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ORIGINAL ARTICLE

Septo-optic Dysplasia

Assessment of Associated Findings with Special Attention to the Olfactory Sulci and Tracts

John C. Benson[1] · David Nascene[1] · Charles Truwit[2] · Alexander M. McKinney[1]

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Abstract

Purpose Septo-optic dysplasia is a congenital disorder consisting of optic nerve hypoplasia and absent septum pellucidum. While associated anomalies have been described, olfactory sulcus and bulb-tract hypoplasia have been scantily reported and was the focus of this study.

Methods The picture archival and communications system and radiology information system (PACS-RIS) was searched over 15 years for patients with suspected septo-optic dysplasia ($n = 41$) and cerebral magnetic resonance imaging (MRI). Included patients had coronal (≤ 3 mm), axial (≤ 4 mm), and sagittal (≤ 4 mm) imaging reviewed by two staff neuroradiologists by consensus. Both olfactory sulcus and bulb-tract hypoplasia were ascribed a grade of 0 (normal) to 3 (complete hypoplasia). Other associated congenital anomalies were recorded, if present. Incidence of anomalies were compared to age-matched and gender-matched control patients.

Results Out of 41 septo-optic dysplasia patients 33 were included (mean age = 120.7 months), with 8 excluded due to isolated septum pellucidum absence ($n = 5$), isolated bilateral optic hypoplasia ($n = 2$), or inadequate imaging ($n = 1$). An olfactory sulcus was hypoplastic on one or both sides in 14/33 (42.4%). Olfactory bulb hypoplasia was noted in one or both tracts in 15/33 (45.4%). A significant correlation was found between degree of olfactory sulcal and bulb-tract hypoplasia ($\varrho = 0.528$, $p = 0.0009$). Other anomalies were: anterior falx dysplasia ($n = 16$, 48.5%), incomplete hippocampal inversion ($n = 14$, 42.4%), polymicrogyria ($n = 11$, 33.3%), callosal complete or partial agenesis ($n = 10$, 30.3%), schizencephaly ($n = 8$, 24.2%), ectopic posterior pituitary ($n = 6$, 18.2%), and nodular heterotopia ($n = 4$, 12.1%). Of the age-matched control patients 10/33 (30.3%) had at least mild anterior falx hypoplasia, and 1 control patient was noted to have unilateral incomplete hippocampal inversion (IHI); none of the age-matched control patients had olfactory sulcus or bulb-tract hypoplasia.

Conclusion Olfactory sulcus and bulb-tract hypoplasia are fairly common in septo-optic dysplasia and can be discordant between sides. Of the other associated anomalies, anterior falx dysplasia seems to be the most common.

Keywords Falx dysplasia · Congenital anomalies · Callosal agenesis · Schizencephaly

Abbreviations

IHI	Incomplete hippocampal inversion
PMG	Polymicrogyria
PVNH	Periventricular nodular heterotopia
SOD	Septo-optic dysplasia
SOD-plus	Septo-optic dysplasia and schizencephaly

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✉ John C. Benson
benso905@umn.edu

[1] Department of Radiology, University of Minnesota Medical Center, MMC 292, B-212 Mayo, 420 DelawareStreet SE, Minneapolis, MN 55455, USA

[2] Department of Radiology, Hennepin County Medical Center, Minneapolis, MN, USA

Introduction

Septo-optic dysplasia (SOD), previously termed de Morsier syndrome, is characterized by a diagnostic triad of optic nerve hypoplasia, pituitary abnormalities, and midline brain

