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Pharyngeal pituitary: development, malformation, and tumorigenesis

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Abstract The development of the pharyngeal pituitary (PhP) in the fetal period was morphologically and, for the first time, immunohistochemically examined. PhP, found in every individual, begins its hormone production at the 17–18th week of gestation, that is, 4–8 weeks later than that of sellar pituitary (SP). Only 1 of 25 examined fetuses without any stigmata of developmental anomalies showed a residual pituitary fragment in the craniopharyngeal canal (craniopharyngeal pituitary, CPhP). An adult case of a rare clivus pituitary adenoma that we examined is demonstrated in discussing its relationship to PhP. Extracranial ectopic pituitary adenomas in the literature describe an exclusively sphenoid sinus/nasopharyngeal/clivus location of the tumor. Their location corresponded exactly with that of PhP, so that the origin of the tumors can be reasonably speculated as PhP, although another origin, e.g., CPhP, can not be excluded. A variety of malformations of PhP, although very rare, have been described for the fist time during the systemic examination of 16 fetuses with different cranioneural malformations, such as agenesis, unseparated PhP from SP (pharyngosellar pituitary), fragmentation, and residual pituitary tissue in the open craniopharyngeal canal. However, developmental anomaly of PhP was not specifically associated with cranioneural malformations except in cases of chromosomal aberrations. The hormone production in PhP in malformation cases tended to be retarded. Absence of SP was recorded in 50% of anencephalics in the literature; however, PhP was identified in all anencephalics in our series, independent of the existence of SP. This supports the opinion that agenesis of SP in anencephalics seems to be false information.

Key words Development of pituitary gland · Ectopic pituitary adenoma · Pharyngeal pituitary · Pituitary hormone · Pituitary malformation

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Introduction

The pharyngeal pituitary (PhP) exists life-long in every individual. It is known that PhP produces the anterior pituitary hormones. However, its function is doubtful since its volume is about one-thousandth, if calculated from the data of McGrath [25], of the ordinary anterior pituitary gland [the term sellar pituitary (SP) will be used for the ordinary anterior pituitary gland in this report in contrast to PhP]. PhP has neither a portal system nor contact to the hypothalamus. Nevertheless, it possesses vascular connection with SP and may react in altered endocrinological states though not always adequately [26].

The purpose of this study was to determine the morphology, location, and the hitherto-unknown differentiation of the PhP cells in normal fetal stages and in malformations, comparing them to those of SP, and we discuss the possible relationship to the extracranial "ectopic" pituitary adenomas, demonstrating our own case of pituitary adenoma in the clivus which occurred independently of SP. The residual pituitary tissue in the craniopharyngeal canal (craniopharyngeal pituitary) will be abbreviated as CPhP.

Materials and methods

From the routine necropsy series, 25 fetuses between the gestational weeks 15 and 36 (Table 1) without major CNS anomalies were randomly selected. After prefixation of whole calvaria in 4% buffered formalin, the middle skull base was dissected including pharyngeal roof, sella turcica, SP, and clivus. The specimens were divided into two blocks through the midline and further fixed in formalin for several days. Both the right and left blocks were embedded in paraffin and sectioned serially in 5-μm thickness. (Since the cranial base does

Table 1 Hormone production in SP and PhP and morphology of PhP in fetuses. A *blank value* indicates no evaluation for technical reasons [*SP* sellar pituitary, *PhP* pharyngeal pituitary, *STH* somatotropic (growth) hormone, *PRL* prolactin, *FSH* β-follicle-stimulating hormone, *LH* luteinizing hormone, *TSH* β-thyroid-stimulating hormone, *ACTH* adrenocorticotropic hormone, *lt.* left, *rt.* right, *med.* median line, *ant.* anterior to the sella bottom, *post.* posterior to the sella bottom, *mid.* middle = subsellar position, ++ rich in immunopositive cells, + several immunopositive cells, ± immunopositive cells exist but few, – no immunopositive cells, *(–)* no immunopositive cells but not suitable for evaluation because of too small mass of the examined PhP]

No./age/sex		STH	PRL	FSH	LH	TSH	ACTH	Location	Form
1	SP	+	+	+	±	+	±		
15 weeks/M	PhP	–	±	++	–	+	±	lt. ant.	Round
2	SP								
15 weeks/M	PhP	(–)	–	–	–	–	–	lt. post.	Round
3	SP	±	±	–	±	±	+		
16 weeks/M	PhP	–	–	–	–	–	–	lt. post.	Round
4	SP	±	±	±	±	+	++		
16 weeks/M	PhP	–	–	±	–	±	–	lt. mid.	Oval
5	SP	++	±	+	+	+	++		
17 weeks/F	PhP	±	(–)	(–)	–	(–)	–	lt. mid.	Round
6	SP	+	+	+	++	+	++		
17 weeks[a]	PhP	–	–	–	–	–	–	median ant.	Long/round
7	SP	++	++	+	++	+	++		
17 weeks/F	PhP	–	–	–	–	–	–	rt. ant.	String
8	SP	++	++	++	++	++	++		
17 weeks/M	PhP	–	–	–	±	±	±	lt. mid.	Round
9	SP	+	–	–	–	+	++		
17 weeks/M	CPhP	–	–	–	–	–	–		Very small
	PhP	(–)	(–)	(–)	(–)	(–)	(–)	lt. ant.	oval, small
10	SP	++	+	+	+	+	+		
18 weeks/M	PhP	++	+	+	+	+	++	lt. ant.	Round
11	SP	++	++	++	++	++	++		
18 weeks/F	PhP	±	+	++	++	++	±	lt. ant.	String
12	SP	+	++	+	+	±	++		
18 weeks/M	PhP	–	+	–	–	–	(–)	rt. ant.	Long-oval
13	SP	++	++	++	++	++	++		
19 weeks/M	PhP	(–)	(–)	(–)	(–)	(–)	(–)	rt. mid.	String
14	SP	+	±	+	++	+	±		
20 weeks/F	PhP	±	±	+	+	+	±	lt. ant.	Oval, large
15	SP	+	++	±	±	+	++		
20 weeks/F	PhP	–	+	+	–	+	±	lt. ant.	Round
16	SP	++	++	++	++	++	+		
21 weeks/F	PhP	±	±	++	++	++	±	lt. ant.	Long
17	SP	++	++	++	++	++	++		
21 weeks/M	PhP	++	++	+	±	++	++	lt. ant.	Round
18	SP	+	++	±	±	+	±		
22 weeks/M	PhP	–	–	–	–	+	+	rt. ant.	Oval
19	SP	++	++	+	++	++	+		
23 weeks/M	PhP	+	+	++	++	++	–	lt. mid.	Long
20	SP	+	+	+	+	+	+		
23 weeks/M	PhP	–	+	++	++	(–)	–	rt. ant.	Long-oval
21	SP	++	++	++	++		++		
23 weeks/M	PhP		+	(–)	++		+	lt. ant.	Long
22	SP	++	++	++	++	++	++		
25 weeks/F	PhP	–	+	++	++	++	–	lt. ant.	Long
23	SP	++	±	++	+	+	±		
26 weeks/M	PhP	±	+	++	++	++	+	lt. ant.	String
24	SP	++	++	++	(–)	(–)	(–)		
26 weeks/F	PhP	±	±	++	(–)	(–)	(–)	lt. ant.	Long, large
25	SP	++	+	++	++	++	++		
36 weeks/F	PhP	+	++	++	+	+	++	rt. ant.	Protrusions

