Review

Cranial nerve I: clinical anatomy and beyond

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Abstract: Examination of the cranial nerves is an important part of complete neurological assessment of the patient. With the development of imaging techniques, there is an increased awareness of the possible anatomical variations and anomalies and although there is extensive data on the anatomical variations of some of the cranial nerves, cranial nerve I is relatively understudied. Although the data on olfactory nerve is not abundantly present, there are several types of developmental anomalies, which can be present as aplasia, hypoplasia, olfactory bulb ventricles, and duplication/triplication of the olfactory bulb. There are also several genetic conditions, in which olfactory system malformation are common and require further evaluation. The purpose of this review is to sum up the current data on the clinical anatomy, malformations of olfactory nerve, bulb, tract and associated conditions.

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Introduction

Examination of the cranial nerves is an important part of complete neurological assessment of the patient [1]. With the development of imaging techniques, there is an increased awareness of the possible anatomical variations and anomalies, which are important to consider in clinical practice. Although there is extensive data on the anatomical variations of some of the cranial nerves, cranial nerve I is relatively understudied.

What is usually referred to as the olfactory nerve is properly the olfactory tract and bulb, and is an outgrowth of the forebrain [2]. Two groups of neurons are found in the nasal mucosa. The first group is the lateral olfactory nerves (12–20) which can be found at the level of the superior nasal concha. The second group is the medial olfactory nerves (12–16) which descend along the nasal septum [3]. Primary sensory neurons of this nerve are bipolar and are present in the olfactory epithelium. Their central processes make up the numerous nerves, which pass through the cribriform plate of the ethmoid bone and dura matter. There they synapse with secondary sensory neurons (deutoneuron or mitral cell) forming the olfactory bulb (average length 12 mm, width 5 mm) and tract (average length 30 mm with a transverse diameter of 5 mm in the anterior portion and 2 mm in the posterior portion). The olfactory bulb lies over the cribriform plate and anatomically is seen as an ovoid structure on the inferior surface of frontal lobe (between the right gyri and the medial orbital gyri), above the orbital plate of frontal bone [2, 4, 5]. In front of the anterior perforated substance, the tract divides in lateral, medial and intermediate stria [4].

Nevertheless, surgeons mention that the circumstances in which they find the olfactory neve, bulb and tract differ. The length and thickness of the olfactory nerve may be different as well as is resistance against compression and tension. The olfactory bulb may sometimes be adherent to the olfactory fossa or inversely easily detachable. The olfactory tract may tear off just behind the bulb and the bulb remains, as chained on strong fila olfactoria [6].

Damage to the olfactory bulb and tract is a frequently described complication of brain surgery in the frontal region [7]. Dissecting the olfactory nerve from the orbitofrontal cortex can be performed during operations without its damage but bilateral protection is not always possible [8]. Overall mobilization of the olfactory bulb and tract is limited (29.3±6.4 mm in length) as well as frontal lobe retraction (10 to 15 mm) without compromising of the olfactory function [5, 7].

The list of conditions, which cause olfactory dysfunction, is extensive and any dysfunction in olfaction requires a radiological exploration comprising the nasal cavity, the anterior base of the skull, in particular the frontal and temporal lobes [4, 9].

The most predominant causes of olfactory dysfunctions are upper respiratory infections, head trauma, and nasal and paranasal sinus disease that damage the olfactory neuroepithelium [9].

Significant correlations between olfactory bulb volumes in relation to olfactory function were observed, independent of the subjects' age in adults [10]. Olfactory bulb volumes and olfactory function increased with age in children and adolescents, although it seems that the correlation between structure and function is mediated by the subjects' age [11]. The difference in volume between the right and left olfactory bulbs may be partly responsible for lateralized differences in olfactory function [12]. Their volume seem to increase in case of early blindness [13] and

decrease in a variety of conditions ranging from common like postinfectious [14] and posttraumatic [15] loss of smell to less common as fibromyalgia syndrome [16], snake venom [17] and leprosy [18] (*Table* 1).

