Olfactory Evaluation in Children: Application to the CHARGE Syndrome

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ABSTRACT. Objective. To find an efficient tool for testing olfactory function in children and use it to investigate a group of children with CHARGE (coloboma, congenital heart disease, choanal atresia, mental and growth retardation, genital anomalies, and ear malformations and hearing loss) syndrome.

Methods. We adapted for children an olfaction test that had just been validated in an adult French population and investigated a control group of 25 healthy children aged 6 to 13 years. We then tested the olfactory capacity of a group of 14 children with CHARGE syndrome, aged 6 to 18 years. A questionnaire was completed with the parents about their children’s feeding difficulties and their ability to recognize odors in everyday life. We recorded and scored the histories of feeding behavior anomalies, the visual and auditory status, and current intellectual levels. MRI of the olfactory tracts and bulbs was analyzed for 9 of 14 children.

Results. We showed that healthy children have similar olfactory function to that of the adult control group, which was representative of the general population, without any difference for either gender or age. We also showed that all children with CHARGE syndrome had olfactory deficiency. Half of them were anosmic, and the others had olfactory residual function (hyposmic). We found no association between olfactory deficiency and feeding behavior, visual or auditory impairment, or intellectual level. Parental subjective evaluations were accurate for only half of the group. All of the MRIs showed anomalies of the olfactory tracts and bulbs varying from moderate hypoplasia to complete aplasia, without any relation between the radiologic and the functional results.


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Olfaction has always been and remains the most neglected sense in studies of child development and behavior, the main reasons being the poor knowledge concerning the role of olfaction in human development and behavior and the lack of available tools for investigating olfaction, in particular in children. Development of the olfactory system begins very early in the human embryo; olfactory bulbs have their definitive structure at day 56. Then, cells of the olfactory placode differentiate to gonadotropic cells and migrate to the hypothalamic region along the terminal nerve (cranial nerve 0), the olfactory nerve (cranial nerve 1), and the vomeronasal nerve. One part of the olfactory system projects to the anterior part of the hypothalamus for odor perception and discrimination; the other projects to the limbic system and the hippocampus for the behavioral impact of olfaction and olfactory emotional memory. The Jacobson vomeronasal organ is a fetal structure that reduces after birth and that allows the transmission of odors through aqueous middles, in particular amniotic fluid. Several data have shown that olfaction is functional during prenatal life. At birth, newborns have highly efficient olfactory abilities, allowing them to discriminate the odor of their mother’s skin or milk from those of other mothers and to modify their feeding behavior according to the milk flavor. In mice, olfaction is crucial at birth to lead the pups to their mother’s nipples, and anosmic mice die shortly after birth because they cannot find them. All of these data suggest that human neonatal olfaction probably plays a role both in mother-child bonding and in newborns’ feeding behavior. During the first years of life, the role of olfaction is probably important, although few studies have demonstrated this, principally because olfaction evaluation is difficult in this age range. Nevertheless, in a previous study, we showed that reproducible behavioral modifications (breathing rhythm, mobility, and sight) indicate that healthy infants and toddlers (3 months to 3 years) have good olfactory abilities. Several studies have shown that olfaction improves from the age when it becomes testable (7–8 years of age) until the age of 40 years. These observations may be attributable to the methods of olfaction testing and are discussed later. After puberty, girls have better olfaction.
abilities than boys.\textsuperscript{17,18} From the age of \textasciitilde 40 years, olfaction abilities decrease, which partly explains anorexia in the elderly.\textsuperscript{18} The role of olfaction in adults is likely involved in several fields, such as appetite, emotional memory, and sexual bonding. However, few studies can prove these roles. Studies on behavior in adults with olfaction disorders, in particular patients with Kallmann syndrome, are rare and do not show major effects of hyposmia, suggesting that hyposmic patients compensate for their deficit by other sensorial and cognitive means.\textsuperscript{19–21} Moreover, in humans, especially in Western and so-called developed cultures, the sense of smell is not well taught or stimulated.

