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Olfactory Response in Patients with Cerebral Palsy: Investigation of the Possible Use of Olfactory Testing to Evaluate Patients and Reduce Anxiety of Their Parents

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Abstract : Cerebral palsy (CP) is a developmental disorder associated with lifelong motor impairment and disability. Several studies have investigated the effects of CP on sensory responses, but there has been no research on olfactory function in CP. This study had two specific aims. First, by observing respiratory responses which serve as an index for the ability to detect and recognize odors, we aimed to estimate the patients' ability to distinguish pleasant from unpleasant odors. These responses can also indicate the capacity for an emotional response to pleasant or unpleasant stimuli. Second, we aimed to investigate the psychological response in the parents as they observed the respiratory response in their children during the odor test. Parents were assessed with the Spielberger State-Trait Anxiety Inventory (STAI) to measure their state anxiety levels before and after they had observed their children being tested. In patients with CP, respiratory rate (RR) significantly decreased during pleasant odor stimuli ($P < 0.05$). There was a significant increase in RR during the presentation of the unpleasant odor ($P < 0.05$). All the CP patients showed respiratory changes in response to both pleasant and unpleasant smells, and we found that the parents' anxiety levels decreased after the test. We intend to develop this olfactory test technique to contribute to the neurological rehabilitation for CP patients and to reduce anxiety of their parents.

Key words : cerebral palsy (CP), olfaction, respiratory rate (RR), anxiety, parents' care, emotional response

Introduction

Cerebral palsy (CP) is a developmental disorder associated with lifelong motor impairment and disability. The disorder is caused by damage to the brain before birth or in early childhood, and is characterized by persistent abnormal limb strength, abnormal limb control, or both¹⁾. Clinical diagnosis of CP has been based on neurological examination and the absence of an underlying genetic disorder. Though considered a motor disorder, CP can also affect sensory

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functions such as vision²⁾. Although several studies have investigated the effects of CP on sensory responses for treatment purposes^{3,4)}, there has been no research on olfactory function in CP.

Olfaction involves a unique sensory pathway that differs substantially from other sensory modalities. In olfactory perception, information bypasses the thalamus to ascend directly to olfactory-related limbic structures, including the piriform cortex, entorhinal cortex, amygdala, hippocampus, and orbitofrontal cortex⁵⁾. An important feature of olfactory perception that has been relatively neglected is its dependence on respiratory activity.

Direct stimulation of olfactory-related areas produces respiratory changes⁶⁾. Unpleasant odor stimulation can increase respiratory frequency, leading to rapid or shallow breathing or both. Conversely, pleasant odor stimulation typically decreases respiratory frequency and increases tidal volume, indicating deep and slow breathing⁷⁾. These changes tend to occur unconsciously. Therefore, unconscious respiratory changes induced by odor are used to assess olfactory perception and serve as an index for olfactory-related limbic activation⁸⁾.

In this study, we tested olfactory function of children and adults with CP. The study had two specific aims. First, by observing respiratory responses, we aimed to estimate the patients' ability to discriminate pleasant from unpleasant odors. These responses can also indicate the capacity for an emotional response to pleasant or unpleasant stimuli. Second, we aimed to investigate the psychological response in the parents as they observed the respiratory response in their children during the odor test. The medical management of children and adults with CP requires careful attention from parents, and being a parent to a child with CP may involve a great deal of anxiety and stress. We hypothesized that observation of their children's responses to olfactory stimuli might improve the parents' anxiety levels.

Methods

This study was performed at the Showa Medical University Hospital from April 1st to July 1st in 2012. We tested 6 patients with CP (3 males and 3 females, aged 3~30 years old; Table 1). Four of the CP patients (cases 2~5) regularly visited the Pediatric Department at Showa Medical University Hospital with their parents, and two of the patients (cases 1 and 6) were admitted to the hospital. All patients could breathe spontaneously without the assistance of a mechanical ventilator. In cases 2 and 3, breathing was assisted by continuous positive airway (CPAP) when their breathing was not stable (case 2, 0.5 L/min CPAP, case 3, 1 L/min CPAP). Informed consent was obtained from the parents, and the study was approved by the Human Studies Committee of Showa University School of Medicine.