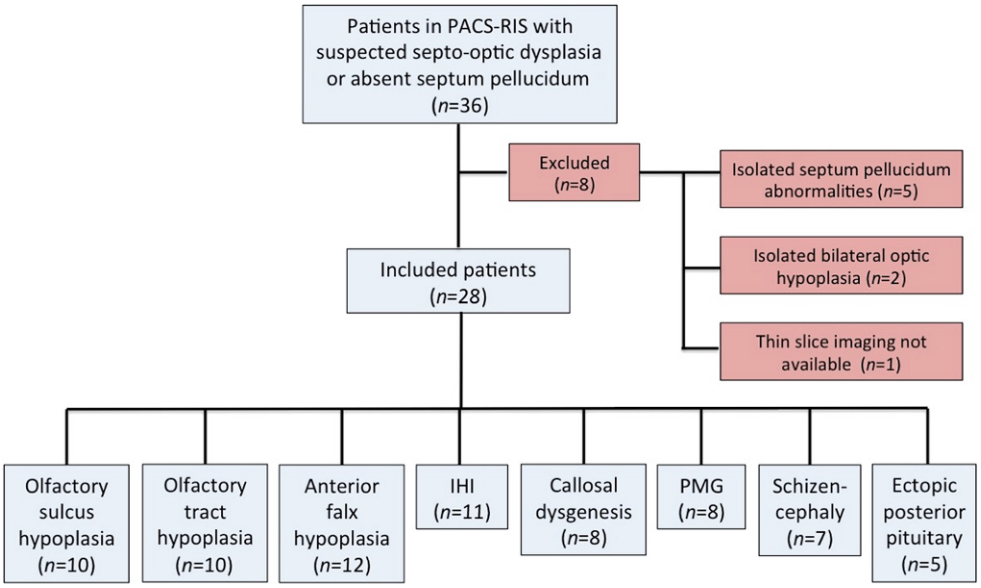

Fig. 1 Patient flowchart. 8 patients were excluded from the initial PACS-RIS database search; 28 patients were included in the study. *IHI* incomplete hippocampal inversion, *PMG* polymicrogyria

defects, such as agenesis of the septum pellucidum or callosal hypoplasia [1]. It occurs equally in males and females, at a reported incidence of 1/10,000 live births [2]. Numerous possible etiologies have been proposed, including maternal diabetes, substance abuse, cytomegalovirus infection, and the use of drugs, such as antiepileptics and quinidine [3, 4]. Genetic mutations have also been implicated, including the developmental genes SOX2, SOX3, and HESX1 [4, 5]. Many associated anomalies have been described with SOD, including schizencephaly (SOD-plus), anterior falx dysplasia, and callosal dysgenesis, to name a few, with significant variability among the expressed phenotypes [6–11]. Common clinical signs include visual impairment, cerebral palsy, and seizures, with the varying presence of other associated neurological deficits, ranging from minor symptoms to global retardation [6, 11–13].

Olfactory sulcus hypoplasia has been briefly reported in SOD patients, being generally discussed only as a secondary finding in patients with olfactory bulb or tract hypoplasia [8, 13]. To date, studies of SOD have yet to address the rate of olfactory sulcus or bulb-tract hypoplasia, or whether such anomalies occur symmetrically or asymmetrically. This may be of import: the existence or lack of an association between SOD and olfactory hypoplasia might provide more information as to the etiology of this process. The presence of other associated anomalies in SOD may also contribute to understanding its pathogenesis, although a complete review of all possibly related anomalies is beyond the scope of this study. Hence, the purposes of this study are to (1) describe the frequency and severity of olfactory sulcus and bulb-tract hypoplasia in patients with SOD and (2) assess the frequency of other prominent associated anomalies.

Materials and Methods

Patient Selection

Institutional review board approval was obtained. A PACS-RIS MRI report search for the terms "septo-optic dysplasia" or "absent septum pellucidum" was obtained to identify patients with imaging features of SOD between 1 January 2002–12 December 2016. Patients were included with: (1) imaging and clinical features of SOD, and (2) orbitofrontal coronal MRI (≤3 mm thickness) as well as axial (≤4 mm thickness) and sagittal imaging (≤4 mm thickness). Patients were excluded who (1) did not have SOD, (2) had isolated septum pellucidum absence or isolated optic hypoplasia, or (3) did not have adequate coronal, axial, or sagittal MR imaging (or the aforementioned thickness; Fig. 1).

Image Acquisition

The patients were imaged using either a 1.5 or 3.0T MRI. Orbitofrontal axial and coronal T1WI and T2WI were used to confirm the diagnosis of SOD, and to assess the degree of olfactory bulb or primary olfactory sulcus hypoplasia, and to assess the hippocampi for the presence of incomplete hippocampal inversion (IHI). Sagittal T1WI or T2WI were available in each included patient at ≤4 mm thickness, and were used to evaluate for the presence or degree of callosal dysgenesis/agenesis. Routine axial ≤5 mm FLAIR, T1WI, T2WI, and DWI were also available in each patient to evaluate and describe any other potential cranial anomalies.

