Transsphenoidal meningocele: an anatomical study using human fetuses including report of a case

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Abstract An asymptomatic transsphenoidal meningoen-cephalocele was discovered incidentally by fiber laryngo-scopic examination in a 62-year-old man suffering from hoarseness due to dysplasia of the vocal cord epithelium. To provide a better understanding of the pathogenesis of this anomaly, we performed histologic observations of paraffin-embedded specimens of 42 human fetal heads at 12–16 weeks of gestation. At these stages, ossification had started in the clivus but the sphenoid sinus was not developed. In contrast to the very low incidence of the intra- or trans-sphenoidal remnant of Rathke's pouch after birth, we found (1) the typical mid-line cleft of the sphe-noid body in two specimens (2/42 or 4.8 %) and (2) a duct-like, sellar inferior protrusion ending in the sphenoid body in 12 specimens (12/42 or 28.6 %). The cyst-like structure in the protrusion (two specimens) seemed to be composed of obstructed veins. The intra- and trans-sphenoidal anom-alies were observed more frequently in specimens without ossification of the sphenoid body than in those with ossifi-cation. However, irrespective of ossification, a cyst-like remnant of the most upper part of Rathke's pouch was always seen between the anterior and posterior lobes of the developing pituitary gland. In addition, the bursa pharyngea was seen in four specimens and we confirmed that the notochord was attached to the bursa in each case. The consistent remnant of the intrasellar Rathke's pouch appeared to explain the high incidence of Rathke's cleft cyst in adults. The relatively high incidence of intrasphenoidal anomalies in fetuses (14/42) suggested that the intra- or trans-sphenoidal remnant of Rathke's pouch was physio-logically closed by ossification of the sphenoid body.

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Introduction

Rathke's cleft cyst is often found in cadaver dissections (13–22 % in Shanklin [1, 2]). Rathke's pouch, a physiological superior pouching of the stomodeal ectoderm along the putative upper pharynx [3, 4], is likely to partly remain to form Rathke's cleft cyst, a well-recognized anomaly [5, 6]. If the entire pouch remains as the craniopharyngeal canal, it can cause a rare anomaly: transsphenoidal meningoencephalocele [7–9]. The "lateral craniopharyngeal canal" or Sternberg's canal [10–12] is also known to pass through the putative synchondrosis between the basisphenoid and the greater wing of the sphenoid; this nomenclature may suggest a similarity to the craniopharyngeal canal, but it is quite different from Rathke's pouch [13, 14]. Here we describe a case of transsphenoidal meningocele that was found incidentally during a fiber laryngoscpic examination to identify vocal cord pathology. The patient is described in the first part of the "Results" section.

The usual entity of Rathke's cleft cyst includes not only intrasellar, intrasphenoidal and suprapharyngeal cysts, which are located along Rathke's pouch, but also the suprasellar and retroclival cysts, according to Famini et al. [15] and Trifanescu et al. [16], both of whom independently investigated 2,598 subjects. Is persistent Rathke's pouch responsible for any of the cysts at the skull base? In spite of the well-known anomalies described above, to our knowledge, few studies have focused on the normal processes of regression of Rathke's pouch in humans, especially the distal (transsphenoidal) part. In addition to Rathke's cleft cyst, another entity—"bursa pharyngea"—has also been reported and, being different from the cyst, the bursa is considered to be formed by traction of the pharyngeal epithelium by the notochord sheath [17–19]. To provide a better understanding of these anomalies in and around the sellar region, we examined the fetal sphenoid body and upper pharynx in histological sections of 42 human mid-term fetuses. At this stage, the pituitary gland as well as the upper pharynx is well developed, but development of the sphenoid sinus has not yet begun. The second part of the "Results" section describes this fetal study.

Materials and methods

The study was performed in accordance with the provisions of the Declaration of Helsinki 1995 (as revised in Edinburgh 2000) [20].

Patient's case report

A 62-year-old man visited a local ENT clinic in 2009 because of hoarseness. He had no symptoms related to meningocele. He was referred to the first author at Sendai Municipal Hospital. He was 154 cm in height and 58 kg in weight, thus being slightly obese. No abnormality was evident in the skeletal system. He provided informed consent for publication of this report, and the study was approved by the ethics committee of the hospital.