[a] No document on sex

not completely ossify throughout the fetal age, optimal comparative immunohistochemical examination of PhP and SP was possible without decalcification of the specimens.) Every tenth slide was stained for histological screening with H&E and Gomori's method for reticulin fibers. The histologically identified PhP was further immunostained together with SP on the same slide for pituitary hormones using commercial antisera (from DAKO, Denmark) against anti-growth hormone (STH; dilution 1:500), anti-prolactin (PRL; 1:200), anti-β-thyroid-stimulating hormone (TSH; 1:600), anti-β-follicle-stimulating hormone (FSH; 1:200), anti-luteinizing hormone (LH; 1:800), and anti-ACTH (1:300) by peroxidase-antiperoxidase method. The rest of the slides was stained, if necessary, by Kossa for phosphate base, PAS for glycogen, and Congo-red for amyloid. (Additional TUNEL examination was done; however, its result was not evaluated since the number of the remaining slides of specimens was limited.)

Sixteen cases of different cranioneural malformations were also investigated in the same manner. The malformations included

Table 2 Hormone production in SP and PhP in fetuses with cranioneural malformation

		STH	PRL	FSH	LH	TSH	ACTH	Location	Form
Dicephalus 17 weeks/F									
Normal right head	SP	+	+	+	–	+	+		
	PhP	–	–	–	(–)	–	–	rt. ant.	Oval
Anencephalic left head	SP	+	+	±	±	+	+		Partly destroyed[a]
	PhP	–	–	–	–	+	+	lt. ant.	Large
Sireniform anomaly	SP	+	+	+	++	+	+		
20 weeks/–	PhP	±	+	++	++	+	+	rt. ant.	Long
Chiari II anomaly	SP	++	++	++	++	+	+		
20 weeks/F	PhP	+	+	+	+	+	+	lt. ant.	Long
Tectocerebellar dysraphy	SP	++	++	+	–	++	++		
17 weeks/F	PhP	–	+	±	–	+	–	rt. ant.	String
Agenesis of CC	SP	+	±	±	+	+	+		
14 weeks/M	PhP	–	–	–	–	–	+	lt. post.	Round
Craniocervical dysraphy	SP	+	++			++	+		
16 weeks/F	PhP	+	+	±	–	++	+	med. post.	Long
Anencephaly[b]	SP	±	+	±	–	+	±		
17 weeks/F	PhP	–	+	±	–	+	–	med. mid.	Long
Anencephaly	SP	++	++	+	+	+	+		
18 weeks/F	PhP	±	±	+	++	+	±	lt. ant.	Long
Anencephaly	SP	No SP							
18 weeks/F	PhP	–	–	–	–	+	±	lt. ant.	Oval
Cerebellar agenesis	SP	++	++	+	+	+	+		
21 weeks/M	PhP	–	–	±	+	+	±	rt. ant.	Long
Triploidy	SP	+	+	–	++	±	+		
17 weeks/M	PhP	–	–	–	–	–	–	lt. post.	Round
Trisomy 18	SP	++	++	+	+	++	++		
22 weeks/F	PhP							Diffuse[c]	[c]
Trisomy 21	SP	++	+	+	+	+	++		
19 weeks/M	PhP	(–)	(–)	–	(–)	–	–	rt. post.	Round
Trisomy 21	SP	++	++	+	++	+	++		
21 weeks/F	PhP	±	±	+	++	++	+	rt. mid.	Oval
Pharyngosellar pituitary		See separate report !							
17 weeks/M		[14]							
Pituitary agenesis	SP	Complete agenesis of SP							
36 weeks/M	PhP	Complete agenesis of PhP							

[a] The pituitary gland was partly destroyed in a same manner as in the area cerebrovasculosa (area pituitovasculosa)
[b] Open craniopharyngeal canal; immunoreaction is less significant because of advanced autolysis
[c] Fragmentation of PhP