Similarly, olfactory sulcal depth was proposed as a biomarker of early embryonic disruption in individuals at risk for schizophrenia [19]. Schizophrenia patients had a significantly shallower olfactory sulcus compared with the controls bilaterally, but there was no group difference in its anterior-posterior length. The olfactory sulcus measures of the patients did not significantly correlate with clinical variables such as onset age, medication or symptom severity [20]. A shallow olfactory sulcus possibly reflects abnormal forebrain development during early gestation. It is still unclear whether this anomaly exists prior to the onset of psychosis. Subjects who later developed psychosis had significantly shallower olfactory sulcus at baseline as compared with who did not develop psychosis and control subjects. The depth of this sulcus became increasingly more superficial as one moved from the group who later developed psychosis to the group with first-episode psychosis to chronic schizophrenia patients. Finally, the depth of the olfactory sulcus in the later developed psychosis subjects was negatively correlated with the severity of negative symptoms. Thus the altered depth of the olfactory sulcus, which exists before psychosis onset, could be predictive of transition to psychosis, but also suggest ongoing changes of the sulcus morphology during the course of the illness [21].

Vascularization

The olfactory nerve has intracranial vascularization by olfactory artery and accessory olfactory artery (arise from anterior cerebral artery or anterior communicating artery) and by anterior and posterior ethmoidal arteries (arise from ophthalmic artery). The extracranial vascular supply is by sphenopalatine artery (arise from external carotid artery), anterior and posterior ethmoidal arteries (arise from ophthalmic artery) [39].

The major source of the vascular supply of the bulb and tract is the olfactory artery. It originates either from the lateral surface of the anterior cerebral artery (segment A2), or from the medial frontobasal artery, and consistently provides supply in front of the olfactory trigone in the medial olfactory sulcus, the olfactory tract and olfactory bulb with a maximum of three terminal branches [40, 41].

The olfactory tract receives blood supply from a variety of sources, which include posterior orbitofrontal artery, medial orbitofrontal artery, posterior orbitofrontal artery and medial striate artery [42].

Persistent primitive olfactory artery (PPOA) is a relatively rare variation of the proximal anterior cerebral artery that originates from the terminal portion of internal carotid artery. It can have an extreme antero-inferior course and take a hairpin turn (type 1); extending to the cribriform plate to supply the nasal cavity (type 2); or coursed anteromedially along the olfactory tract making a hairpin turn posterosuperior to the midline [43, 44]. Its incidence seems to be 0.14-0.64% [45, 46]. There is a high incidence of aneurysms associated with PPOA [43, 44, 47, 48]

Vascular anomalies also should be considered in the differential diagnosis of olfactory impairment. There are a variety of conditions which can cause olfactory impairment like rare aneurysms of PPOA [47] or arteriovenous fistulae involving the anterior ethmoidal arteries [49] or mixed pial-dural arteriovenous malformations that involve PPOA [50].

Aplasia/hypoplasia of the olfactory nerve, bulb or tract

The bilateral absence of olfactory nerve, bulb and tract is a rare anomaly. It can be an isolated unilateral or bilateral anomaly as well a part of other condition.

Over the years, there have been several reports of bilateral absence or dysplasia of olfactory bulbs associated with various degrees of central nervous system (CNS) malformations [51-57]. In one of the cases, the stillborn child had extensive malformations of the CNS, cardiovascular, abdominal and skeletomuscular systems [51]. The other case of a 17-year-old male with severe mental retardation and malformations of the CNS [52].

The isolated hypoplasia or aplasia is considered rare, and may involve only the nerve or the bulb [49, 58-60]. It can also occur along with minor anomalies with little clinical significance [61]. The main feature in this case is loss of smell with no other clinical signs [62].