Anatomical study using human fetuses

We carried out a histologic study of 42 paraffin-embedded human fetal heads at 12–16 weeks of gestation (crown-rump length or CRL, 95–150 mm). All the fetuses were part of the large collection kept at the Embryology Institute of the Universidad Complutense, Madrid, being the products of urgent abortion, miscarriages or ectopic pregnancies managed at the Department of Obstetrics of the University. Approval for the study was granted by the ethics committee of the university. The donated fetuses had been fixed with 10 % v/v formalin solution for more than 3 months. After division into the head and neck, the thorax and upper extremities, and the abdomen and pelvis with the lower extremities, the heads were decalcified by incubating them at room temperature in 5 % v/v nitric acid for 3–5 days. After routine procedures for paraffin-embedded histology, 10-μm-thick sections of the whole head were prepared at intervals of 20–50 μm depending on the size of the fetus. Among the 42 specimens studied, 9 were processed for sagittal sections, 11 for frontal sections, and 22 for horizontal sections. The sections were stained with hematoxylin and eosin (HE) or azan. The sections included not only the skull base but also any surrounding structures such as the brain, nose, ear, eye and palate. Thus, the materials overlapped with those used in our previous studies [21, 22].

Results

Case report

A 62-year-old man suffering from hoarseness visited a local otolaryngology clinic in 2010. Because the right vocal cord showed leukoplakia, he was referred to the first author at Sendai Municipal Hospital rule out cancer. The patient's medical history included rheumatoid arthritis, osteoarthritis of the knee and bronchial asthma, but he was unable to recall any previous episodes of nasal symptoms such as rhinorrhea. Although, for unknown reasons, his left eye had been replaced by an artificial eye in childhood, ophthalmologic examination at our hospital revealed no

visual abnormality of the right eye. Pathohistological examination revealed dysplasia of the vocal cord epithelium, and we decided to check the pathology at intervals. The hemogram suggested slight anemia (red blood cells 367×10^4, hemoglobin 11.9 g/dl), but no abnormalities were demonstrated in other blood parameters (white blood cells 7.2×10^3, platelets 20.2×10^4, urea 20 mg/dl, creatinine 0.93 mg/dl, sodium 142 mEq/l, potassium 4.2 mEq/l, chloride 106 mEq/l).

Notably, during observation with a flexible laryngeal fiberscope, we found a large pulsatile tumor-like object in the posterior part of the nasal cavity (Fig. 1). The mass extended inferiorly from the skull base through an absent posterior part of the nasal septum. No abnormality was seen in the nasal turbinates, palate or pharyngeal wall. Computed tomography (CT) demonstrated complete absence of the bottom of the pituitary fossa (Fig. 2a). However, we did not find any evidence of previous skull base injury or surgery. Magnetic resonance imaging (MRI) showed that the mass was filled with cerebrospinal fluid, thus allowing us to identify it as a transsphenoidal meningocele (Fig. 2b, c). After the diagnosis, we performed endocrinological examinations, which yielded the following values: GH, 0.032 ng/ml, normal; LH, 2.56 mIU/ml, normal; FSH, 2.43 mIU/ml, normal; PRL, 4.07 ng/ml, slightly low; ACTH, 2.2 pg/ml, low; somatomedin C, 9.7 ng/ml, low. Therefore, he showed asymptomatic partial hypopituitarism. Since finding the pathology, up to the time of writing (Oct 2012), we have been regularly checking the patient, but the meningocele has not altered in size. The volume of accumulated fluid has remained stable without signs of leakage into the nasal cavity.

Anatomical study using human fetuses

In the fetal specimens examined, the pituitary gland was well differentiated and, in sagittal sections (Figs. 3, 4), the pituitary fossa displayed a convex or trianguar-shape. The clinod processes were short but identifiable. Because the lateral sellar compartment was not yet developed (Figs. 5, 6), the putative pituitary fossa opened laterally. No definite anomaly of the brain was evident in the 42 specimens. A cyst-like structure (Figs. 3a, 4) lined with cuboidal epithelium was consistently evident in the sellar region between the anterior and posterior lobes of the pituitary gland (the adenohypophysis and neurohypophysis); this corresponded to a remnant of the original lumen of Rathke's pouch [3] and the residual lumen of Rathke's pouch [4]. The notochord ended in the sphenoid body posterior (Fig. 3a) or anterior (Fig. 3b) to the fossa. The ossification center was often (29/42) seen in the sphenoid body, being located just below, or slightly posterior to the pituitary fossa (Fig. 3b, c). The sphenoid sinus had not yet developed in any of the specimens: the paranasal sinus was limited to a pouch of the putative maxillary sinus (Fig. 6). There was thick and dense connective tissue above and along the upper pharynx (i.e., the putative pharyngobasilar facia).