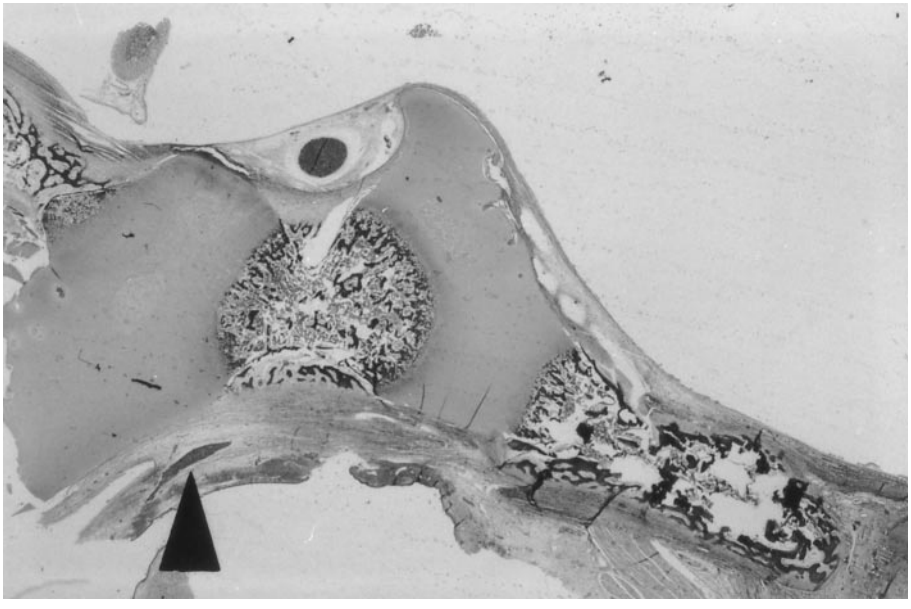

Fig. 1 Typical feature of PhP (*arrowhead*) in relation to SP. Sagittal cut of the cranial base, slightly right to the midline of a fetus of 22 weeks of gestation. H&E, × 4

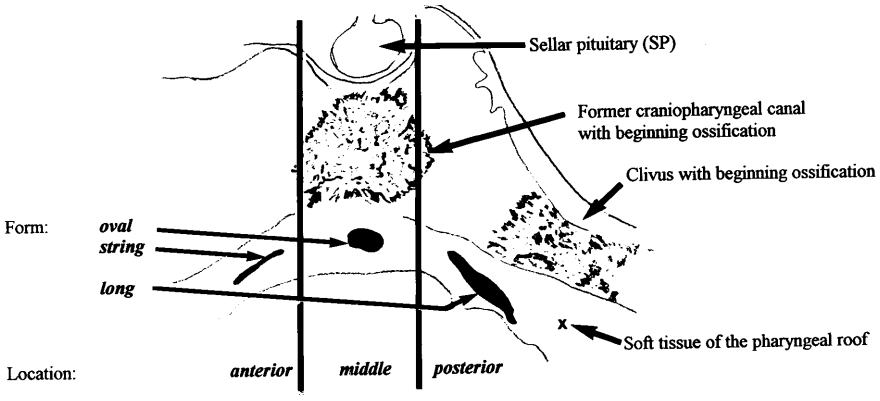

Fig. 2 Definition of the location and examples of the different form of PhP in fetuses. The location is divided into three groups: *anterior*, *middle*, and *posterior*. The form of PhP was either oval, string, or long with one exceptional case, shown in Fig. 3

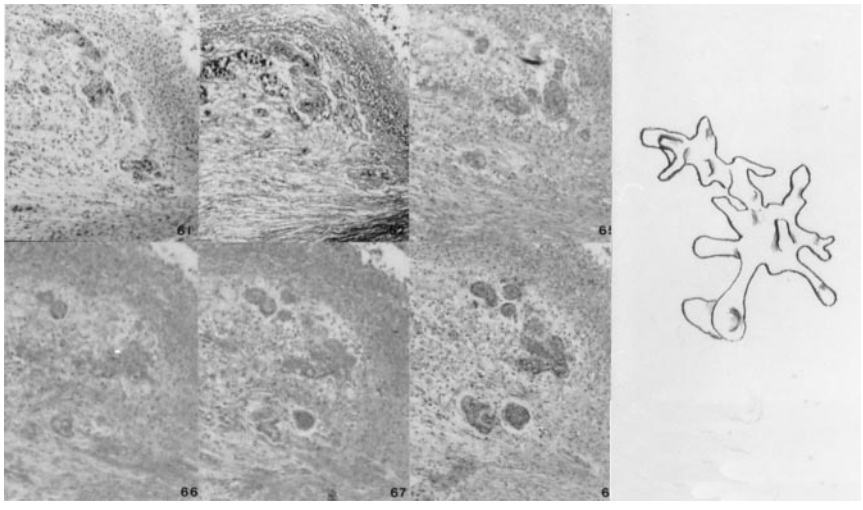

Fig. 3 In case 25, PhP appears fragmented in each slide. Selected slides from serial paraffin sections are shown here. The three-dimensional reconstruction, however, gave the form of this PhP as a mass of irregular protrusions

dicephalus bibrachius, dysraphism (anencephaly and Chiari II anomaly), hypothalamic hamartoma with agenesis of the pituitary gland (Pallister-Hall syndrome), trisomy 13, trisomy 21, and a pharyngosellar pituitary [14]. Agenesis of the cerebellum and agenesis of the corpus callosum were also included (Table 2).

Results

All results are summarized in Tables 1 and 2.

Feature and location of PhP

A typical feature of PhP is shown in Fig. 1. The form and location of PhP were evaluated according to the scheme as illustrated in Fig. 2.

The contours of PhP were relatively simple; some were round, some oval, some elongated, and some even in form of a string. A tendency was noted that round or oval PhP was found more frequently in younger fetuses than the older ones, whose PhP was rather elongated. In two cases, the cut surface of PhP was unusually large, while the lateral diameter was almost the same as in other cases (about 40–50 μm). An exceptional form of PhP was seen in case 25: PhP had many irregular, three-dimensionally extended protrusions (Fig. 3).