Parents were assessed with the Spielberger State-Trait Anxiety Inventory (STAI) あ⁹⁾ to measure their state anxiety levels. After the STAI test, we informed the parents briefly about respiratory responses to olfactory stimuli. The following information was given:

“Olfactory perception is dependent on respiration; for example, you cannot smell if you wear a nose clip. When an odor is presented in front of your nose and you inspire, the molecules trigger a response in the olfactory cortex. Then, your respiration will change. If you find

Table 1. Age, sex and diagnosis of patients

Case No.	Age	Sex	Diagnosis
1	3	F	Cerebral Palsy, Renal Tubular Dysgonosis
2	4	M	Cerebral Palsy, Listeria Meningitis
3	7	F	Cerebral Palsy
4	3	M	Cerebral Palsy
5	30	M	Cerebral Palsy, Melena Neonatorum
6	8	F	Cerebral Palsy, Pseudo Torch Syndrome

the odor pleasant, your breathing pattern will become very slow and deep. If you find the odor unpleasant, your breathing will become very rapid. We are going to present pleasant or unpleasant odors to the patient, and monitor the respiratory responses. If the patient's breathing is very deep and slow, it means that the patient finds the odor pleasant and comfortable. If the patient's breathing is very rapid, it means that the patient finds the odor unpleasant and dislikes it. If the concentration of the odor is too low or if the patient is not focused on the smell because of the experimental situation, we will not be able to see these changes in breathing”.

Measurement of respiration

The CP patients sat on a wheelchair or a bed wearing a respiratory belt (UFI Model 1132 Pneumotrace II, ADInstruments, Bella Vista, NSW, Australia) around their chest to measure the respiratory rate (RR). All data were recorded with an analog-to-digital converter (PowerLab 16SP; ADInstruments) installed on a laptop computer (VAIO VGN-SR91NSA; Sony, Tokyo, Japan).

Olfactory stimuli

The procedure for testing olfactory function normally involves a test of odor detection and odor recognition acuity with a T & T olfactometer (Takasuna Co., Ltd., Tokyo, Japan) prior to experiments. In this procedure, the olfactometer is used to test five odors (odor A, β -phenylethyl alcohol; odor B, methyl cyclopentenolone; odor C, isovaleric acid; odor D, γ -undecalactone; odor E, skatole). Each odorant was presented, dissolved in propylene glycol, at eight different concentrations, each 10 fold the previous concentration; concentrations were labeled from -2 to +5. This T & T olfactometer test requires a verbal response to olfactory stimuli, which our patients were not able to give. Therefore, in this study we excluded the threshold and recognition test and directly examined the effect of odor on RR. As in our previous studies^{6,10}, odor D was used as the pleasant odor, and odor C was used as the unpleasant odor. Odor C is that of rotten food or sweaty clothes and odor D is that of a peach or other sweet fruit. The method of odor presentation was as described previously for normal subjects⁶. The end (> 1 cm) of a strip of litmus paper (140×7 mm) was dipped into a

bottle containing the odorant and then presented in front of the subject.

Respiratory response during olfactory stimuli

After confirmation that the RR was at baseline, the odorant-dipped litmus strip was presented for 30s, with a 30-s interval before the next presentation to minimize adaptation¹¹⁾. We did three trials for each odor. RR was continuously recorded during presentation of odor stimuli and odor-free inter-trial intervals. During the test, the parents of the subjects observed the changes in RR on the computer screen. After the test, the state anxiety levels of the parents were tested with the STAI⁹⁾.

Statistical analysis

All statistical analyses were performed with a commercially available statistical package (SPSS v.11, Tokyo, Japan). Changes in RR were analyzed by using one-way repeated measures analysis of variance (ANOVA) of the three conditions (rest, odor, post-odor). Greenhouse-Geisser correction of the degrees of freedom was applied to correct for violation of the assumption of sphericity. Post-hoc testing was performed with the Bonferroni test. The state anxiety scores were analyzed by the Wilcoxon signed rank test. Data were presented as mean \pm standard deviation (SD).

Results

Respiratory responses during odor stimuli

Fig. 1 shows typical examples of the respiratory response to unpleasant and pleasant odor stimuli. These respiratory maneuvers were measured with the respiratory belt. If a CP patient inspires then inspiration flows upward and if a CP patient expires then expiration flows downward. We get RR counted the peak of each respiratory flow before, during and after odor presentation. In both case 1 and case 2, the unpleasant odor stimuli increased RR, in contrast, the pleasant odor stimuli decreased RR.

Fig. 2 shows the mean (\pm SD) RR before, during, and after odor presentation. RR significantly decreased during pleasant odor stimuli ($P < 0.05$) compared with the rest and post-odor states, and there was a significant increase in RR during presentation of the unpleasant odor ($P < 0.05$).

Anxiety levels in parents before and after the odor test

Fig. 3 shows the mean state anxiety levels of parents before and after observing the respiratory response of their child during odor presentation. The anxiety levels decreased significantly after the test compared with before ($P < 0.05$).