CHARGE syndrome (coloboma, congenital heart disease, choanal atresia, mental and growth retardation, genital anomalies, and ear malformations and hearing loss) is a congenital malformative picture that was described 25 years ago.\textsuperscript{22,23} In addition to the defects cited in the acronym, other anomalies have been described. Some of them have a high frequency, such as vestibular anomalies, facial dysmorphism, asymmetrical facial palsy, and brainstem dysfunction, whereas others have a lower frequency, such as renal, esophageal, osseous, and cerebral malformations.\textsuperscript{24–26} Once the structural anomalies are repaired, children with CHARGE have to overcome multiple sensory impairments, such as visual, auditory, and balance impairments. Olfaction has never been investigated in patients with CHARGE syndrome, although several arguments suggest that olfaction dysfunction is crucial in this malformative condition. First, most children with CHARGE syndrome have initial, severe, and long-lasting feeding disorders that are poorly explained by their swallowing disorders alone. Second, children with CHARGE syndrome may have genital anomalies as a result of hypothalamic luteinizing hormone-releasing hormone deficit.\textsuperscript{27} Some radiologic and anatomic data have already shown arhinencephaly in CHARGE syndrome.\textsuperscript{25,28} Finally, children with CHARGE syndrome often have peripheral orofacial anomalies that may impair olfaction, such as choanal atresia, cleft palate, or upper airway anomalies that sometimes lead to tracheotomy. We wanted to evaluate an additional sense (olfaction) in children with other multiple sensorial deficits. Thus, the aims of this study were dual: first, to explore an olfactory test adapted to young children (>5 years of mental age) or disabled children, and, second, to apply this test to a series of children with CHARGE syndrome.

**METHODS**

**Patients**

**Control Group**

A control group of 25 healthy children who were aged 6 to 13 years and had no known history of olfactory disturbance were investigated. The group was composed of 14 girls aged 7 to 13 years (mean \( \pm \) SD: 10.6 \( \pm \) 2.2) and 11 boys aged 6 to 13 years (mean \( \pm \) SD: 9.5 \( \pm \) 1.9). Three girls had adenoidectomy, 1 boy had adenoidectomy and tonsillectomy, and 1 girl was born prematurely without intellectual sequelae. To compare these children’s olfactory test results with those of adults, we used the results of 52 normal adults tested by Bonfils et al.\textsuperscript{29}

**Patients With CHARGE Syndrome**

Fourteen children with CHARGE syndrome were included. The group consisted of 8 girls aged 7.5 to 18 years (mean \( \pm \) SD: 12.5 \( \pm \) 4) and 6 boys aged 6 to 10 years (mean \( \pm \) SD: 7.8 \( \pm \) 1.4). The diagnosis of CHARGE syndrome was made according to Blake and Amiel’s criteria (5 major criteria or 4 major criteria and 3 minor criteria\textsuperscript{30,31}). We asked the families to participate when their child had speech and mental age corresponding to a 5- or 6-year level. Their visual ability had to be good enough to allow them to recognize drawings representing the odors on 10 10-cm pictures. Six patients had peripheral risk factors for olfactory deficit: patients 2 and 3 had cleft lip and palate; patients 2, 3, 8, and 9 had transient tracheostomy; and patients 5, 9, and 14 had unilateral choanal atresia. Patient 14 had previously been tested with a different method. She was excluded from the results but included in the association calculation and the discussion.

Parents and children of both groups all were volunteers for this prospective study. Consent of all of the families was obtained in accordance with the ethics rules of our hospital.

**Olfactory Tests**

The French Biolfa olfactory test, recently validated in healthy young adults, was adapted to children.\textsuperscript{29} The Biolfa test uses 2 series of 30-mL glass sniff bottles that contain odorous chemical substances. The first series measures the olfactory thresholds of 3 different substances (eugenol, aldehyde C14, and phenyl ethyl alcohol [PEA; quantitative trial]). The second series is an odor identification test to determine quality of olfactory function using a large panel of odors that are common to Southern European countries (qualitative trial).