PhP was not always located on the midline but deviated laterally with a prevalence to the left (Table 3). Although the left deviation was mathematically significant ($0.025 < P < 0.5$), it should be regarded practically insignificant due to the smallness of PhP which was usually found inside the width of SP, with one exceptional case in which the left deviation of PhP exceeded the lateral diameter of SP (case 2 in Table 1). The rostro-caudal location was variable. The majority of PhP (18/25, i.e., 72.0%) were found in the anterior pharyngeal roof, but some were found in the soft tissue just under the sella turcica or in the posterior pharyngeal roof (Table 4). These variable locations and forms of PhP were not related to sex difference.

Table 3 Laterality of PhP location ($n = 25$)

		(M : F)
Left	17	(10 : 7)
Median	1	(?)[a]
Right	7	(5 : 2)

[a] Sex was not documented in case 6

In a male fetus of 17 weeks of gestational age (case 9), we found an aberrant small pituitary cell group in the craniopharyngeal canal (CPhP). The canal was ossified only at the side of the pharyngeal roof (Fig. 4). In this case, PhP existed but was very small. The immunoreactions to each pituitary hormone were all negative in both CPhP and PhP.

In fetuses generally, the regions of the former craniopharyngeal canal and the central clivus were found to os-

Table 4 Comparison of rostro-caudal location of the normal PhP to location of extracranial pituitary adenomas (extracted from Table 1 and Table 5)

Location of PhP (n = 25)		Extracranial "ectopic" pituitary adenomas (n = 27)	
Anterior	18 (72.0%)	Sphenoid sinus and cavernous sinus	22 (81.5%)
Middle	5 (28.0%)	Clivus and (naso-)pharynx	5 (18.5%)
Posterior	2	(Sphenoid sinus + nasopharynx)	1

(ant.) : (middle + post.) = 18 : 7; (sinus + nasopharynx) : (clivus) = 23 : 5

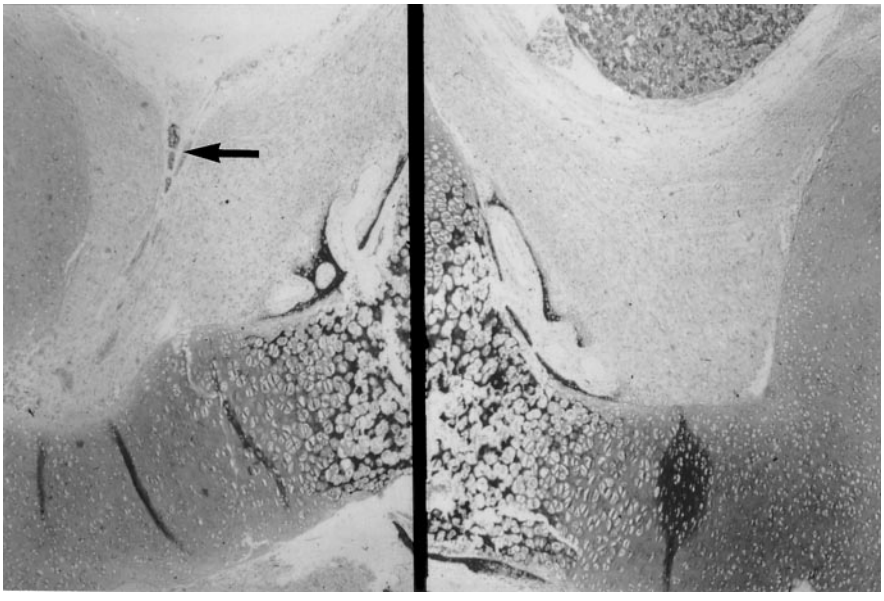

Fig. 4 There are fragments of pituitary cells (*arrow*) in the craniopharyngeal canal that show a retarded closure (case 9 in Table 1; 17 weeks of gestation). H&E, × 23

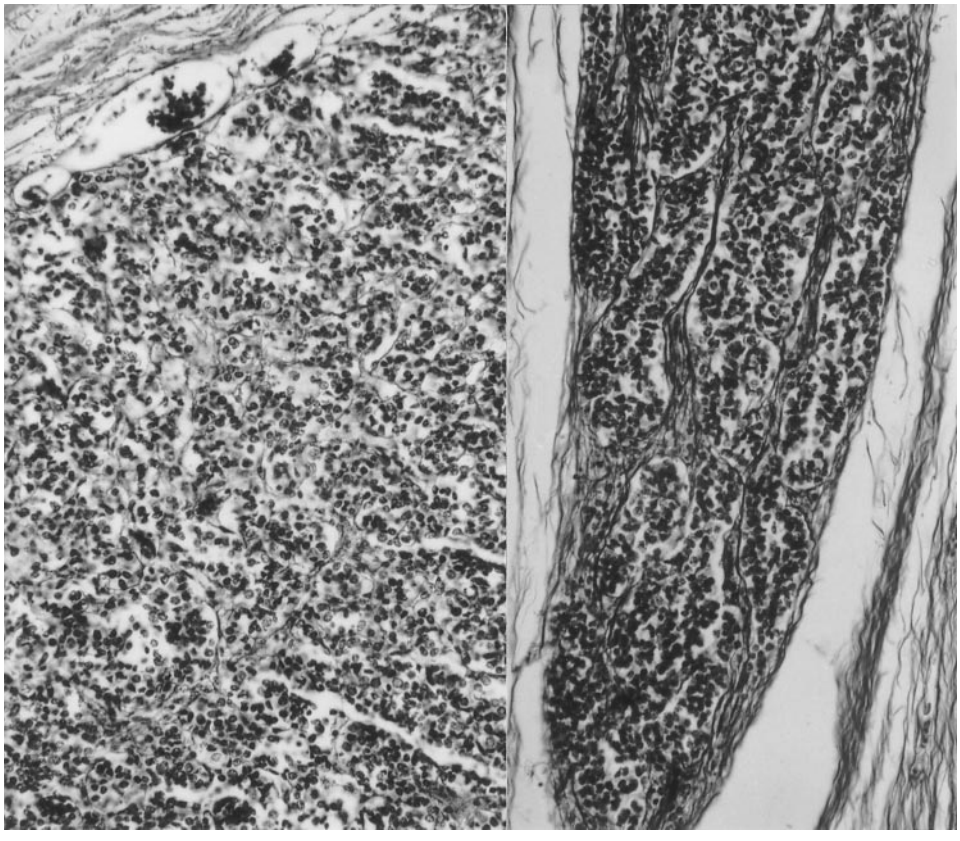

Fig. 5 Comparison of the histological features of SP and PhP stained for reticulin fibers (Gomori). Fine reticulin fibers separate pituitary cell groups into lobuli in SP (*left*), while lobuli are large, crude and irregular in PhP (*right*) and reticulin fibers here are thicker than those in SP. × 175