The anomaly can be classified morphologically into three types [63-65]: hypoplasia of the olfactory bulbs with olfactory tracts present; aplasia of the olfactory bulbs with olfactory tracts present; and aplasia of both olfactory bulbs and olfactory tracts.

Anomalies of the olfactory bulb may also be underestimated. In patients with abnormal ciliary motion and congenital heart disease, 28.5% of patients had brain abnormalities including of the olfactory bulb [66]. It seems possible that there are more conditions, which may be associated with olfactory malformations.

Accessory olfactory bulbs

In a study of 220 patients who undergone magnetic resonance imaging (MRI) with high-resolution coronal T2-weighted fast-spin echo images in the orbitofrontal region. Olfactory bulbs appeared duplicated in 11 patients and triplicated in one (5.4% of the total group). Whereas olfactory sulcal depth was similar in all patients, olfactory bulb diameter in patients with duplicate or triplicate bulbs was significantly smaller than those in subjects with single bilateral olfactory bulbs. One patient with congenital hyposmia and olfactory bulb duplication had significant impairment in olfactory acuity. In each of the 12 patients, olfactory grooves were abnormal (widened, flat or absent) [67]. Interestingly, an accessory olfactory bulb are present in animals and it receives sensory input from the vomeronasal (Jacobson's) organ [68]. Thus, the presence of an accessory olfactory bulb may be an evolutionary remnant.

Olfactory bulb ventricles and cysts

Rarely, olfactory bulb cysts can develop and represent incidental findings [69]. In some species an embryologic cavity inside the olfactory bulb persists and are called olfactory bulb ventricles. It may very well be that this embryological remnants can be found in humans. An MRI study of 122 individuals and dissection of 42 cadavers demonstrated that olfactory bulb ventricle-like structures were present in 72 out of 122 (59%) participants and in 3 out of 42 postmortem olfactory bulbs contained histologically detectable ventricles [70]. Later it was demonstrated that the fluid filled structure can be seen less frequently in 5.5% of cases and might be associated with interstitial or finely dispersed cerebrospinal fluid or with tiny, histologically detectable remnants of called olfactory bulb ventricle [71].

Table 1. Clinical implications of olfactory bulbs volume assessment

Condition	Clinical implications	Refs
Temporal lobe epilepsy	Olfactory function was significantly impaired and olfactory bulbs were smaller in patients compared to healthy controls. The deficit seen at the level of the olfactory bulb did not correlate with the side of the epileptic focus. Thus, the olfactory deficit in patients is due to the central nervous epileptic focus and it appears that the olfactory bulb volume is not only subject to changes in the periphery of the olfactory system, but also changes as a consequence to changes at a cortical level.	[22]
Parkinson's disease	Both the left and the right olfactory bulb volume were significantly smaller in patients than in healthy controls. A significant difference in the lateralized olfactory bulb volume was observed with a larger right olfactory bulb volume than left.	[23]
Multiple sclerosis	Olfactory bulb volume correlates with its function. It also correlate with disease duration, attack frequency and higher depression scores.	[24-26]
Major depression	There is a significant negative correlation between olfactory bulb volume and depression scores. The volume correlates with the change of depression severity and can be a predictor factor of therapeutic outcome.	[27, 28]
Schizophrenia	Patients exhibited 23% smaller bilateral bulb volume than comparison subjects, independent of acute clinical, demographic, or treatment measures. It may also me lower in first-degree relatives of patients with schizophrenia.	[29, 30]
Obstructive sleep apnea	The apnea-hypopnea index was significantly negatively correlated with odor identification score and both olfactory bulb volumes	[31]
Smoking	Olfactory function was not different between the smokers and non-smokers groups, but olfactory bulb volumes were smaller possibly indicating a subclinical effect on the olfactory system.	[32]
Septal deviation	Olfactory function was significantly lower at the narrower side. When correlating relative scores and volumes (wider minus narrower side), a significantly positive correlation between the relative measures emerged for olfactory bulb volume and odor identification, discrimination, and thresholds.	[33]
Sinonasal polyposis	There are significant reduction in olfactory bulb volume in patients with bilateral sinonasal polyposis as compared to controls. Olfactory bulb volume correlated with the degree of sinonasal inflammation.	[34, 35]
Chronic rhinosinusitis	The increase in olfactory bulb volume correlated significantly with an increase in odor thresholds, but not with changes in odor discrimination or identification.	[36]
Radiotherapy in patients with nasopharyngeal cancer	The loss of olfactory bulb volume might be a contributing factor to lack of appetite, cancer cachexia and consequent lowered quality of life.	[37]
Postinfectious and posttraumatic olfactory loss	Significant correlation between changes in olfactory functions and initial measurement of the total olfactory bulb volume. Larger volumes are linked to a higher improvement of olfactory function. Total olfactory bulb volume of 40 mm(3) or less seems to indicate permanent loss of olfactory function.	[14, 15, 38]