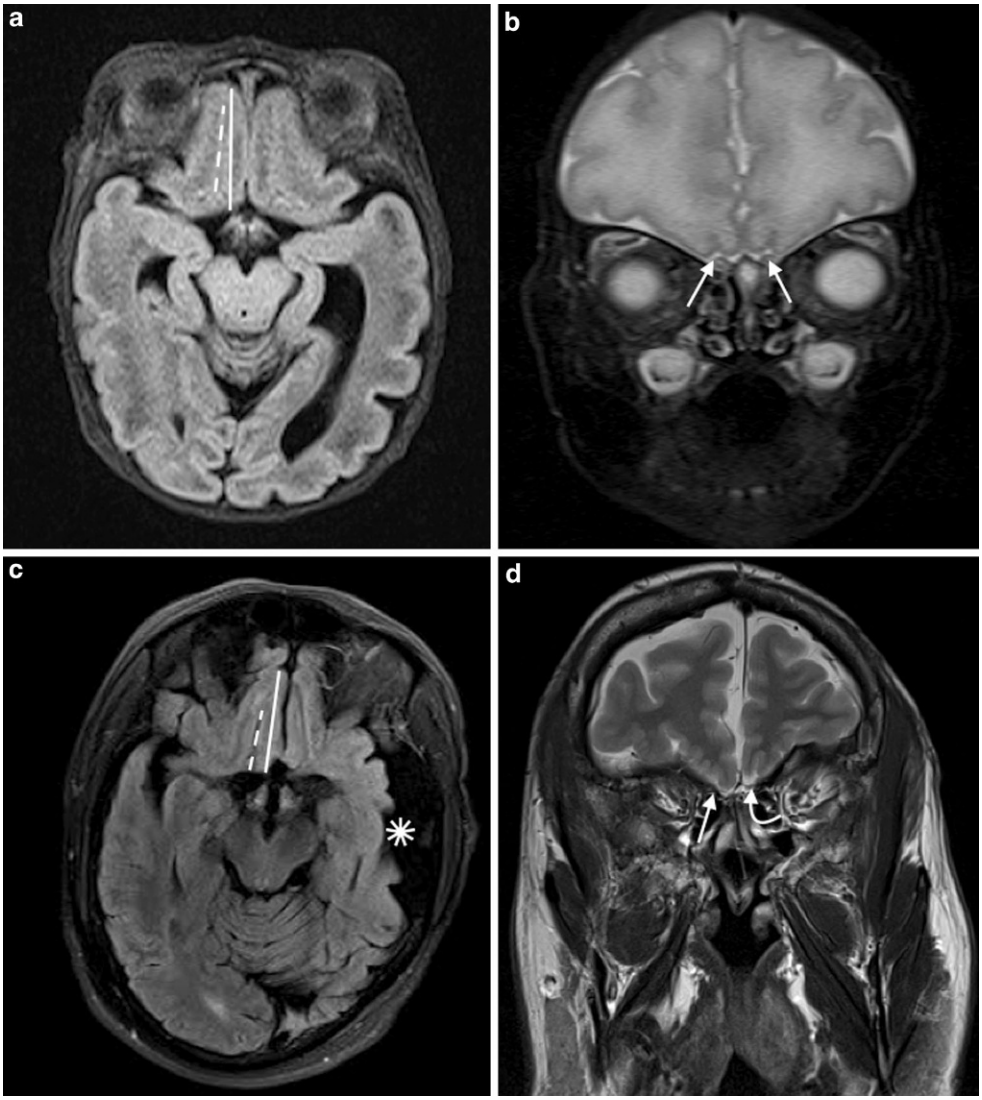

Fig. 2 Examples of olfactory sulcus grading. 3 T images of a 2-week-old female (**a**, **b**) demonstrate grade 0 olfactory sulcus hypoplasia (considered normal) bilaterally. Axial FLAIR images show both sulci (*dotted line* on the right in **a**, unmarked for comparison on the left) measuring over 80% of the anterior-posterior length of the nearby rectus gyrus (*straight line* on the right in **a**); coronal T2 images confirm normal sulcal formation (*arrows* in **b**). Axial 3 T FLAIR images of a 46-year-old male (**c**, **d**) show grade 1 hypoplasia of the right olfactory sulcus (*dotted line* in **c**), measuring 50–79.9% of the rectus gyrus (*straight line* in **c**); the left olfactory sulcus was grade 0 (unmarked in **c** for comparison). Corresponding coronal T2 images confirm hypoplasia of the right olfactory sulcus anteriorly (*straight arrow* in **d**) with normal left sulcal formation (*curved arrow* in **d**)

Image Review and Interpretation

The MR images were reviewed by two staff pediatric neuroradiologists (AM and DN, each with >7 years experience) by consensus. The imaging characteristics of SOD were first confirmed in each patient. The presence or absence of any associated anomalies was noted, with the following specifically evaluated for: anterior falx dysplasia (whether interdigitation of the gyri across the midline was present), callosal complete or partial agenesis, gray matter heterotopia (periventricular nodular heterotopia, PVNH), pituitary anomalies, IHI, schizencephaly, and polymicrogyria (PMG, occurring at a site remote from an associated schizencephaly). Any other congenital anomalies were also recorded. The degree of IHI was graded 0 (normal) to 3 (absolutely no inversion/infolding).

For the assessment of the olfactory sulci, a grading scale was created based on the location and degree of hypoplasia by comparing the anterior-posterior length of the olfactory sulcus to the length of the rectus gyrus: *grade 0* = olfactory sulcus length is within 80% of the gyrus rectus, *grade 1* = olfactory sulcus length is 50–79.9% of the rectus gyrus, *grade 2* = olfactory sulcus length is <50% of the rectus gyrus, and *grade 3* = complete sulcal aplasia (Fig. 2). The degree of sulcal hypoplasia was recorded on each side to allow for the evaluation of unilateral versus bilateral hypoplasia. If there was discordance between sides, the more severe degree of hypoplasia was recorded as the overall grade for the patient.