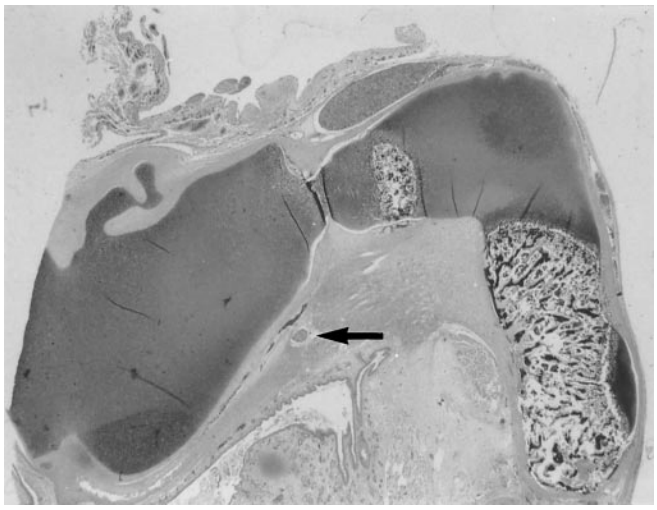

Fig. 6 PhP (*arrow*) at a distant anterior dislocation in an anencephalic. The cranial base is deformed. H & E, × 4

sify earlier than parasellar regions. There was no sphenoid sinus in the fetal skull base.

Histology of PhP

The histological feature of the PhP cells did not differ from that of SP cells. If classically described, cell constituents of PhP were chromophob, eosinophil, and basophil. Calcified concrements were frequently observed in SP and were very rare in the PhP when examined by Kossa-staining.

The fundamental difference between PhP and SP could be found in the Gomori staining: typical lobuli were separated by fine reticulin fibers in the SP, while in the PhP the lobular structure was crude, large, and irregular, and the reticulin fiber bundles were thicker (Fig. 5). SP was subjectively more richly vascularized than PhP. There was no evidence that PhP may regress. There was neither degeneration nor necrosis, nor karyorhexis in these cells.

Table 5 Extracranial pituitary adenomas from the literature (*SS* sphenoid sinus, *Nph/Ph* nasopharynx/pharynx, *Cliv* Clivus, *CavS* cavernous sinus, *X* chromophob, *E* eosinophil, *B* basophil, *A* amphophil, – no description)

Author(s) year	Patient age/sex	Location	Initial or main symptoms	Histology	Immunocytology
Erdheim [9] 1909	53/M	SS	Acromegaly	E	
Kepes & Fritzlen [18] 1964	40/M	SS, CavS, bones	Ocular pain	X	
Chessin et al. [6] 1976	64/F	SS, Nph	Nasal congestion	X	
Borit & Blanshard [3] 1979	62/F	SS	Diplopia	X	
Rasmussen & Lindholm [28] 1979, case 1	36/M	middle meatus	Visual disturbance	X	
Rasmussen & Lindholm [28] 1979, case 2	54/M	SS	Visual disturbance	X	
Corenblum et al. [7] 1980		SS	Acromegaly	A(X, E)	GH
Kammer & George [17] 1981	51/F	SS	Cushing's	X	ACTH
Warner et al. [36] 1982	40/F	SS	Acromegaly	X	GH, PRL
Matsushita et al. [24] 1984	40/F	SS	Headache	X	PRL
Burch et al. [4] 1985	43/F	SS	Cushing's	–	
Shenker et al. [32] 1986	49/M	Cliv	Hyperparathyroidism, polycystic kidney	E	PRL
Lloyd et al. [21] 1986	49/M	SS	Hyperparathyroidism, polycystic kidney	X	PRL
Lloyd et al. [21] 1986	49/F	SS	Cushing's	X	ACTH, TSH, β-endorphin
Schteingart et al. [31] 1987	49/M	SS	Cushing's	–	ACTH
Heitzmann et al. [12] 1989	17/F	SS	Amenorrhoe	B	PRL
Tovi et al. [35] 1990	65/F	SS	Headache, epistaxis	E	PRL
Anand et al. [1] 1993	58/F	Cliv, Nph	Nasal obstr., anosmia, visual disturb.	X	ACTH in a few cells
Slonim et al. [34] 1993	76/F	Ph	Cushing's	A	ACTH
Kikuchi et al. [19] 1994	49/F	SS	Headache, vomiting	E	Null cell
Wilson et al. [37] 1995	50/F	CavS	Cushing's	–	ACTH
Wong et al. [38] 1995, case 6	67/M	Cliv		–	(no ACTH; no PRL)
Luk et al. [22] 1996, case 3	55/F	SS	Headache	–	PRL
Siegert et al. [33] 1996	36/F	SS	Sinusitis	–	Null cell
Esteban et al. [10] 1997	/F	SS	Nelson syndrome	(clinical case)	
Horiuchi et al. [15] 1997	75/M	SS	Visual disturbance	X	(ACTH)
Present case 1999	63/M	Cliv	Visual disturbance	X	Null cell