Among the 42 specimens examined, we found three types of anomalies of the pituitary fossa or upper pharynx in 17 specimens: (1) the typical mid-line cleft of the sphenoid body in two specimens (Fig. 4); (2) a duct-like, sellar inferior protrusion ending in the sphenoid body in 12 specimens (Figs. 5, 6); (3) the bursa pharyngea in four specimens (Figs. 7, 8). Among these specimens with abnormality, one carried both the inferior protrusion and bursa pharyngea. In two of the 12 specimens with inferior protrusion, the duct-like structure contained a large cyst-like element; it contained debris of red blood cells and its lining epithelium was unclear (insert of Fig. 5e). The sphenoid cleft originated from the bottom of the pituitary fossa and communicated with the pharyngobasilar facia (Fig. 4). The inferior protrusion of the pituitary fossa was seen extending antero-inferiorly into the sphenoid body and reaching the base of the nasal septum. This inferior end corresponded to a site between the bilateral otic capsules (Fig. 5e, f). The protrusion, when the cyst-like structure was not associated, was 0.2–0.3 mm in diameter and 0.5–1.5 mm in length and contained veins and loose fibrous tissue continuous with that in the pituitary fossa.
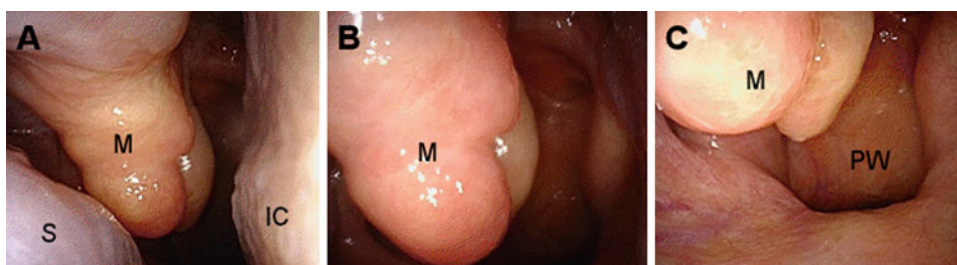

Fig. 1 Observations of transsphenoidal meningocele using endonasal fiber scope. The tip of the endoscope is located in 2 cm (**a**), 4 cm (**b**) or 5 cm (**c**) from the anterior nasal opening. The meningocele (M) is *yellow* in color and forms a lobulated tumor. *IC* inferior concha, *PW* posterior wall of the pharynx, *S* nasal septum

Fig. 2 CT and MR imaging of transsphenoidal meningocele. All are sagittal images. **a** CT, **b** T1-weighted MR image, **c** T2-weighted MR image. The *bottom* of the pituitary fossa is absent. A fluid collection in the meningocele is evident. Leakage of cerebrospinal fluid to the nasal cavity appears to be unlikely because of clear demarcation of the tumor

Fig. 3 Normal pituitary fossa and the sphenoid body. Almost mid-sagittal sections. The left-side of each panel corresponds to the anterior side of the head. **a–c** different three fetuses at 12 weeks. Ossification of the sphenoid body starts in **b** and **c**, but not in **a**. The ossification center is located just below the fossa in **b**, but in the posterior side in **c**. The remnant of the most upper part of Rathke's pouch (*star* in **a**) is seen behind the adenohypophysis (AH), but it is located outside of the figure in the other two specimens (**b** and **c**). *Asterisks* in **c** indicate artifactual spaces due to histological procedure. All panels are prepared at the same magnification (*scale bar* in **a**). *NC* notochord, *ph* pharyngeal cavity