Similarly, a grading scale for the assessment of olfactory bulb-tract hypoplasia was created based on the visual degree of hypoplasia and caliber of the bulb-tract: *grade 0* = normal, *grade 1* = mild hypoplasia, *grade 2* = moderate-severe hypoplasia if the tract was clearly visible, *grade 3* = complete hypoplasia of the tract or it was entirely invisible (but not due to artifact). The hypoplasia

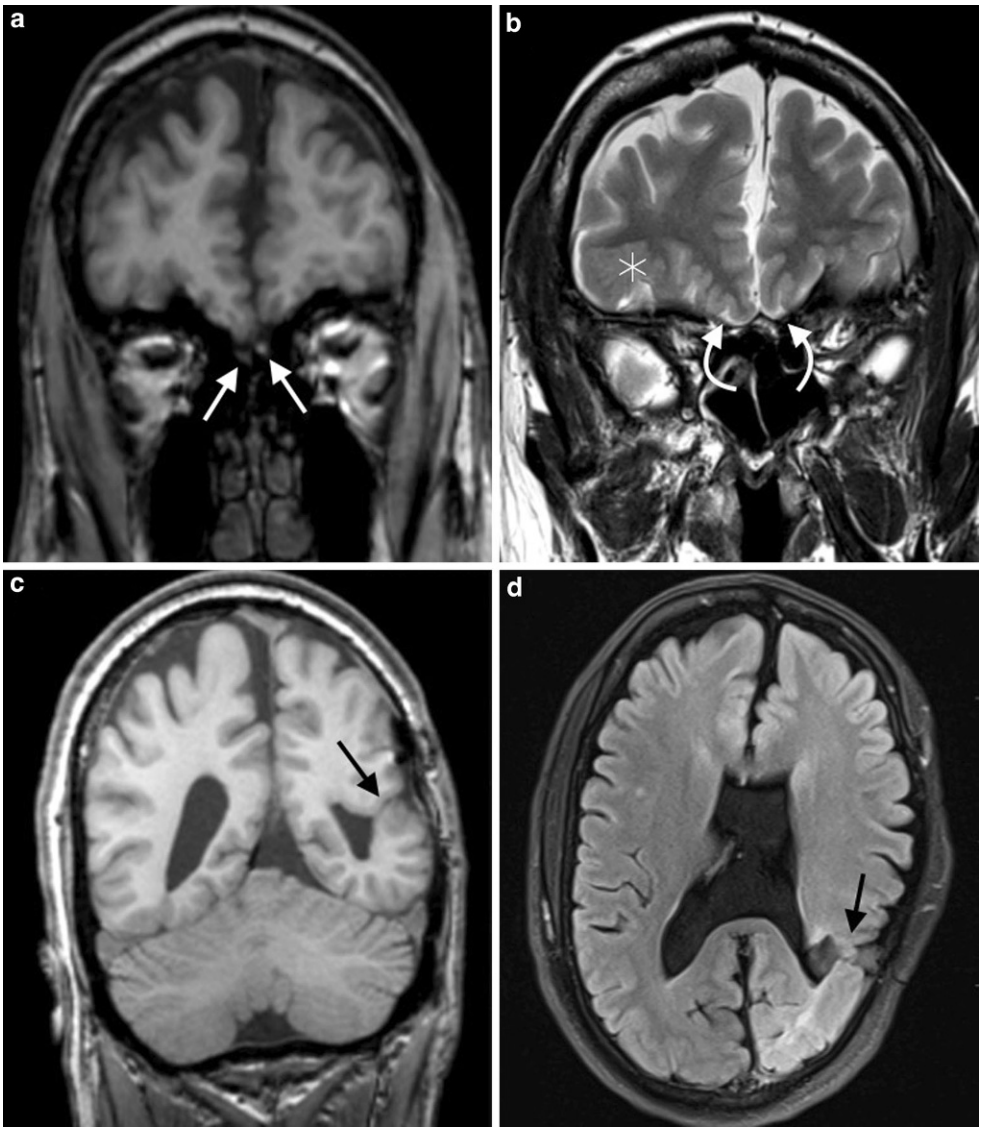

Fig. 3 3 T MRI of a 46-year-old male, shown with coronal T1 (**a**, **c**), coronal T2 (**b**), and axial FLAIR (**d**). Hypoplasia of the bilateral olfactory tracts was observed (**a**); grade 2 on the right and grade one on the left (*arrows*). Bilateral olfactory sulci hypoplasia was also noted (**b**): grade 2 on the right, and grade 1 on the left (*curved arrows*). Associated findings included polymicrogyria (**b**; *asterisk*) and schizencephaly (*black arrows* in **c** and **d**)

severity was noted between sides, if present. If discordance between sides existed, the more severe grade was recorded as the overall grade. *Note*: the terms olfactory "bulb" and "tract" are used here rather than "nerve" to prevent confusion, as the nerves are typically considered collections of individual fibers that pass through the cribriform plate [14].