SS (n = 20), Nph/Ph (n = 4), Cliv (n = 4), CavS (n = 2)
X (n = 13), E (n = 4), B (n = 1), A (n = 2), – (n = 6)

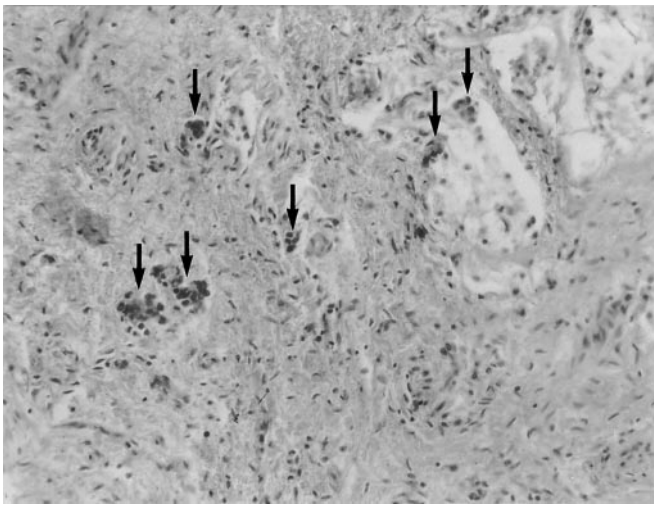

Fig. 7 Fragmented PhP (*arrows*) in a case of trisomy 18. H&E, × 50

Hormone production of the PhP cells

On immunohistochemical examination, the hormone production of PhP began around the 17th gestational week and the anterior pituitary hormones were demonstrable almost constantly from the 18th week on, although some variation or deviation of the hormone-containing cells in the examined cases was recognized. Such differences were considered as individual developmental differences. For example, case 4 (Table 1) was clinically 16 weeks of gestational age; however, the developmental parameters at necropsy corresponded to those of 18 weeks. A male fetus (case 18) of 22 weeks showed no production of STH, PRL, FSH and LH in the PhP. This fetus had no particular abnormality in the fetal stage but died of abortion due to precocious amniotic rupture.

Malformation of PhP

The morphology and immunohistochemistry of PhP in malformation cases are summarized in Table 2. Hormone production in PhP in malformation cases were found to be slightly retarded when compared with the control group (Table 1). However, we could not definitively draw conclusions since individual variation could not be excluded.

PhP existed in four anencephalic cases examined (including one of anencephaly in dicephalus). One of them had no SP, probably due to destruction. Distant dislocation of PhP either in an anterior or posterior direction (Fig. 6) may be due to the cranial base dysmorphism. In an anencephaly (b in Table 5), an open craniopharyngeal canal was found. The PhP of this case was elongated and existed partly inside the craniopharyngeal canal. There was a connection of fibrous tissue between the SP and PhP in this case.

Malformation of PhP itself was very rare. Fragmentation of PhP was found in a fetus with trisomy 18 (Fig. 7), in whom craniofacial anomaly without brain malformation was observed. Agenesis of PhP accompanied by SP agenesis was found in a case of Pallister-Hall syndrome (not illustrated; see discussion). The detailed results of hormone production of an extremely rare pituitary malformation called "pharyngosellar pituitary" have been reported separately [14].

Extracranial infrasellar pituitary adenoma – a case report

A 63-year-old male patient complained of increasing visual disturbance over a 9-month period. Ophthalmological examination revealed a bitemporal hemianopsia. Computed tomography indicated a space-occupying lesion in the extradural sella-clivus region (Fig. 8 a). Sella and clivus were destroyed by the infiltrating tumor. The patient was sent to the neurosurgical unit of our university for surgical treatment.

At surgery, a transfacial approach to the tumor was performed. The tumor was located extradurally in the clivus, did not damage the dura, and had no contact to SP.

On intraoperative cryostat examination, a pituitary adenoma was diagnosed. Neuropathological examination of the formalin-fixed specimen revealed an pituitary adenoma without nuclear polymorphism or mitosis (Fig. 8 b), proliferating inside the osseous tissue (Fig. 8 c). Immunohistochemically, tumor cells reacted negatively with all antisera against the anterior pituitary hormones. In a small area of the tumor tissue, a fragment of lobulated, differentiated anterior pituitary tissue was found (Fig. 8 d), which immunoreacted positively to PRL (Fig. 8 e), STH, ACTH, FSH, LH, and TSH. This tissue fragment was, therefore, thought to be a normal pituitary gland tissue fragment found in the extracranial null cell pituitary adenoma.

Discussion

PhP is a physiological constituent in every individual

The German term "Pharyngealhypophyse" was used by Erdheim [8] for the first time. Romeis [29] noted that PhP was found only in one third of the examined cases. However, later revision showed that PhP exists in every individual. The absence of PhP in "normal" cases is, therefore, thought to be due to insufficient technical skill. During our pilot study, technical problems in the search for PhP were completely overcome after a short training on dissection and slicing. The lateral deviation of PhP in location might have been one of the reasons for the difficulty in detection of PhP. However, this deviation was slight, actually insignificant (as stated in Results), and PhP was found within the width of the lateral diameter of SP in all cases but one.

