Diagnosis of isolated congenital anosmia using simultaneous functional magnetic resonance imaging and olfactory event-related potentials: Our experience in six patients

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May 11, 2020

Key Points

- Congenital anosmia is usually associated with Kallmann syndrome, which is characterized by hormonal abnormalities such as hypogonadotropic hypogonadism.

- On very rare occasions, an isolated congenital anosmia presents as olfactory bulb agenesis without this associated syndrome.

- In previous studies of such cases, diagnosis is usually based on the absence of an olfactory bulb on structural MRI, rather than on objective functional measures.

- Simultaneous functional MRI and olfactory event-related potential recordings can provide highly objective evidence of olfactory function.

- We examined both structural and functional MRI and olfactory event-related potential data to diagnose isolated congenital olfactory bulb agenesis, gaining objective evidence of olfactory function.

Keywords

Anosmia, Congenital, Functional magnetic resonance imaging, Olfactometry, Olfactory event-related potential

Main text

Materials and Methods

Ethical considerations

The study was approved by the ethics committee of [removed for blind peer review], and written informed consent was obtained from patients.

Patients and Endoscopic exam

6 patients who had exhibited anosmia since early childhood were included in this study (5 males, 1 females; age range 15-55 years). Patients had no history of sinusitis or chronic congestion and no other complaints, and demonstrated normal psychomotor development and appropriate Tanner classification for their age. They also had no family history of anosmia or delayed puberty. Endoscopic examination revealed no mucoid discharge or polyps, and both olfactory clefts were patent.

Olfactory function test, and chemical and electro-gustatory test

An olfactory function test (the Korean version of Sniffin's Stick Test, KVSS II, Burghart, Germany) was performed on all patients. A chemical and electro-gustatory test was also performed using an electro-gustometer (Gustometer; Rion, Tokyo, Japan).

MRI scans

MRI scans were performed in 5 patients using a 3T scanner (Signa HDxT; GE Healthcare, Milwaukee, Wisconsin) to exclude anatomical causes of olfactory loss in 5 patients. To check the olfactory bulb, T2-weighted 3D images in the coronal plane were obtained using a spin-echo sequence (field of view 150 × 150 mm2; section thickness 0.8 mm).

Simultaneous functional MRI and olfactory event-related potential (OERP)

Simultaneous functional MRI and OERPs were performed in 5 patients. Simultaneous functional MRI and OERP recording can achieve high spatial and temporal resolution. Patients wore a specialized 32-channel electroencephalogram monitoring device (Professional Braincap; Easycap, Herrsching, Germany) compatible with the MRI environment. MRI was performed using the same 3T scanner as for the structural scan, using an 8-channel head coil (Figure 1). First, T1-weighted 3D images in the axial plane were obtained using a fast-spoiled gradient-recalled sequence (field of view 240 × 240 mm2; section thickness 1.3 mm). The functional imaging sequence used was gradient recalled echo-planar imaging (field of view 240 × 240 mm2; section thickness 3.5 mm). Functional MRI and OERP data were obtained during a five-minute timespan consisting of five odor exposure periods and five normal breathing periods. Odorants were presented to patients through a custom-built olfactometer with continuous air flow (4 L/min). In the exposure period, we presented odors to patients for 10 seconds followed by 20 seconds of odorless air. The periods of odor presentation were marked on the electroencephalograms. In the normal breathing periods, patients continuously received odorless air. We used two odorants: CIT (0.2 mL of 10 mmol/L citral) as a pleasant odor, and BME (0.2 mL of 1 mmol/L β-mercaptoethanol) as an unpleasant odor. In the first five-minute session, CIT was presented via the olfactometer and the patient breathed regularly without sniffing. In the second session, BME was presented with the same protocol.[1] To minimize noise, the lights were dimmed, and there was no other stimulation except the odorants.

Endocrinological study

An endocrinological study was performed to detect hypogonadotropic hypogonadism in 6 patients. Follicle-stimulating hormone, luteinizing hormone, and testosterone levels were checked.

Results

All patients were classified as anosmic on the olfactory function test (Figure 2). Chemical and electro-gustatory test results indicated normogeusia.

MRI revealed no gross abnormalities in the brain parenchyma and a normal appearance of the pituitary gland, but the olfactory bulb could not be visualized bilaterally in 5 patients. Shallow olfactory sulci were observed in 4 patients and this suggested congenital agenesis of the olfactory bulb (Figure 3A). Relatively deep olfactory sulci were observed in 1 patient and it suggested early traumatic olfactory disorder (Figure 3B).

On functional MRI, 5 male patients showed no significant activation in primary olfactory cortex in both CIT and BME session. And no OERPs were recorded during their exam (Figure 4A). The one female patient showed mild activation in CIT session, but OERPs were not recorded (Figure 4B).

Follicle-stimulating hormone levels were within normal limits in 6 patients, as were luteinizing hormone levels, and testosterone levels. We therefore concluded that the patients' anosmia was not associated with other structural and hormonal abnormalities such as Kallmann syndrome.

Four patients were confirmed as isolated congenital anosmia. And the olfactory sulci were relatively deep in MRI scan, so one male patient could not absolutely rule out early traumatic anosmia. One female patient

seemed to be acquired anosmia.