The MR images of 33 age-matched and gender-matched asymptomatic control patients were reviewed for the presence of observed anomalies. Patients were chosen as asymptomatic controls if they did not have known congenital syndrome, active infection, prior central nervous system (CNS) insult, or CNS anomalies; all MRIs of control patients were interpreted as normal. The typical reason for imaging examination of control patients was developmental delay.

Statistical Analysis

Wilcoxon signed rank tests were utilized to compare between the sides for olfactory sulcus and bulb hypoplasia grades. Spearman's correlation was used to correlate the degree of sulcus with bulb hypoplasia. The threshold for significance for each test was set to $p < 0.05$.

Results

Patient Population

The PACS-RIS search identified 41 patients with suspected septo-optic dysplasia or absent septum pellucidum. Of these 41 patients, 5 were excluded due to isolated septum pellucidum absence without optic hypoplasia, 2 being excluded

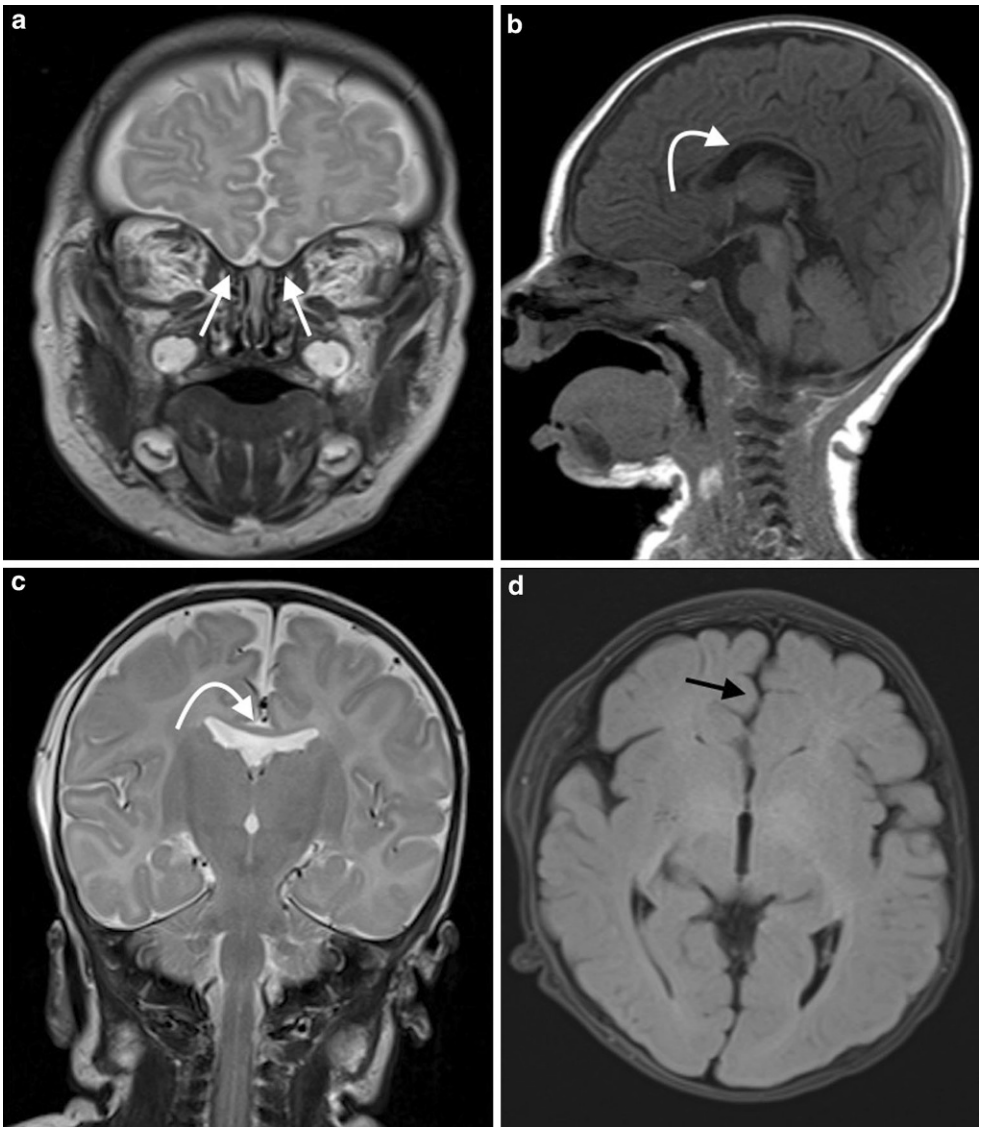

Fig. 4 3 T MR of a 2-month-old female, shown with coronal T2 (**a, c**), sagittal T1 (**b**), and axial FLAIR (**d**) images. Grade 3 (*left*) and grade 2 (*right*) olfactory sulcus hypoplasia (*arrows* in **a**) was present. The olfactory tracts were also hypoplastic: grade 3 on the left and grade 1 on the right; neither tract can be seen in image **a**. Associated anomalies included corpus callosum dysgenesis (*curved arrows* in **b** and **c**) and anterior falx dysplasia with interdigitation of cerebral sulci (*black arrow* in **d**)