Discussion

We investigated whether CP patients perceive and recognize odor stimuli by observing odor-induced changes in RR, which has been used as an index of emotional responses. In addition,

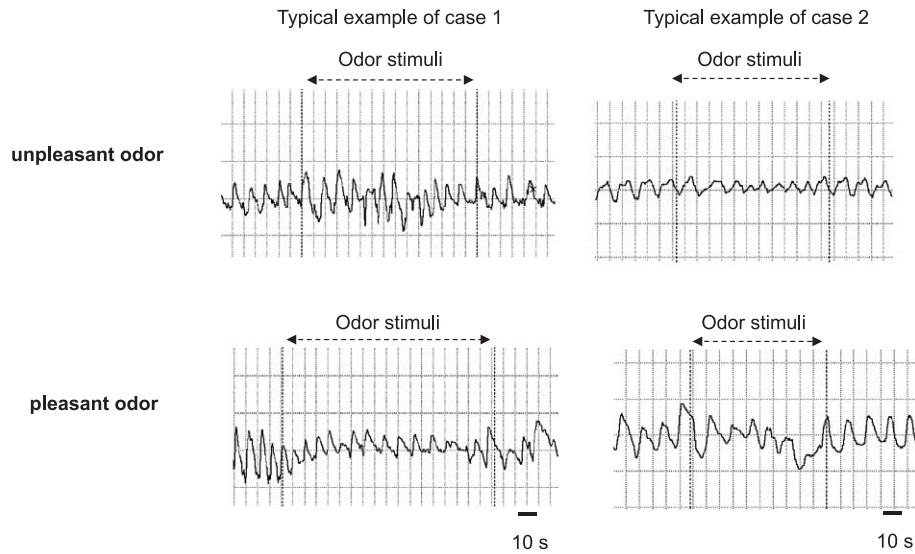


Fig. 1. Typical examples of the respiratory response to unpleasant and pleasant odor stimuli. Inspiration flows upward and expiration flows downward. Respiratory rate (RR) before, during and after odor presentation.

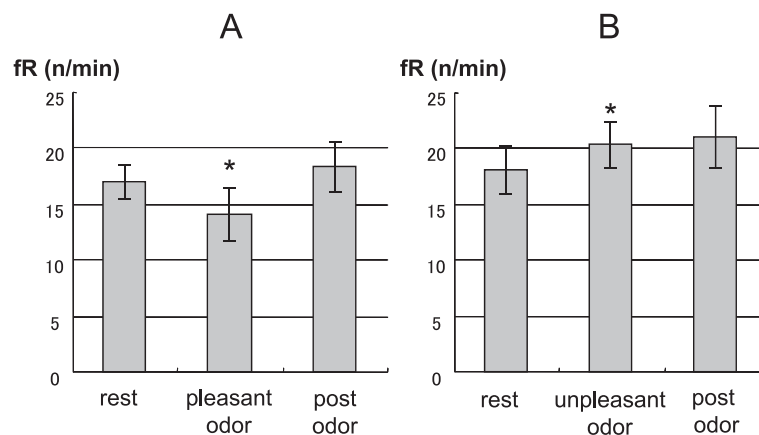


Fig. 2. A : Respiratory rate (RR) before, during pleasant odor and after odor presentation in CP patients. B : RR before, during unpleasant pleasant odor and after odor presentation in CP patients. * $P < 0.05$

we measured the anxiety levels in parents before and after they observed the RR in their children during the odor test.

Olfactory recognition and odor-induced emotions in CP patients

We found that the RR decreased in response to pleasant odors and increased in response to unpleasant odors in CP patients. Since odor perception and recognition are subjective phenomena, we have suggested that measurement of respiratory responses during an olfactory

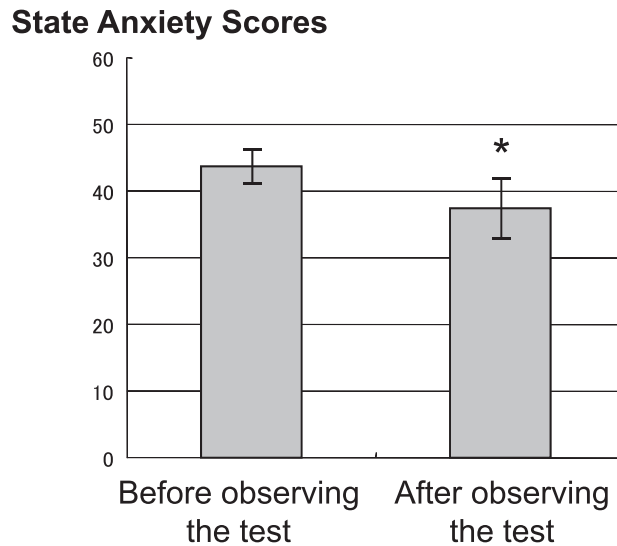


Fig. 3. State anxiety levels of parents before and after observing the respiratory response of their CP-affected children during odor presentation.