Discussion

Olfactory disorders can be classified as conductive, sensorineural, or due to an impairment in the olfactory central nervous system. The vast majority of olfactory dysfunction occurs as a result of upper respiratory tract infection (18–45%), sinonasal disease (7–56%), or head trauma (8–20%), whereas the prevalence of congenital anosmia is low (0.4%).[2]

Synopsis of key findings

Clinical investigation of olfactory disorders involves examination for chronic nasal obstruction, with or without associated infection, as well as the performance of olfactory functional tests. In the cases presented here, nasal endoscopic examination was unremarkable, but olfactory functional tests revealed anosmia. Chemical and electro-gustatory test results indicated normogeusia.

Imaging is not routinely performed for olfactory dysfunction, as findings are negative in most cases. Imaging may be beneficial in certain inflammatory, structural, neurodegenerative, traumatic, and neoplastic conditions. MRI scans can confirm congenital agenesis of olfactory bulbs in cases such as those with Kallmann syndrome.[3,4] We performed MRI scans for these 6 patients because detailed histories and physical examinations were negative. MRI results were suggestive of congenital agenesis of the olfactory bulb.

Agenesis of the olfactory bulb does not necessarily mean olfactory dysfunction. A recent study revealed that human olfactory function can be normal without an olfactory bulb apparent on structural MRI.[5] Therefore, objective tests for olfaction are needed. We recorded OERPs alongside the functional MRI scan to provide a highly objective assessment of olfactory function. Functional MRI can identify areas in the brain activated in response to olfactory stimulation, and OERPs can indicate residual olfactory function.[6] In our study, 5 patients exhibited no activation in response to olfactory stimulation across the whole brain when family-wise error was corrected for ($P = 0.05$). No OERPs were observed in response to olfactory stimulation. These functional MRI findings and OERP results provide objective evidence for anosmia in these patients. Our study has clinical significance as objective olfactory tests such as these have not previously been described in patients with congenital anosmia.

Agenesis of the olfactory bulb is conventionally associated with Kallmann syndrome. However, Powell recently reported that congenital anosmia is more frequently an isolated diagnosis.[7] We therefore assessed the baseline levels of follicle-stimulating hormone, luteinizing hormone, and testosterone to eliminate the possibility of Kallmann syndrome, although signs of puberty were not delayed or absent in these patients. Endocrinological results were within normal limits.

Clinical applicability of the study

In the absence of other structural and hormonal abnormalities, patients with congenital anomalies of the olfactory bulb can be diagnosed with isolated congenital anosmia. Patients with congenital anosmia should be carefully investigated to exclude more serious conditions such as Kallmann syndrome before making this diagnosis. However, agenesis of the olfactory bulb identified on structural MRI does not necessarily mean olfactory dysfunction. Therefore, to further evaluate congenital anosmic patients, simultaneous functional MRI and OERP recording can detect activated areas in the brain and help to provide high objective evidence for the diagnosis of anosmia.

References

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Figure legends

Figure 1: Patients wore a specialized 32-channel electroencephalogram monitoring device compatible with the MRI environment. MRI scans were performed with a 3T scanner using an 8-channel head coil. Odorants and odorless air were presented to patients via a nasal canula.

Figure 2: In all panels: control mean in blue, patients in another color and all error bars are SD. Scores at olfactory threshold(T), discrimination(D), and identification(I) using the sniffin sticks test. All patients were classified as anosmic on the olfactory function test. (Patient A: threshold 1, discrimination 6, identification 4, total 11; Patient B: threshold 1, discrimination 3, identification 4, total 8; Patient C: threshold 1, discrimination 5, identification 4, total 10; Patient D: threshold 1, discrimination 2, identification 3, total 6; Patient E: threshold 1, discrimination 4, identification 3, total 8; Patient F: threshold 1, discrimination 7, identification 4, total 12)

Figure 3: T2-weighted pre-contrast coronal section MRI scans. In normal patients, an olfactory bulb (yellow arrow) and sulci (yellow arrowhead) can be found. However, in patients A and B, the olfactory bulb (red arrow, orange arrow) and olfactory sulci (red arrowhead, orange arrowhead) could not be visualized bilaterally.

Figure 4: Olfactory functional MRI of a normal patient revealed bilateral activation in the orbitofrontal cortex, right uncus, and left primary olfactory cortex in the CIT (citral) session, and mild activation in the gyrus recti in the BME (β-mercaptoethanol) session. OERPs were recorded in both session as seening that the P2 waves were visible.

(A) In the first patient, no activation was observed in the primary olfactory cortex in the CIT session, but activation was seen in the left basal frontal lobe (orbitofrontal cortex), bilateral insula, left inferior frontal operculum, and the right inferior parietal lobule (uncorrected comparison, $P < 0.01$). In the BME session, diffuse activation was seen, possibly due to noise (uncorrected comparison, $P < 0.01$). No OERP was recorded.

(B) In the second patient, activation was observed in the primary olfactory cortex and orbitofrontal cortex in the CIT session. In the BME session, no activation was seen. OERP was recorded in CIT session.