because they had isolated bilateral optic hypoplasia, and 1 due to a lack of coronal ≤3 mm thickness imaging to evaluate the olfactory sulci and bulbs-tracts. Hence, 33 patients met the inclusion criteria for this study, and their MR images were jointly reviewed (Figs. 1, 2, 3 and 4). Regarding the patient demographics, 17/33 (51.2%) were female, and the average age of the included patients was 120.7 ± 165.5 months (range: 0.1–564 months). In the 5 patients with isolated septum pellucidum absence, only one had an associated congenital anomaly, which was bilateral IHI grade 3. Of the 33 patients 26 had clinical evidence of SOD recorded in the available electronic medical record (EMR); records of other patients were either very limited or absent, due to either (1) imaging performed prior to the initiation of the EMR at our institution, or (2) images transferred from an outside institution. Of the patients whose birth histories were available, 2 were born prematurely (<37 weeks gestational age).

Imaging Findings

All 33 included patients had imaging findings consistent with SOD. Only 3 of the studied patients had isolated features of SOD without other associated congenital anomalies. Thus, 30 of the 33 (90.1%) patients had at least one other associated congenital anomaly.

Regarding the degree of olfactory sulcal hypoplasia, at least some degree of hypoplasia on one or both sides was identified in 14/33 (42.4%) patients (Fig. 2). When present, hypoplasia of the olfactory sulcus was bilateral in 11/14 (78.6%) patients, and 4/11 (36.4%) of these patients had equal severity of hypoplasia between sides. When reporting the maximum grade of either side, 5/33 had grade 1 (15.2%)

Table 1 Frequency of olfactory tract/bulb and olfactory sulci hypoplasia, given in number of patients. In patients for which grades were discrepant between sides, the more severe grade was used for analysis

	Olfactory bulb-tract (in %)	Olfactory sulcus (in %)
Grade 0 (normal)	18/33 (54.4)	19/33 (57.6)
Grade 1 (mild)	1/33 (3.0)	5/33 (15.2)
Grade 2 (moderate)	9/33 (27.3)	4/33 (12.1)
Grade 3 (severe)	5/33 (15.2)	5/33 (15.2)

Table 2 Frequency of associated anomalies identified in patients with SOD. Other incidental findings included a tectal hamartoma ($n = 1$, 3.0%), Chiari II ($n = 1$, 3.0%), and a choroidal fissure cyst >5 cm ($n = 1$, 3.0%)

	Frequency (n)	In %
Anterior falx hypoplasia	16/33	48.5
IHI	14/33	42.4
Polymicrogyria	11/33	33.3
Callosal complete or partial agenesis	10/33	30.3
Schizencephaly	8/33	24.2
Ectopic posterior pituitary	6/33	18.2
PVNH	4/33	12.1

IHI incomplete hippocampal inversion, *PVNH* periventricular nodular heterotopia

on at least 1 side, 4/33 patients had grade 2 (12.1%) on at least 1 side, and 5/33 (15.2%) had at grade 3 olfactory hypoplasia on at least 1 side (Table 1).

The olfactory bulb-tract was normal in 18/33 patients (54.4%), while some degree of hypoplasia was present on 1 or both sides in 15/33 patients (45.5%). When present, hypoplasia of the olfactory bulb-tract was bilateral in 11/15 (73.3%); 1 of these 15 had bilateral grade 1 olfactory bulb-tract hypoplasia, while mild grade 1 hypoplasia was noted unilaterally in 5 patients. When reporting the maximum severity on each side, 1/33 (3.0%) had grade 1 on at least 1 side, 9/33 (27.3%) had grade 2 on at least 1 side, and 5/33 (15.2%) had grade 3 olfactory tract/bulb hypoplasia on at least 1 side (Table 1).

Other associated anomalies are noted in Table 2. Of these, anterior falx hypoplasia ($n = 16$, 48.5%) was the most common (Fig. 3). Other findings included IHI ($n = 14$, 42.4%, the most common being grade 1 IHI in 5 patients), PMG ($n = 11$, 33.3%, being remote from the schizencephaly), corpus callosum complete or partial agenesis ($n = 10$, 30.3%), schizencephaly ($n = 8$, 24.2%), ectopic posterior pituitary ($n = 6$, 18.2%), and PVNH ($n = 4$, 12.1%). In addition, some patients were noted to have other incidental findings, such as tectal hamartoma ($n = 1$, 3.0%), Chiari II ($n = 1$, 3.0%), and a choroidal fissure (neuroepithelial) cyst that was >5 cm size ($n = 1$, 3.0%). None of the patients demonstrated hypomyelination for their age; in the two premature infants, the myelination appeared normal and as expected for term equivalent age.