Genetic syndromes

There is a link between malformations of the olfactory system and a variety of genetic conditions like Kallmann's syndrome (KS), CHARGE-syndrome (the acronym "CHARGE" came into use for newborn children with the congenital features of coloboma of the eye, heart defects, atresia of the nasal choanae, retardation of growth and/or development, genital and/or urinary abnormalities, and ear abnormalities and deafness. These features are no longer used in making a diagnosis alone of CHARGE syndrome, but the name remains), septo-optic dysplasia (SOD), Waardenburg syndrome (WS) and other.

KS represents a genetic syndrome the key features of which are anosmia and hypogonadotropic hypogonadism. In KS cells that normally express luteinizing hormone-releasing hormone fail to migrate from the medial olfactory placode along the terminalis nerves into the forebrain. Additionally failed neuronal migration from the lateral olfactory placode along the olfactory fila to the forebrain results in aplasia or hypoplasia of the olfactory bulbs and tracts. This explains the two key features of KS – reproductive and olfactory dysfunction [64].
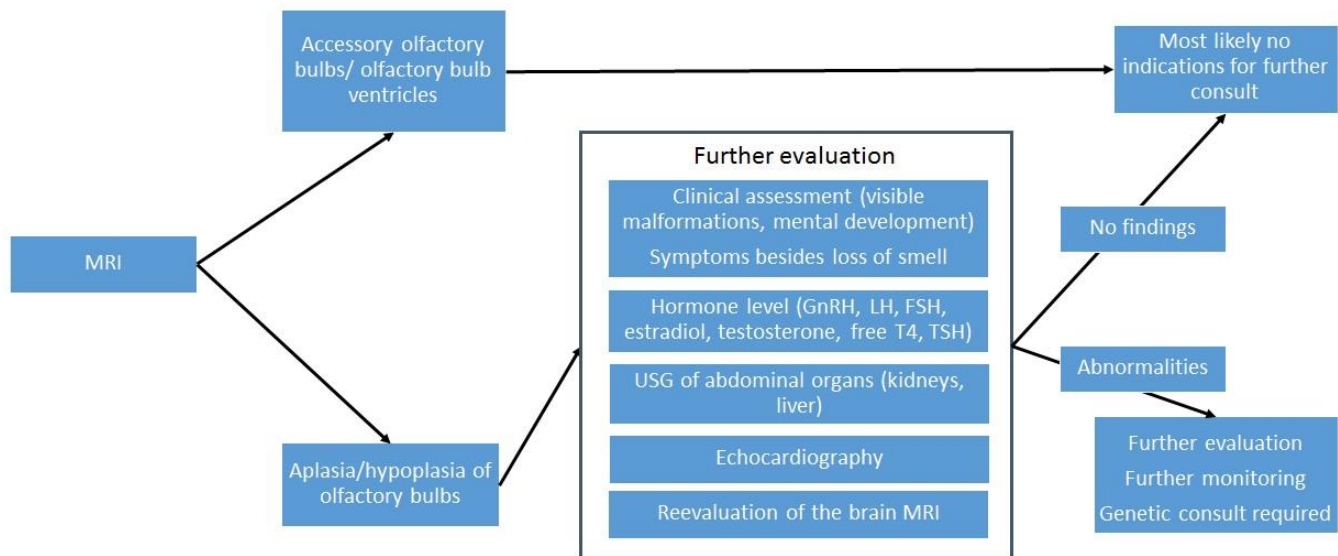
The anosmia in KS is caused by absence of olfactory bulbs and tracts in 68-84% and by hypoplasia in 16-32%. Other CNS abnormalities may include temporal, frontal lobe volume loss [72] abnormalities of the rhinencephalon [73] bilateral loss of distinction between the gyrus rectus and medial orbital gyrus [74] corpus callosum defects [75] arachnoid cyst [76, 77], empty sella [77, 78], pituitary hypoplasia [79] and multiple sclerosis-like white matter abnormalities other changes [80]. Craniofacial malformations mau include tooth agenesis, increased mandibular inclination and mandibular angulation, extreme retrognathism of both maxilla and mandible, cleft lip and/or palate and altered bone morphology [75, 81, 82]. Finally, other organ and structures can be affected [83].