**Olfactory Thresholds**

The threshold test consisted of aqueous dilutions of 3 components (eugenol, aldehyde C14, and PEA), the mean detection thresholds of which (0.5, 0.15, and 7.5 ppm, respectively) were published by the French Association for Normalization in 1989.\textsuperscript{32} These concentrations defined the level 3 on the difficulty scale of 9 concentration levels used in the test (Table 1). The lowest concentration at which 1 of these odors was detected was termed “detection threshold.” In each test, we asked the child which of 2 stimuli (an odor or a blank), presented sequentially and in random order, smelled stronger (the forced-choice procedure). The first test began at the third level of difficulty. When a child failed to detect an odor, the next test was performed at the next higher concentration level. For normal patients, the threshold results are expressed in concentration (parts per million). This calculation cannot be used for anosmic patients because they cannot detect any odor (infinite threshold). Then, for analyzing the olfactory function in such cases, a test score was calculated for each component (eugenol, aldehyde C14, and PEA). For each child, the eugenol score was the value [1/eugenol threshold], the PEA score was the value [1/PEA threshold \( \times \) 100], and the aldehyde C14 score was the value [1/aldehyde C14 threshold]. In anosmic patients, the olfaction threshold concentration tends to the infinite; thus, the test score tends to 0 and was estimated as 0.

**Odor Quality Identification**

The second part of the test is a qualitative evaluation in which the patient was asked to recognize an odor presented at a concent-

**TABLE 1. Odorant Concentration as a Function of the 9 Levels of the Test**

<table>
<thead>
<tr>
<th>Level</th>
<th>PEA, ppm</th>
<th>Eugenol, ppm</th>
<th>Aldehyde C14, ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.5</td>
<td>0.1</td>
<td>0.05</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>0.3</td>
<td>0.10</td>
</tr>
<tr>
<td>3</td>
<td>7.5</td>
<td>0.5</td>
<td>0.15</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>0.7</td>
<td>0.20</td>
</tr>
<tr>
<td>5</td>
<td>8.5</td>
<td>1</td>
<td>0.25</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>1.5</td>
<td>0.50</td>
</tr>
<tr>
<td>7</td>
<td>20</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>30</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>9</td>
<td>40</td>
<td>10</td>
<td>5</td>
</tr>
</tbody>
</table>
tion corresponding to his or her own olfactory detection threshold previously measured. Among the 8 odors proposed for adults, we chose the 6 that are most familiar to children, to be sure that we were specifically testing olfaction and not the cognitive processes of the children: citronella (lemon), cis-3-hexenol (grass), t-carvone (mint), 1-octene-3-ol (mushroom), vanillin (vanilla), and para-cresyl acetate (horse dung). Moreover, drawings representing 10 odors were systematically presented to the child to help his or her memory and oral expression. The test was scored as the number of olfactory items out of 6 correctly identified. The same investigator performed all of the tests. For children with CHARGE, 1 parent was present during the test, to avoid communication difficulties with the investigator.