The specimen with the inferior protrusion usually carried no ossification in the sphenoid body, i.e., the ossification appeared to be delayed (9/12). The bursa pharyngea was lined by squamous or cuboidal epithelium continuous with the pharyngeal epithelium (Figs. 7, 8). In two of the four specimens with a bursa, the notochord was attached to the latter (Fig. 8b). The bursa did not communicate with the sellar inferior protrusion in a single specimen showing both
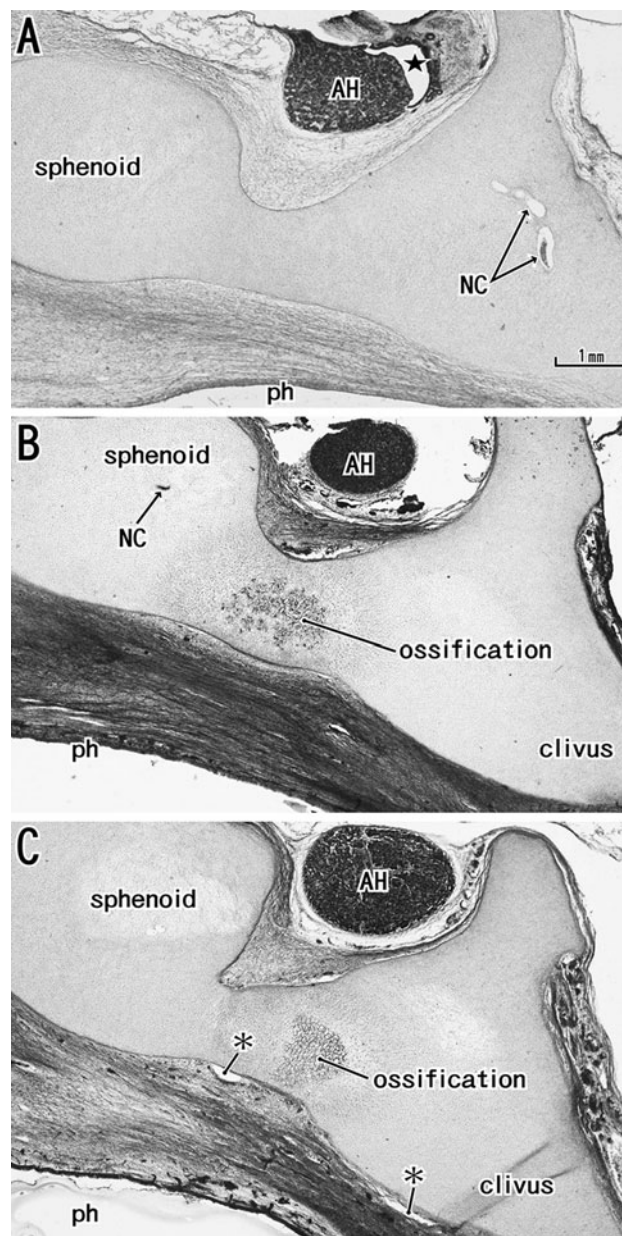
anomalies: the inferior end of the protrusion was located on the far anterosuperior side of the bursa. In addition, in two specimens (Fig. 6f), we found a cell cluster, possibly an ectopic adenohypophysis [23, 24], along the upper
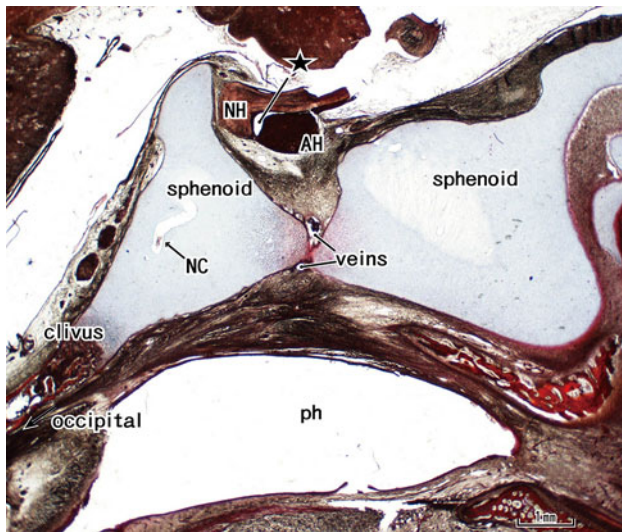
Fig. 4 Cleft of the sphenoid body in a 13-week fetus. Almost mid-sagittal section. The sphenoid body carries the typical cleft through which loose tissues are communicated between the pituitary fossa and the suprapharyngeal tissue (i.e., the pharyngobasilar fascia). The cleft contains veins. *Star* indicates the remnant of the most upper part of Rathke's pouch between the adenohypophysis (AH) and neurohypophysis (NH). Ossification is not seen in this sphenoid body. *NC* notochord, *ph* pharyngeal cavity

pharyngeal wall, although we did not confirm the immunohistochemical phenotype.

