactory Loss in Usher Syndrome: Another Sensory Deficit?

To the Editor:

Usher syndrome (USH), the most frequent type of hereditary combined deafness and blindness in adults, represents a heterogenous group of autosomal-recessive disorders characterized by congenital sensorineural hearing loss (SNHL), retinitis pigmentosa (RP), and, in some cases, vestibular dysfunction. The standard classification of this multisensory disease usually recognizes two distinct clinical presentations: type 1 (USH1), which manifests profound hearing deficit, RP, and vestibular dysfunction; and type 2 (USH2), which is characterized by mild-to-severe hearing loss, RP, and normal vestibular function. Clinically, the sense of smell has attracted little attention in USH patients, and the few studies have been contradictory and based on crude, nonstandardized tests [Bruno and Ioli-Spada, 1962; Usher, 1914]. Although the cause of this disorder remains unknown, ciliary dysfunction has been strongly implicated in the pathogenesis of USH [Arden and Fox, 1979; Barrong et al., 1992; Hunter et al., 1986]. Since olfactory receptor cells are ciliated, we sought to determine, using modern quantitative olfactory tests, whether USH patients do in fact experience olfactory loss. If olfactory problems exist, olfactory testing may prove useful as a means of identifying new genotypic and phenotypic forms of USH.

The University of Pennsylvania Smell Identification Test (UPSIT) was administered to 8 patients classified as USH1 and 14 classified as USH2, as well as 22 age-, gender-, and smoking-habit-matched controls. This reliable and sensitive test of odor identification correlates well with a number of more time-consuming measures [Doty, 1989]. In addition, a single-staircase phenyl ethyl alcohol (PEA) odor detection threshold test was given to 7 USH1 and 10 USH2 patients. A trained tester administered both tests to each subject, taking particular care that the test procedure and items were completely understood. In the case of the UPSIT, the tester read each question aloud to the subject (or, if needed, communicated through an interpreter), presented each odorant, and recorded each answer.

The median UPSIT scores of the USH patients (Table I) were significantly lower than those of controls (Wilcoxon signed-ranks test, $Z = 2.841$, $P < 0.005$). The USH1 and USH2 scores did not differ significantly from one another (Mann-Whitney U test = 61.50, $P = 0.700$). Eleven USH patients (50%) evidenced olfactory dysfunction by scoring ≤ 25th centile of a normal reference group, and 6 (27.3%) of these 11 patients scored ≤ 10th centile. Olfactory deficit was present among both USH1 and USH2 patients (5 USH1 and 6 USH2 patients scored ≤ 25th centile). While the average PEA thresholds were higher in the USH group relative to controls, this difference was not statistically significant (respective medians, $10^{-5.19}$ and $10^{-6.13}$; $Z = 1.677$, $P = 0.094$), perhaps due to the smaller number of subjects who received this test.

Our results, in a small cohort, suggest an association between olfactory loss and USH; confirmation is required in a larger, better-defined patient population. The presence of olfactory dysfunction, in combination with losses in vision, audition, and balance, amplifies further the consequences of Usher syndrome. Given the evidence linking ciliary abnormalities to USH-related pathology of the retina and inner ear, a ciliary-associated gene mutation might well explain the olfactory deficits present in some USH patients. Indeed, Weil et al. [1995] recently showed that a defective myosin protein is responsible for Usher syndrome type 1b. This molecule is likely an important cytoskeletal component of cilia. Additionally, several reports have demonstrated abnormal microtubules within the axonemes of photoreceptor-connecting cilia in USH2 patients [Barrong et al., 1992; Berson and Adamian, 1992; Hunter et al., 1986].

Although the evidence implicating a ciliary abnormality in the pathogenesis of USH is convincing, the genetic heterogeneity of both USH1 and USH2 (five loci identified to date) warrants continued investigation into defects of alternative, and shared, qualities of the eye, ear, and olfactory neuroepithelium. Our results suggest olfactory testing should be included as a part of test batteries used for comprehensive evaluation of patients with USH1 and USH2 [e.g., Smith et al., 1994].

TABLE I. Median UPSIT Scores and Proportion of Subjects Falling at or Below the 25th and 10th Centiles of a Normal Reference Group [Doty, 1989]

Group	UPSIT	25th centile	10th centile
Usher	34.00 (33–37)[a]	11/22 (50.0%)[b]	6/22 (27.3%)[b]
Control	37.00 (36–38)[a]	4/22 (18.2%)[b]	0/22 (00.0%)[b]

[a] Interquartile range.
[b] Proportion.

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Such testing may aid in the classification of specific genotypic and phenotypic forms, and in the identification of the subset of patients with significant smell deficits, thereby providing the clinician with an opportunity to counsel individuals with USH-related olfactory dysfunction.

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