Clinical Investigation in Patients With CHARGE Syndrome

In addition to the olfaction test, a questionnaire was discussed with the parents on their child’s feeding difficulties and ability to smell and recognize odors in everyday life. This subjective evaluation of their olfactory capacity was scored at 3 levels: normal olfaction, residual olfaction, and no olfaction. Factors that are likely to decrease olfactory capacities, such as tracheostomy, cholangitis, and cleft palate, were noted (even when they were no longer present at the study time). The severity of 2 other sense impairments (auditory and visual) was noted. Because the group was small, they were scored in 2 grades. For visual ability, “minor” impairment meant no coloboma, or unilateral coloboma, or bilateral coloboma but outside the macula and the papilla; “major” impairment meant large, bilateral coloboma, including the macula. For auditory ability, “minor” impairment meant hearing loss <60-dB deficit, and “major” impairment meant hearing loss ≥60 dB. The severity of the feeding disorders was scored after analysis of the medical history, taking into account both the duration of artificial feeding (nasogastric tube or gastrostomy) and the abnormal feeding behavior (poor appetite and delay before achieving normal chewing and swallowing). Feeding disorders were scored in 4 grades: absent, minor, moderate, and major. The current intellectual status of the children with CHARGE was evaluated according to their school level, school system, and rehabilitation programs. They were scored in 5 classes, using a previous protocol, from class 0 (the best) to class 4 (the worst).

Radiologic Data

For ethical reasons, brain MRI was not performed only for this study. However, we reanalyzed previous MRIs, only 9 of which pass through thin sections of coronal planes, correctly showing the olfactory tracts and bulbs. Olfactory bulb and tract anatomic anomalies were scored as follows: normal, moderate, or major hypoplasia or absence. The radiologist was blinded to the results of the olfactory evaluations.

Statistical Methods

To compare the olfactory thresholds of the children of the control group (n = 25) with the series of normal adults previously investigated (n = 52), we used the nonparametric Wilcoxon test. To compare children with CHARGE syndrome with the control group, because our sample was small, we used nonparametric tests, the Wilcoxon test for continuous data, and Fisher’s exact test for categorical data. Fisher’s exact tests were performed to test the relation among the olfactory deficiency and feeding disorders, current intellectual levels, and radiologic results. Concordance between objective olfaction test results and familial subjective evaluations was evaluated using the κ coefficient.

RESULTS

Control Group

We first showed that healthy children have olfactory capacities similar to a control group of adults, representative of the general population. Comparison between the children’s and adults’ threshold concentrations for the 3 components (eugenol, aldehyde C14, and PEA) showed no difference (Table 2). There were no differences between girls’ and boys’ detection thresholds (Fig 1). For the qualitative test, children tended to have better results than adults (Fig 2). The 2 odors that are the most familiar in infancy (vanilla and mint) were recognized by 84% and 88%, respectively, of the healthy children, although they were recognized by only 55% and 51% of the adults, respectively. Sixty-eight percent of healthy children recognized lemon (63% for adults), which was better recognized by the older children, and 56% of all children (42% for adults) recognized horse dung (they all were city dwellers!).

Overall, we found no difference between boys and girls, and the younger children had results similar to older children. Results of children with a history of ears, nose, and throat problems were similar to those without such a history. Children of the control group had a very good understanding of the test whatever their age, showing that it was suitable for young children and suggesting that it was valid for disabled children, provided that they have reached speech and intellectual levels of ∼5 years.

CHARGE Group

The control group and the group of children with CHARGE did not differ for age or gender.

Quantitative Evaluation

All children with CHARGE syndrome, except for 1, had severely decreased olfactory thresholds. One child has a detection threshold in the normal range for aldehyde C14 and PEA (7.5 and 0.15 ppm, respectively) but no detectable threshold for the third component. Nine of the 13 children who were tested by Biofa (70%) had 0 detection scores. Detection scores differed highly between CHARGE and control children (Table 3).

Qualitative Evaluation

All children with CHARGE syndrome had severe olfactory discrimination difficulties. Only the patient who had correct detection threshold at the quantitative evaluation had a qualitative score (4 of 6) in the normal range. All of the others had lower scores. Seven of the 9 children who had a null detection threshold could not recognize any odor. These 7 children can clearly be considered anosmic (7 of 13 = half of the series). The other 2 children (with a null detection threshold) had a very good understanding of the test whatever their age, showing that it was suitable for young children and suggesting that it was valid for disabled children, provided that they have reached speech and intellectual levels of ∼5 years.