There was no significant difference found between the right and left sides regarding the olfactory sulci ($p = 0.973$) or bulbs ($p = 0.717$), using Wilcoxon signed rank test. There were strong and significant correlations between the degree of olfactory sulcal and bulb-tract hypoplasia for both the right ($\varrho = 0.691$, $p < 0.0001$) and left side ($\varrho = 0.788$, $p < 0.0001$). There was also a significant, moderate correlation overall between the degree of sulcal and bulb-tract hypoplasia, when combining the most severe grade of both sides ($\varrho = 0.808$, $p = 0.0001$).

Of the 8 excluded patients olfactory bulb-tracts could not be evaluated in 3 patients, and olfactory sulci could not be evaluated in 2 patients due to lack of thin-section imaging. Noted abnormalities in the excluded patients included: absent septum pellucidum ($n = 5$), isolated optic nerve hypoplasia ($n = 2$), partial or complete corpus callosum agenesis ($n = 2$), PVNH ($n = 2$), bilateral IHI ($n = 1$), and aqueductal stenosis ($n = 1$).

None of the age-matched control patients were found to have olfactory sulcus or bulb-tract hypoplasia. Of the other studied anomalies, 10/33 (30.3%) had some degree of anterior falx hypoplasia, with some interdigitation of gyri, 1 patient had mild unilateral IHI, and 1 adolescent patient had borderline tonsillar ectopia.

Discussion

The aim of this study was to describe the frequency and severity of olfactory sulcus and bulb-tract hypoplasia in SOD, with a secondary aim to assess some of the other known associated anomalies. The results indicate that olfactory sulcus and bulb-tract hypoplasia are present in just over one third of patients with SOD, and is usually bilateral when present. Of the other noted anomalies, anterior falx hypoplasia was the most frequently found, followed by IHI, which was not noted to be the most commonly associated congenital anomalies in prior larger studies [8, 9, 15–17].

Nearly all the associated anomalies identified in the present study have been noted before, although the frequency of these anomalies has varied greatly amongst those prior studies. For example, a study by Al-Senawi et al. found ectopic pituitaries in 5/5 patients, and Barkovich et al. noted schizencephaly in 5/11 patients, with a hypoplastic falx in 1/11 patients [8, 9]. A recent study by Alt et al. found cortical abnormalities (including schizencephaly, polymicrogyria, and PVNH) in 76% of cases [18]. The differences in the reported frequencies of such associated anomalies are likely related to both the phenotypic variability of SOD, the small sample sizes of prior studies,

the anatomic focus of the study (i.e. which associated anomalies were searched for), and whether such studies were initially based on clinical or imaging designations of the diagnosis of SOD. In particular, the descriptions of such frequencies within the syndrome of SOD are confounded by the fact that the greatest-sized patient cohorts of SOD have been described as part of a larger cohort of patients with optic hypoplasia, and thus in such papers the SOD subpopulations are often not-well described [19, 20]. Additionally, the numbers of patients in the few studies of larger cohorts of SOD have ranged from 20–28 patients, are not entirely focused on MRI for imaging confirmation, and do not mention olfactory anomalies [15–17]. Thus, this study is not only likely the largest study to describe associations of olfactory anomalies with SOD, but may also be one of the larger MRI-based studies to focus solely on SOD. Additionally, to the knowledge of the authors of this study, no prior studies have described an association between the presence of SOD and IHI.

Prior reports of olfactory bulb, tract and/or sulcus hypoplasia in the setting of SOD have described it as a rare phenomenon [9, 13]. In the present study, at least some degree of olfactory sulcus and tract hypoplasia was observed in approximately one third of patients, representing somewhat of a discrepancy from prior studies. Although the definite reason for this discrepancy is uncertain, it is likely at least partially related to the current study's particular emphasis on these findings. Also, the imaging acquisition parameters have varied greatly between studies; the authors of the current study opine that $\leq$3 mm imaging (preferably T2WI) is necessary to detect olfactory sulcus or bulb-tract hypoplasia. If coronal images do not extend through the anterior cranial fossa, as may be the case in many pituitary MRI protocols, the olfactory bulbs may not be optimally assessed. Nevertheless, it appears that presence of hypoplasia of the olfactory sulci and bulbs-tracts are related to each other, as the present study noted a correlation between both the presence and the severity of these findings on each side.

It appears that the presence of olfactory sulcus and bulb-tract hypoplasia is associated with SOD, as none of the age and gender-matched control patients demonstrated any degree of hypoplasia. The current study also noted a higher degree of anterior falx hypoplasia than prior studies. Interestingly, the rate of anterior falx hypoplasia was slightly higher than the rate observed in the control patients, suggesting that there may be some association of this finding to SOD, though it is still unclear if anterior falx hypoplasia is directly related to the same pathogenesis as SOD.