Discussion

The present case of transsphenoidal meningocele produced no symptoms and was found incidentally. Although slight hypopituitarism was also evident, we obtained no histological data on the tumor, especially the distribution of pituitary gland tissues along and within it. While taking care to avoid fluid leakage, we have continued to observe the intranasal tumor without any surgical intervention. MR images in this case were similar to those reported by Formica et al. (an 8-month-old girl; 2002) [7], Franco et al. (six patients aged between 6 months and 15 years; 2009) [25] and Hughes et al. (19 and 27-year-old males; 1999) [9]; the common feature appeared to be absence of the posterior part of the nasal septum. Actually, the present anatomical study demonstrated that the inferior protrusion of the pituitary fossa ended at the root of the septum. However, the partial absence of the septum might have been a secondary effect of the large meningocele.

Fig. 5 Duct-like inferior protrusion of the pituitary fossa seen in a 12-week fetus. Horizontal sections. **a** (**f**) displays the most superior (inferior) side of the figure. Intervals between panels are 0.3 mm (**a–b**, **b–c**), 0.6 mm (**c–d**) and 0.1 mm (**d–e**, **e–f**), respectively. The bottom of the pituitary fossa (*arrow*) is seen in **d**. Inserts in **e** displays a higher magnification view of the inferior protrusion of the fossa (*arrow*) shown in **e**. All panels are prepared at the same magnification (*scale bar* in **a**). The "ear" indicates the cartilaginous capsule of the cochlea. Ossification is not seen in this sphenoid body. *AH* adenohypophysis, *NC* notochord, *NH* neurohypophysis, *NS* nasal septum, *ON* optic nerve