### Table 2. Comparison Between Healthy Children and Adults.

<table>
<thead>
<tr>
<th></th>
<th>Children</th>
<th>Adults</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>7.06 (0.46)</td>
<td>7.07 (0.40)</td>
<td>NS</td>
</tr>
<tr>
<td>Median</td>
<td>7</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Minimum–maximum</td>
<td>6.5–8.0</td>
<td>6.5–7.5</td>
<td></td>
</tr>
<tr>
<td>Eugenol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.364 (0.21)</td>
<td>0.410 (0.18)</td>
<td>NS</td>
</tr>
<tr>
<td>Median</td>
<td>0.30</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>Minimum–maximum</td>
<td>0.1–0.7</td>
<td>0.1–0.7</td>
<td></td>
</tr>
<tr>
<td>Aldehyde C14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.148 (0.09)</td>
<td>0.104 (0.05)</td>
<td>.03</td>
</tr>
<tr>
<td>Median</td>
<td>0.15</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>Minimum–maximum</td>
<td>0.05–0.50</td>
<td>0.05–0.20</td>
<td></td>
</tr>
</tbody>
</table>

Detection threshold concentrations (in parts per million) are shown.

* Wilcoxon test.

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detection threshold) were able to recognize only 1 and 2 odors, respectively. The children who had residual abilities in the quantitative evaluation could identify from 2 to 5 odors. The difference in scores between children with CHARGE syndrome and control subjects is shown in Fig 3. Comparison of these discrimination tests between children with CHARGE syndrome and control subjects showed highly significant differences except for horse dung (Table 4).

To grade olfactory deficit is difficult because both threshold and discrimination have to be considered and because the olfactory stimulus is not a linear variable. Nevertheless, results for our group of children with CHARGE syndrome can be summarized as follows: half of the children were anosmic ($n = 7$), the other half were hyposmic ($n = 6 +$ the child who was previously tested with another test and who was considered hyposmic). Of the 6 children who had hyposmia, 2 were severe, 3 were moderate, and 1 was mild.

To search for associations with the clinical parameters, because the sample was small, we divided the results of the children with CHARGE syndrome into 2 groups: anosmic and hyposmic. We did not find any statistical relation between olfactory test and clinical parameters. Comparison between subjective evaluation (parents’ opinion) and objective results of the Biolfa test showed a poor concordance ($\kappa < 0$). The parents’ assessments agreed with the Biolfa results for only 6 of 13 children (patient 14 tested with another technique). Of the 6 children with peripheral risk factors for olfaction deficit, 3 were anosmic and 3 were hyposmic. This ratio was not different from that for the whole group. Surprising, we found no
relation between the olfactory deficits and the severity of the feeding disorders. We found no association between the olfactory deficits and the current intellectual levels of the children, despite that all of the children of the low intellectual level groups were anosmic. However, children of the high intellectual level group could also have severe hyposmia or anosmia. We found no relation between the olfactory deficit and either visual or auditory impairment.

All 9 MRIs showed anomalies of the rhinencephalon. The olfactory tract and bulb anomalies varied from moderate hypoplasia to complete aplasia. No association could be found between the radiologic and the functional results.

**DISCUSSION**

Olfactory evaluation of children is now possible using the French Biolfa test, which has been adapted and validated in healthy children. We found no statistical difference between the results of the healthy children and those of adults, although the qualitative part of the test had been simplified for children. The results of children were better than those of adults for the 2 infantile odors. We found no differences for either age or gender. Our results differ from those of Richman et al, who tested children aged 3 to 17 years. They showed better olfactory abilities in older children than in younger and in girls than in boys. These differences may be attributable to methodologic bias. Because the wider the age range is and the more complex the test, the more likely differences between the youngest and oldest children are. Even in our simplified procedure, we observed that the less usual odors, such as lemon or dung, were the least well recognized by normal children. This suggests that the main problem in child olfaction testing is to determine whether the test evaluates olfaction or cognitive function. No girl of our control group was pubescent, whereas some of the Richman’s group may have been because they were older than ours. This may also explain the lack of difference between genders in our study.