Mutation in one of the KS genes can be found in up to 30% of cases. There a significant phenotypical overlaps with other conditions like CHARGE-syndrome [84], combined pituitary hormone deficiency, and SOD [85]. Thus, the current data indicate that olfactory nerve, bulb and tract hypoplasia can be a part of septo-optic dysplasia or be an overlap with KS [86-88].

In patents with CHARGE-syndrome, MRI demonstrated olfactory anomalies including either absence or hypoplasia of the olfactory bulbs and olfactory sulci [89]. It is even proposed that rhinencephalon anomalies should be included as a major criterion for the diagnosis of CHARGE-syndrome [90]. Other studies go further and demonstrate that CHARGE-syndrome include the main features of KS (hypogonadotropic hypogonadism combined with a defective sense of smell and abnormal olfactory bulb development) [91].

In WS, a genetic disorder characterized by the association between pigmentation abnormalities and deafness. However, SOX10 mutations cause a variable phenotype that spreads over the initial limits of the syndrome definition. Particularly olfactory-bulb agenesis in WS can also be present since SOX10 is also involved in KS [92, 93].

Figure 1. Evaluation of incidental abnormalities of olfactory bulbs.

GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; TSH, thyroid-stimulating hormone; USG, ultrasonography.

Based on these findings MRI should be performed in patients with congenital deafness and in case when adequate sequences are available other CNS anomalies including olfactory bulb malformation can be detected [94, 95].

Malformations of the olfactory nerves, bulbs and tract can also be seen in other genetic conditions like Meckel-Gruber syndrome (occipital encephalocele, cystic dysplastic kidneys, and postaxial polydactyly) [96], Fryns syndrome [97, 98], short rib-polydactyly syndrome [99, 100], Jacobsen syndrome [101], Johanson-Blizzard syndrome [101], DiGeorge sendrome [101], trisomy 13 [102], trisomy 18 [101] and other genetic abnormalities [101, 103, 104].

In children with olfactory malformations syndromic associations can be found in up to 22%. Patients may also have developmental delay (59%), seizures (34%) and neuroendocrine dysfunction (34%). Children commonly had multiple presenting symptoms (61%) [101].

Therefore, patients with malformations of the olfactory system should be evaluated to exclude the presence of any underlying genetic condition (*Figure* 1).

Conclusion

Variations of the development of olfactory nerve, bulb and tract are underdiagnosed. Isolated aplasia or hypoplasia is generally a rare phenomenon. Patients with aplasia and hypoplasia should be evaluated since this condition is frequently a part of other malformations and genetic syndromes. Olfactory bulb duplications and triplications, olfactory bulb ventricles seem to be a benign variations of development but the data on these subject is currently limited.

Conflict of interest: none declared.

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