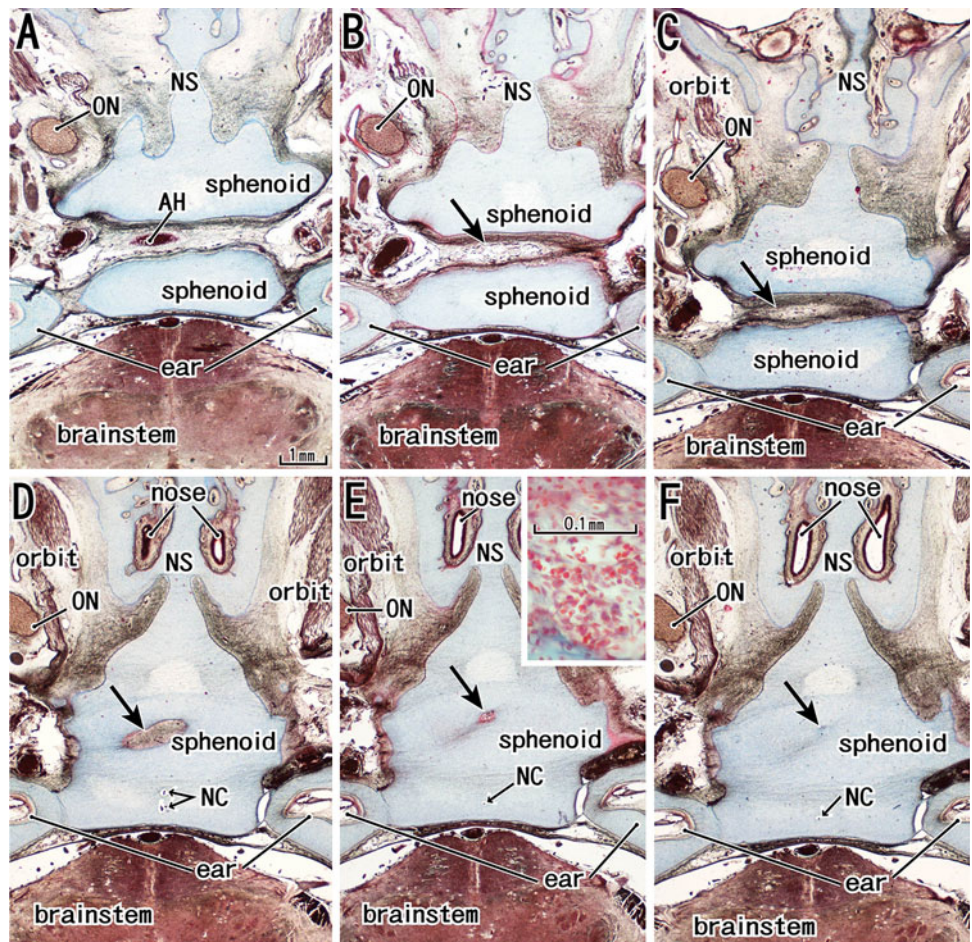
Fig. 6 Duct-like inferior protrusion of the pituitary fossa with a large cyst seen in a 14-week fetus. Frontal sections. **a** (**g**) displays the most posterior (anterior) side of the figure. Intervals between panels are 0.6 mm (**a–b**, **b–c**), 0.8 mm (**c–d**), 0.3 mm (**d–e**) and 0.2 mm (**e–f**), respectively. *Arrow* indicates the inferior protrusion of the pituitary fossa. The protrusion contains a large cyst-like structure in **f**. Insert in **f** displays an ectopic adenohypophysis below the sphenoid in **e** (*square*). The protrusion reaches the root of the nasal septum in **g**. Ossification is seen in this sphenoid body. All panels are prepared at the same magnification (*scale bar* in **a**). *ACP* anterior clinoid process, *AH* adenohypophysis, *MX* maxilla with an initial stage of the maxillary sinus, *PB* palatine bone, *ph* pharyngeal cavity
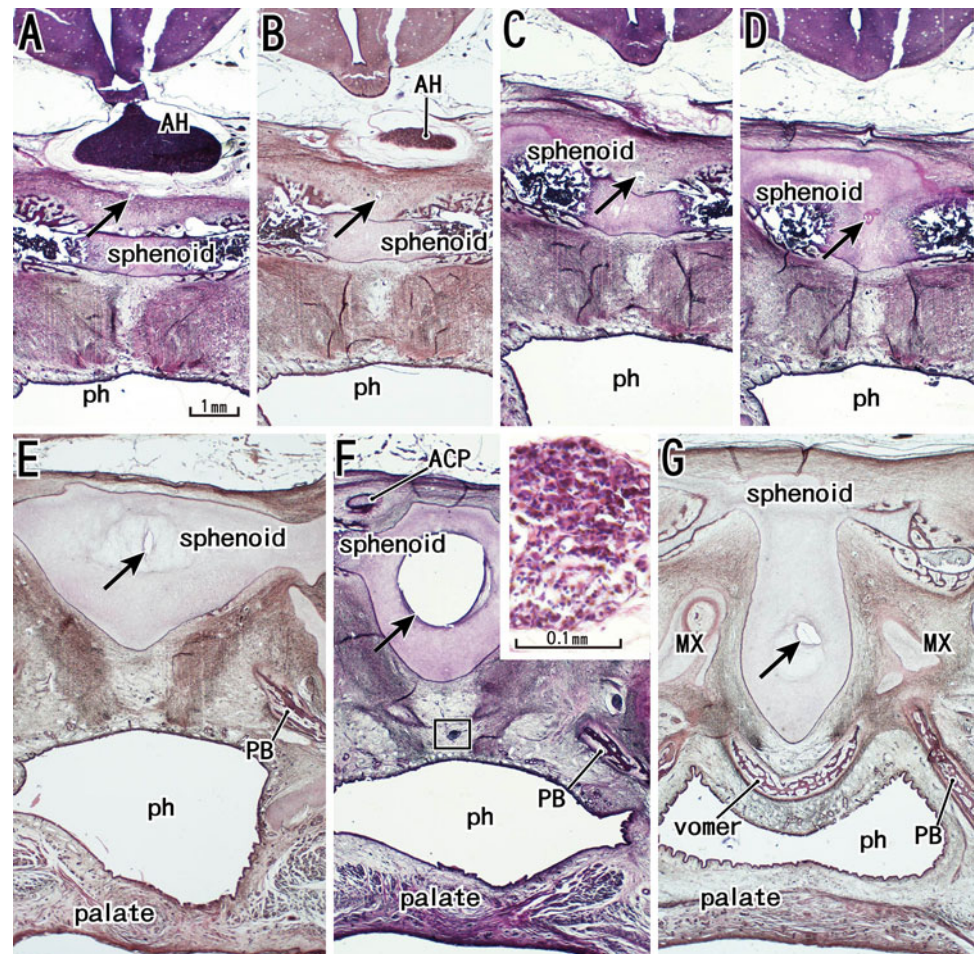
Transsphenoidal meningoencephalocele is often accompanied by visual impairment [8, 26], but this was not the case in our patient. In spite of the large tumor occupying the nasal cavity, our patient did not have any breathing difficulty that is a common feature of transsphenoidal meningocele [7, 9]. Transsphenoidal meningocele seemed to form along a cleft of the sphenoid body, but as clearly demonstrated in the present fetuses, the cleft was not always accompanied by meningocele or other anomalies of the brain. Therefore, the meningocele seemed to have arisen due to another cause, such as partial absence of the dural lining of the skull base in the initial development.