Since the mass of PhP is very small and each immunoreaction requires one corresponding slide, the evaluation of immunoreactivity (++ or +), particularly of PhP,

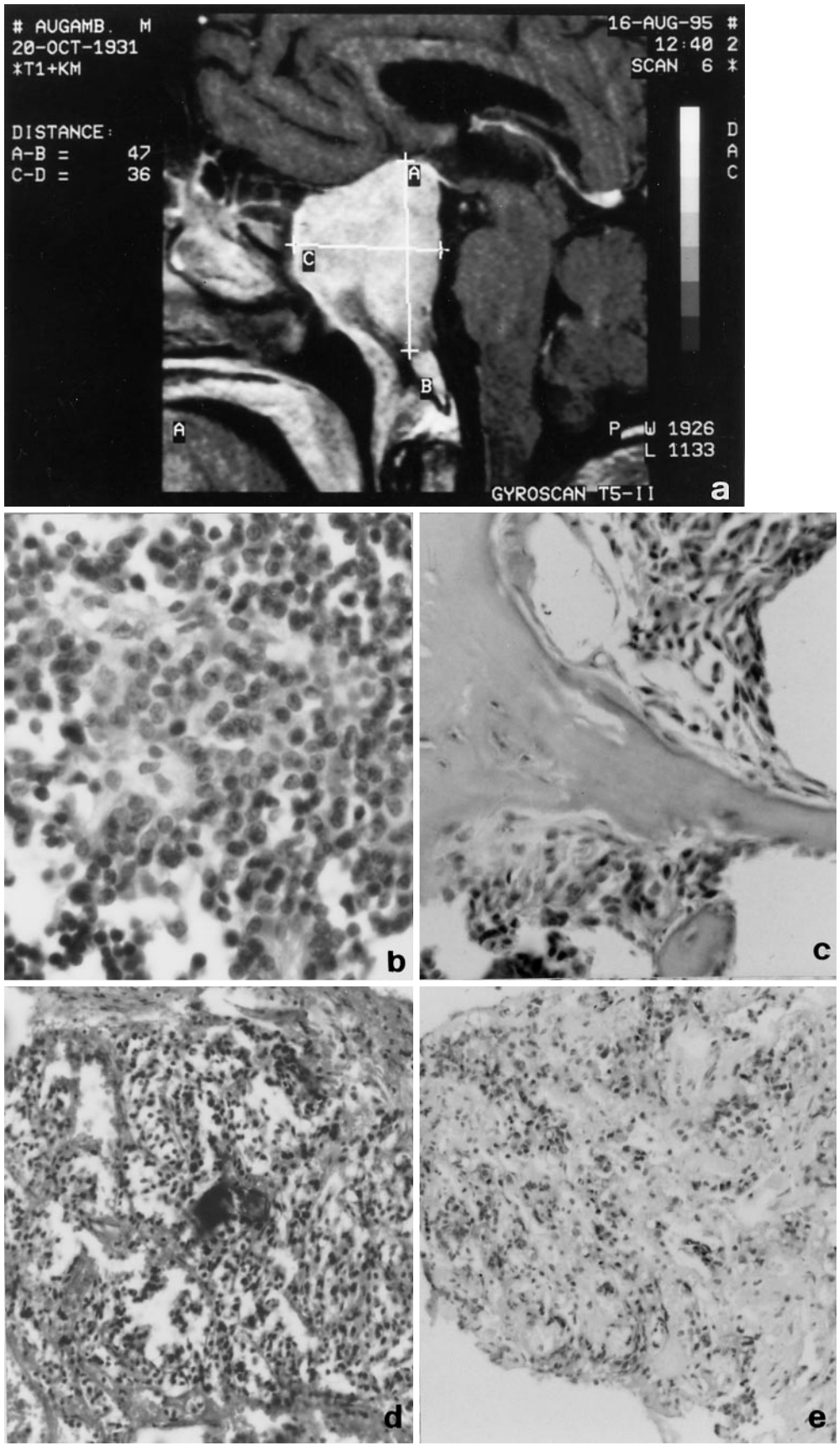

Fig. 8 **a** Computed tomography of a 63-year-old patient showing a clivus tumor. **b** Relatively monomorph pituitary adenoma cells without signs of malignancy; H&E. **c** The tumor cells infiltrate the clivus; H&E. **d** A small fragment of normal lobulated pituitary tissue is found inside the tumor tissue; H&E. **e** These cells were immunostained positively for all pituitary hormones tested; here PRL immunostaining. **b** × 460; **c** × 350; **d**, **e** × 175

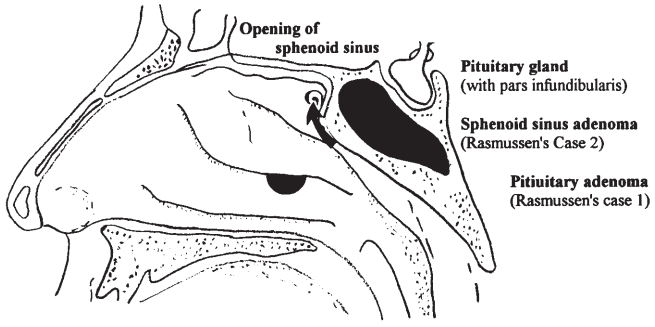

Fig. 9 Possible expansive route of an extracranial pituitary adenoma into the sphenoid sinus supposed to originate from PhP (*curved arrow*), and the location of pituitary adenomas illustrated by Rasmussen and Lindholm [28]. Present authors' illustration based on [28]

could not be used for precise quantitative analysis. For this reason, the negative immunoreaction to all hormonal antibodies in a very small CPhP as well as in PhP (case 9) does not indicate the complete failure of hormone production.

PhP probably does not respond in the same manner to the same stimuli as SP, for example, in pregnancy, in cases of compression necrosis of SP, or inner secretory disturbances [27]. Rasmussen and Lindholm's patients [28], who underwent pituitary adenomectomy (in SP), developed a recurrence of adenomas from an "ectopic" extracranial region. Scacchi et al. [30] found a unique, functioning PhP in a girl in whom SP was lacking. At endoscopy they observed a mucosal cleft of the nasopharynx, compatible with PhP. Thus, PhP can react in altered hormonal states but its reactions may differ from that of SP. The different reaction mechanisms of PhP may be understood by its anatomical characteristics: PhP has neither a portal system nor direct contact to the hypothalamus (no hypothalamic innervation), so that it may be excluded (at least partly) from the hypothalamo-pituito-plus axis. In conclusion, PhP is one of the physiological tissue constituents and not a pathological embryonic remnant, although its function is enigmatic.