Although the pathogenesis of SOD is still uncertain, it has been proposed that the condition is related to an in utero vascular insult [12, 21]. According to Lubinsky, the rationale for this hypothesis is in part related to the developmental timing of the involved structures: the optic nerve develops by the seventh week, but the septum pellucidum does not form until weeks 15–21 [21]. Hence, the discrepancy between the formation of these structures makes it unlikely that SOD represents a developmental anomaly related to ventral induction. In addition, some features of SOD, such as porencephaly, would not be expected in a process related to midline anomalies, and are better explained by a vascular insult before the 3rd trimester [21]. Furthermore, both a Lubinsky article and a Stevens and Dobyns article have noted the close embryological proximity of structures often involved in SOD, including the optic chiasm and infundibulum, as additional evidence of a vascular insult [21, 22]. According to Lubinsky, a vascular disruption at the proximal anterior cerebral artery trunk could account for the anomalies commonly observed in SOD [21]. In contrast, Kallmann syndrome, another anomaly associated with incomplete olfactory development, is characterized by isolated hypogonadotropic hypogonadism and either hypo-osmia or anosmia [23]. Therefore, the pathogenesis of Kallmann syndrome is distinct from that of SOD, and is considered related to a disturbance in the migration of gonadotropin-releasing hormones and olfactory axons from the olfactory placode to the hypothalamus [23, 24].

If the hypothesis that SOD is related to vascular disruption is true, then this offers a possible pathogenesis for the observed olfactory tract and sulcus hypoplasia. The formation of the olfactory bulb begins at Carnegie stage 18 (corresponding with week 7); by stage 21 (week 8), the structure of the olfactory bulb is usually evident [25]. Levine et al., citing the close temporal proximity of the development of the olfactory pathways to the anterior visual pathway, proposed that a single vascular disruption could explain the co-existent findings of SOD and olfactory tract hypoplasia. The anatomic proximity of the involved structures also may support a vascular insult; anatomic analysis of the olfactory artery by Favre et al. noted that the olfactory artery usually arises from the A2 segment of the anterior cerebral artery, courses within the olfactory sulcus, and supplies the olfactory tract and bulb [26]. Hence, disruption to the arterial supply at the level of the proximal artery cerebral artery trunk could cause anomalies within the olfactory bulbs and sulci. This hypothesis may also explain the unique finding in this study that anterior falx hypoplasia was the most common anomaly in SOD. Nevertheless, the relative inconsistency with which olfactory bulb/tract and sulcus hypoplasia is associated with other anomalies may suggest that the pathogenesis of SOD is either (1) developmental, and susceptibility of different areas is based on a variety of factors, or at least (2) this association is often overlooked from a neuroimaging and clinical standpoint.

There are several potential limitations of this study. First, there are inherent limitations of any retrospective study. Also, the section thickness of MR examinations varied,

perhaps affecting the grading of observed olfactory sulcus and bulb-tract hypoplasia. The authors sought to mitigate this by only including examinations with thinner (≤3 mm thickness coronal and ≤4 mm axial and sagittal) images. Additionally, future larger studies may be useful to further explore the frequency of associated anomalies in SOD, as some might consider this study's sample size too small to confirm such associations. Next, there are other anomalies that have been described as being associated with SOD; however, the aim of the current study was to focus on olfactory sulci and tract-bulb hypoplasia; secondary assessment of other associated anomalies focused on anomalies that had been well described in prior literature given the small patient sample size. Next, a comprehensive medical record of the patient population was not sufficiently present to remark on the clinical severity associated with imaging findings, as many examinations were performed prior to the institution of an electronic record (thus unavailable) or transferred from an outside institution. In addition, clinical assessment of olfactory bulb-tract deficiency is not routinely assessed in a neuro-ophthalmological evaluation of patients with suspected SOD [27]. Finally, it remains uncertain whether SOD is related to mild anterior falx hypoplasia, since it appears to be a common finding in control patients as well; this could be further evaluated in future studies. Hence, it is not known whether the observed abnormalities within the olfactory sulci and/or tracts are of clinical importance.

Conclusion

Some degree of olfactory sulcus and bulb hypoplasia is present in approximately one third of patients with SOD, and such findings are typically bilateral when present, although severity may be asymmetric. Of the other associated anomalies observed, anterior falx hypoplasia was most common, followed by IHI. Future studies with a greater number of patients may be useful to further characterize the frequency of olfactory sulcus and bulb hypoplasia, and to correlate these findings with symptomatology.

Compliance with ethical guidelines

Conflict of interest J.C. Benson, D. Nascene, C. Truwit and A.M. McKinney declare that they have no competing interests.

Ethical standards Institutional Review Board (IRB) approval was obtained for this retrospective study.

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