In the fetal specimens, we found the typical cleft of the sphenoid body: it suggested that Rathke's pouch extended over the whole distance from the adenohypophysis to the upper pharynx. If found on CT images of adult patients, the cleft seems to have been included within the category of a craniopharyngeal canal [5, 6, 14]. We also demonstrated the duct-like, inferior protrusion of the pituitary fossa. This protrusion was likely to contain a cyst. It is possible that this may develop into a tumor in the sphenoid sinus exhibiting or lacking communication with the pituitary fossa [27, 28]. In contrast to the sphenoid cleft or

craniopharyngeal canal, the inferior protrusion ended at a site anterior to the upper pharynx. We speculated that, without fixation to the pharyngeal epithelium or the tight pharyngobasilar fascia, the remnant of Rathke's pouch would tend to move anteriorly because of changes in topographical relationships during development of the clivus and nasal septum. Notably, between the anterior and posterior lobes of the pituitary gland, we consistently found a remnant of the original lumen of Rathke's pouch; this morphology was consistent with that reported by Hamilton and Mossman and O'Rahilly and Müller [3, 4]. This physiological remnant of the upper end of Rathke's pouch was the most likely origin of intrasellar Rathke's cleft cyst.

Our present observations demonstrated that the physiological remnant of the pouch did not extend into the sphenoid cleft or the inferior protrusion of the pituitary fossa. Instead, the inferior protrusion and the sphenoid cleft contained abundant veins. Moreover, the cyst-like structure in the protrusion contained debris of red blood cells. The epithelium of the physiological remnant of Rathke's pouch differed from the lining of the cyst-like structure, suggesting that the latter did not originate from Rathke's pouch, but from obstructed veins. The usual entity of
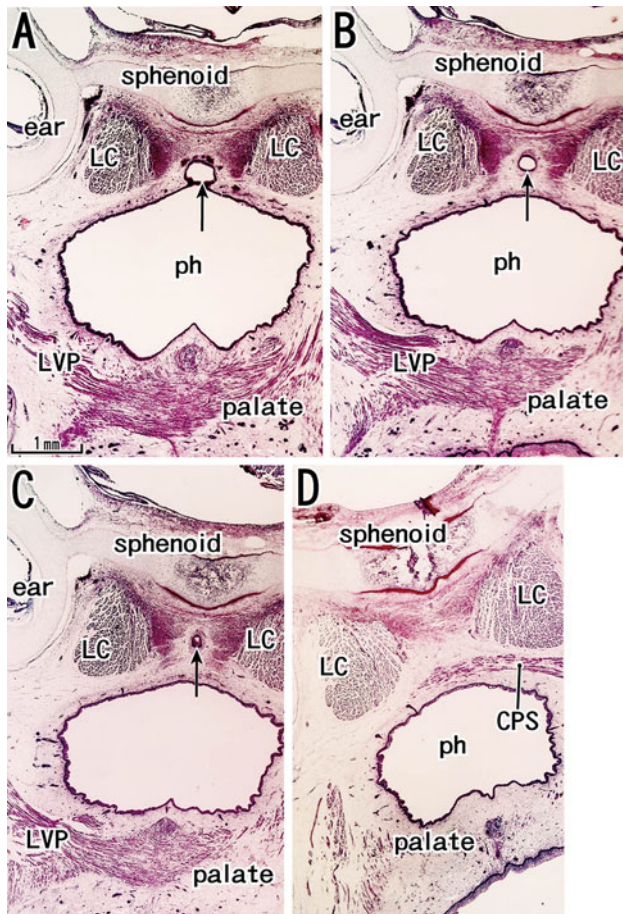
Fig. 7 Bursa pharyngea seen in a 14-week-fetus. Horizontal sections. **a** (**d**) displays the most superior (inferior) side of the figure. Intervals between panels are 0.2 mm (**a–b**), 0.1 mm (**b–c**) and 0.4 mm (**c–d**), respectively. The bursa (*arrow*) opens to the pharyngeal cavity (ph) at the superior end (**a**). The bursa extends inferiorly to reach a site 0.4 mm superior to the upper end of the constrictor pharyngis superior muscle (CPS in **d**). All panels are prepared at the same magnification (*scale bar* in **a**) *LC* longus capitis muscle, *LVP* levator veli palatini muscle