The Biolfa test is an interesting tool for evaluating olfaction in normal children as well as in children with disabilities. Olfaction certainly has more influence than we know on children’s development and behavior, especially on feeding behavior and maybe on affective and psychological behavior. Olfaction is a primitive sense that is efficient early in life but receives no training and must be forgotten or neglected when higher methods of communication, especially speech, set in. Nevertheless, it might be interesting to look for olfactory dysfunction in children with disorders that affect appetite or behavior, such as nonorganic failure to thrive, for which the decrease in ingested food is often not understood, attention-deficit/hyperactivity disorder, and autism. Finally, the olfactory system could be impaired in children with congenital or acquired lesions of the forebrain or of the brain midline. Having an efficient test for olfactory evaluation may now change the pediatrician’s approach to this question and lead to additional studies on the effects of introducing olfactory stimulation in rehabilitation programs for children with disabilities.

In CHARGE syndrome, olfaction seems to be a crucial question. In this series, olfactory deficiency and rhinencephalon radiologic anomalies were always present. Our sample of MRIs is small, but the results are very coherent. If this high frequency of radiologic rhinencephalon anomalies is confirmed in larger series, then this radiologic feature could become a major criterion for the diagnosis of CHARGE syndrome.

**TABLE 3.** Comparison of the Detection Thresholds of Children With CHARGE Syndrome and Control Subjects

<table>
<thead>
<tr>
<th>Odor</th>
<th>Control (n = 25)</th>
<th>CHARGE (n = 13)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>14.22</td>
<td>1.67</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Median</td>
<td>14.29</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Minimum–maximum</td>
<td>12.5–15.38</td>
<td>0–13.33</td>
<td></td>
</tr>
<tr>
<td>Eugenol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>4.34</td>
<td>0.07</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Median</td>
<td>3.33</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Minimum–maximum</td>
<td>1.43–10</td>
<td>0–6.67</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Aldehyde C14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>9.37</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>6.67</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>Minimum–maximum</td>
<td>2–20</td>
<td>0–6.67</td>
<td></td>
</tr>
</tbody>
</table>

* Wilcoxon test.
Rhinencephalon anomalies have already been described in CHARGE syndrome, at autopsy or in brain imaging, but these anomalies are not yet systematically sought. Thin sections of coronal planes, showing olfactory bulbs and tracts, are now recommended in brain imaging of patients who are suspected to have CHARGE syndrome. Rhinencephalon congenital anomalies are rare and are mostly observed in isolated congenital anosmia, holoprosencephaly spectrum, Kallmann de Morsier syndrome, and Johnson-McMillin syndrome. Isolated congenital anosmia is usually described in adults who complain of smell disorders late in life, and very few cases have been published in children. In this situation, the patients are otherwise healthy and the differential diagnosis of CHARGE syndrome is not considered. Johnson-McMillin is a rare autosomal dominant syndrome associated with alopecia, hypogonadotrophic hypogonadism, atresia of the external auditory canal, tooth defects, cardiac defects, and mental retardation. It induces embryologic anomalies of the ectoderm and neuroectoderm of the first and second brachial arches, Rathke’s pouch, and the diencephalon. Overlaps between Johnson-McMillin and CHARGE syndrome exist because CHARGE syndrome also induces anomalies of neuroectoderm development and neural crest migration. Overlaps between CHARGE and Kallmann syndromes are interesting for several reasons. Kallmann syndrome, in its typical phenotype, is associated with hypogonadotrophic hypogonadism and olfaction deficit. Some cases of Kallmann syndrome have been described with additional features such as hearing loss, choanal atresia, and mental retardation. In these situations, searching for semicircular canal anomalies could be useful to confirm or not CHARGE diagnosis. Moreover, endocrinologic anomalies of Kallmann syndrome are useful for understanding and investigating genital anomalies of patients with CHARGE syndrome. The lack of relationship that we found between functional and radiologic anomalies in CHARGE syndrome is not surprising, because the same observation has already been made in Kallmann neuroradiologic studies.