acuity test can be used to test for physiological responses that accompany subjective feelings⁸⁾. Several studies^{6,7,10)} have confirmed that respiratory responses are correlated with the subjective sensation of odor and also with brain activities. Increases in RR in response to unpleasant odors were synchronized with activity in amygdala and orbitofrontal cortex, which play important roles in emotion⁶⁾. Decreases in RR in response to pleasant odors were, in addition to the above areas, synchronized with activity in wider areas of the brain, including the hippocampus, superior frontal area, and motor areas. Based on these previous findings, we suggest that the CP patients in this study were able to both detect the odor and experience emotions through olfactory stimuli.

It is difficult to evaluate the function of limbic areas based on magnetic resonance imaging findings in these CP patients. However, the olfaction test used in this study may help us determine whether or not patients have normal olfactory function, and confirm their capability of emotional responses, at least those induced by pleasant or unpleasant odors. Previous studies have suggested that it is difficult to distinguish different negative emotions, such as fear, anxiety, and anger by only observing respiratory responses. To discriminate between these categories of emotions it might be necessary to use various imaging techniques to study differences in brain activation patterns. A limitation of this study was that we did not measure physiological responses such as electroencephalogram (EEG) changes, or other respiratory variables such as tidal volume and end-tidal CO₂ concentration. However, the observation of RR alone may be an index for the assessment of olfactory abilities and odor-induced emotions.

Anxiety levels in parents of CP patients

We also measured anxiety levels in the parents of the subjects before and after the parents

observed the olfaction test. All the CP patients showed respiratory changes in response to both pleasant and unpleasant smells, and we found that the parents' anxiety levels decreased after the test. Many factors may be involved in determining the levels of anxiety in these parents. However, our results indicate that one of the factors might be related to the fact that parents always look for physical signs that can help them guess their children's intentions and thoughts. It has been reported that parents of children with CP have significantly poorer psychosocial well-being¹³). Evidence-based therapy can be effective not only for the patients, but also for the parents by reducing stress and anxiety¹³). Observation of respiratory changes that correspond to emotional responses in children or adults with CP might be quite effective for reducing anxiety in caregivers. After the test, parents reported that they would try aromatherapy in the patient's room at their house, or that they would try stimulation with many kinds of odors. In addition to odors, emotions such as anger, fear, and joy also induce respiratory changes¹²). We suggested that the parents could use observation of respiratory changes in daily life as an index for the emotional state of their children in many circumstances.

Clinical care and rehabilitation in CP patients

Patients with neurobehavioral impairments need effective rehabilitation that is based on neuroscience, and management strategies for primary neurological manifestations such as epilepsy have been developed by neurologists. Advances in evidence-based approaches to clinical care of CP patients have been rather slow. As a consequence of the increasing evidence of neuroplasticity, the recent focus has shifted towards neurological rehabilitation in CP management. This approach aims to improve development and function by capitalizing on the innate capacity of the brain to change and adapt through life²). Holt and Mikati¹⁴). suggested that exposure to an enriched sensory environment is associated with improved cognitive outcomes and increased brain growth in infants with prenatal brain damage. There is evidence that intervention with movement-specific neurological rehabilitation could improve function for children with CP^{15, 16}), and rehabilitation of hearing and visual abilities may also have potential improvement^{3, 4}).

Olfaction is quite a primitive sense and the regions related to olfaction are located in the old parts of the brain. However, olfactory stimulation activates many brain areas, such as the hippocampus, which is related to memory, the visual field, which is caused by a special memory induced by olfactory stimuli, and the motor cortex, which is activated by voluntary breathing during smelling¹⁷). Based on these wide areas of activation by olfactory stimulation, we propose that it might be possible to use olfactory stimulation in the rehabilitation of CP patients to improve cognitive abilities. This study was preliminary, and in future research we intend to monitor responses using additional techniques such as EEG dipole analysis to investigate brain processing.

The anxiety-reducing effect in parents observing the respiratory effects of olfactory stimuli in their children might suggest that their anxiety levels may also be modulated by observation of other cognitive tests. However, with other visual or hearing tests it is more difficult to find meaningful physiological outputs that are suitable for use in CP patients. We intend to develop

this olfactory test technique to contribute to the neurological rehabilitation for CP patients and to reduce anxiety of their parents.

Conflict of interest

The authors have declared no conflict of interest.

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