Fig. 8 Bursa pharyngea attaching to the notochord seen in a 12-week-fetus. Horizontal sections. **b** is located 0.1 mm superior to **a**. The notochord (*arrows* in **b**) is attached to the bursa (*arrow* in **a**). *Asterisk* in **a** indicates an artifact during histological procedure. Insert in **a** is a higher magnification view of the bursa. All panels are prepared at the same magnification (*scale bar* in **a**). *LC* longus capitis muscle, *ph* upper end of the pharyngeal cavity

Rathke's cleft cyst includes not only intrasellar, intrasphenoidal and suprapharyngeal pathology, but also suprasellar and retroclival pathology [15, 16]. In view of the variety of sites affected, we hypothesize that Rathke's cleft cysts have heterogeneous origins. Choudhry et al. [29] postulated a possible spectrum between Rathke's cleft cyst and craniopharyngioma based on histology, especially calcification of the cyst. However, this spectrum may assume a single origin of Rathke's cleft cysts. According to the so-called vascular theory (reviewed by Pinilla-Arias et al.) [30], the craniopharyngeal canal represents the persistence of a vascular channel during osteogenesis of the sphenoid body. Although we are unable to rule out this theory, both the inferior protrusion and the sphenoid cleft were usually evident in specimens before ossification.
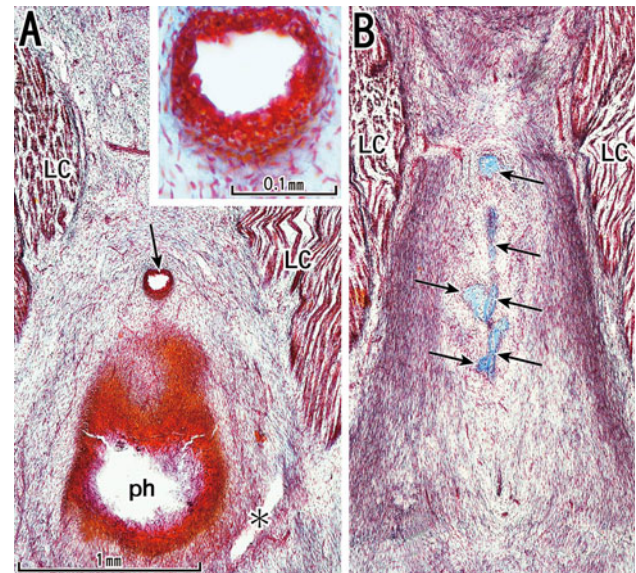
The bursa pharyngea arises through traction of the pharyngeal epithelium by a fibrous sheath of the notochord [17–19]. In fact, the bursa in fetuses was characterized by a close topographical relationship with the degenerating notochord. Although not well known, the cranial part of the notochord runs outside (antero-inferior to) the developing clivus and then re-enters the sphenoid body [19, 31–33]. Thus, as demonstrated in the present study, the notochord is able to make contact with the pharyngeal epithelium. However, the notochord was not attached to (even distantly from) the inferior protrusion of the pituitary fossa. Thus, traction of Rathke's pouch by the notochord would seem unlikely, suggesting some doubt about the cause-effect relationship between the notochord and Rathke's cleft cyst [34]. The effects of the notochord on development of the sellar region, such as a hypothetical contribution to the differentiation of hypophyseal tissues [35], may have been overestimated. The role of the notochord seems to be limited to non-specific pouching of the pharynx to form Rathke's pouch [36].

Irrespective of whether ossification of the sphenoid was delayed, a cyst-like remnant of the upper end of Rathke's pouch was always evident between the anterior and posterior lobes of the developing pituitary gland. This consistent remnant of the intrasellar Rathke's pouch appeared to explain the high incidence of Rathke's cleft cyst in the adult sellar region. The relatively high incidence of intrasphenoidal anomalies in fetuses suggested that the

intra- or trans-sphenoidal remnant of Rathke's pouch was physiologically closed by ossification of the sphenoid body. However, the cyst-like structure in the inferior protrusion of the pituitary fossa appeared not to originate from the pouch itself, but from veins. In addition, traction of the pharyngeal epithelium by the notochord provided the bursa pharyngea. Consequently, cyst-like structures at and around the sellar region appear to have different origins.

Conflict of interest The authors declare no conflict of interest.

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