Finally, several autosomal genes have been implicated in Kallmann syndrome and may be candidate regions when a mutation in the CHD7 gene has been excluded. Our results suggest that olfactory deficiency of CHARGE syndrome is attributable not only to central anomalies but also to peripheral ones, which worsen olfactory function. We observed children with associated choanal atresia and different types of rhinencephalon radiologic anomalies. No child of this series had bilateral and complete choanal atresia, explaining why 2 of the 3 children with choanal atresia had residual olfactory abilities. Only bilateral choanal atresia has been shown to be responsible for anosmia in a small sample, suggesting that choanal atresia plays a deleterious role by its reduction of airflow through the olfactory nasal epithelium. Similarly, tracheotomy and cleft palate in children without central olfactory system anomalies have been incriminated in olfaction disorders.

The consequences of olfactory deficiency in children with CHARGE syndrome are difficult to quantify because these children have multiple causes explaining their disabilities. That is probably why we did not find any association between olfactory deficiency and most clinical aspects of our series. A more subtle analysis than ours that focuses on the description of feeding behavior and cognitive function could provide more information. Hence, it is possible that olfactory deficiency participates in the phenotype of the affected children, especially regarding their feeding disorders, mother-child attachment, behavior disturbance, communication difficulties, and maybe cognitive outcome. When it becomes possible, evaluation of olfactory abilities of children with CHARGE syndrome should be included in the investigations that are used to analyze their disabilities.

**Table 4.** Qualitative Olfactory Acuity in Children With CHARGE Syndrome Compared With Control Subjects

<table>
<thead>
<tr>
<th>Odor</th>
<th>Control</th>
<th>CHARGE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vanilla</td>
<td>21/25</td>
<td>5/13</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Mint</td>
<td>22/25</td>
<td>3/13</td>
<td>.0001</td>
</tr>
<tr>
<td>Mushroom</td>
<td>22/25</td>
<td>3/13</td>
<td>.0001</td>
</tr>
<tr>
<td>Grass</td>
<td>24/25</td>
<td>3/13</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Lemon</td>
<td>17/25</td>
<td>0/13</td>
<td>.0001</td>
</tr>
<tr>
<td>Horse dung</td>
<td>14/25</td>
<td>3/13</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are number of successes/number of children.
Even if olfactory deficiency cannot be measured in children who have CHARGE syndrome and whose mental age and speech level are below 5 years, radiologic data could suggest functional anomalies and lead to various suitable actions. First, olfactory deficiency has to be taken into account in the understanding of the abnormal feeding behavior of most children with CHARGE syndrome. For those who have major difficulties in achieving normal feeding behavior, especially difficulties in swallowing solids even after improvement of their organic swallowing disorders, it is likely that food texture plays an important role. Healthy children recognize and appreciate food by its visual aspect, taste, texture, and smell. If vision and olfaction are impaired, then children surely give more value to taste and texture. Their preference for salty or spicy tastes becomes understandable, as well as their preference for smooth textures. Moreover, children with olfactory dysfunction may benefit from rehabilitation programs. Sense of smell does not pass exclusively via olfactory bulbs, tracts, and nerve. Specific odors, such as lemon and vinegar, pass through the sensory branch of the fifth cranial nerve. In CHARGE syndrome, these odors should be preferred to odors that pass exclusively through the classical olfactory system. From early in life, olfactory residual capacities need to be stimulated by increasing the concentration of the fragrances that surround the child by giving him or her tasty food. Stimulation by games may educate their olfactory memory. Finally, olfaction must be part of the multisensorial stimulation programs that are essential for children with CHARGE syndrome.

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