Development and differentiation of PhP

During the organogenesis of the pituitary gland, the separation of the primitive pituitary gland into pharyngeal and distal parts takes place at the 8th gestational week. In contrast to some opinions stating that PhP cells degenerate and die, we found that they survive and differentiate. Early studies in adults [26] or in aged people [25] also confirmed the life-long existence of the PhP. Based on his observation in 51 cases, Haberfeld [11] stated that most of the PhP growth occurred in the fetus and during the first few postnatal months, but that there was little to no growth thereafter. This was confirmed by Melchionna and Moore [27] who studied the size of PhP in different postnatal and adult age groups. They additionally found that there was as much variation of size within the decades as between the decades. McGrath [25] also ascertained the volume increase of PhP during the fetal period. Asa et al. [2] examined 140 human fetal pituitary glands (SP) immunohistochemically and found cells immunopositive for ACTH, β-endorphin, and STH at gestational week 8. Immunoreaction for β-TH, FSH, LH and PRL was positive at week 12. Ikeda et al. [16] found the earliest hormone production (ACTH) in SP during the 9th gestational week. Further immunohistochemical reaction to pituitary hormones (STH, TSH, and FSH) was, according to their report, positive at the 13th week of gestation. In our youngest case, 15 weeks of gestation, all hormones were immunohistochemically displayed in SP but not in PhP. Constant immunopositivity of hormones in PhP was observed from the 18th week on (Table 1). This means that the functional development (hormone production) of the PhP cells is 4–8 weeks later than that of SP.

Extracranial "ectopic" pituitary adenomas in relation to location of physiological PhP

If all the cases of "ectopic pituitary adenoma" recorded in the literature are divided into intracranial and extracranial groups, it is obvious that the adenomas of the latter group have a stereotypical location (Tables 4, 5). The number of adenomas located in the sphenoid or cavernous sinus was 22 out of 27 recorded cases including our own (81.5%; Table 4), corresponding to the anterior location of PhP in 18 out of 25 (72.0%). The frequency of adenoma location in the clivus and nasopharynx (6 of 27; 22.2%) corresponded to that of the middle and posterior location of PhP (7 of 25; 28.0%). A tumor (with expansive development) in the nasopharyngeal region can reach the sphenoid sinus through its physiological opening (Fig. 9), although the cavernous sinus and clivus can only be reached by the infiltrative development of the tumor through the epithelium and the osseous tissue. Pituitary adenomas are usually benign and develop non-infiltratively. In particular, the location of adenomas in the nasopharynx [6], middle meatus of the nose (case 2 of [28]; Fig. 9), and similar cases [34] corresponded exactly to that of PhP. Thus, it is reasonable to speculate that extracranial "ectopic" pituitary adenomas are of PhP origin. The variable location of PhP may explain the difference of adenomas in the nasopharyngeal area, sphenoid sinus, and clivus; i.e., the rare clivus location corresponds to rare posterior location of PhP. In the patient reported here, the normal pituitary tissue fragment was found inside the tumor. The origin of the tumor, therefore, might well be extracranial pre-existent pituitary tissue. If a pituitary adenoma arises from pre-existent "physiological" pituitary tissue, the term "ectopic pituitary adenoma" might not be adequate to describe extracranial pituitary adenoma because the original tissue is orthotopic. Since the term "ectopic" extracranial pituitary adenoma is established in the literature, new terminology should be avoided. However, knowledge of the background of the possible origin of the tumor, the physi-

ological PhP, should be retained. Another possibility for the origin of extracranial pituitary adenoma, i.e., a remnant pituitary tissue in the craniopharyngeal canal, may alternatively explain the occurrence of intraosseous (clivus) adenomas. We found remnant pituitary tissue in the pharyngeal canal in a male fetus of 17 weeks of gestational age (case 9). The incidence of this finding was 1/25 (4%) – the final percentage is open since this occurred only once in all examined fetuses (confidence interval was ± 7.7%; i.e., between 0 and 11.7%, but the small sample number must be borne in mind). It may be speculated that the existence of CPhP might have caused the retarded closure of the craniopharyngeal canal. In humans, an open craniopharyngeal canal without any other anomalies is very rare (0.2%), while this was found in 64% of chimpanzees, 35% of gorillas, 14% of orangutans [5]. In our malformation series, an open craniopharyngeal canal was found without CPhP in an anencephalic fetus with dislocation of PhP. It should be emphasized that the cranial base is always malformed in anencephaly, a cephalic dysraphism, so that the craniopharyngeal canal as well as distant dislocation of PhP should not be regarded as exceptional in dysraphism (see next section).

The prevalence of ACTH productivity in ectopic pituitary adenomas has been discussed [23]. This tendency was only found in intracranial ectopic pituitary adenomas and not in the extracranial group, in which the production of different hormones has been observed (Table 5). The fact that PhP consists of cells producing different types of hormones may reflect the variable hormone production of extracranial pituitary adenomas. In a case reported by Kepes and Fritzlen [18], a suprasellar as well as an infrasellar origin of the ACTH-productive adenomas was discussed because of its wide distribution and invasive character. A possible origin of ectopic intracranial (suprasellar) pituitary adenomas has also been discussed [13].

Malformation of PhP

A very rare malformation, a pharyngosellar pituitary, has been reported elsewhere [14]. Kjaer et al. [20] examined the sella turcica (cranial base) of 14 fetuses with trisomy 18 and found a craniopharyngeal canal in 8 cases, 1 of which contained a continuous adenohyophyseal structure from SP to PhP (their Fig. 3c), identical to the pharyngosellar pituitary [14]. In our series of malformations, a fragmented PhP was found in a fetus with trisomy 18. This was one of the rare malformations of PhP. In trisomy 18, therefore, there may not be characteristic malformation of PhP but rather an unspecific malformation. In trisomy 21, we found no anomaly of PhP.

In an anencephalic fetus with open craniopharyngeal canal (anencephaly b in Table 2), an elongated PhP was found partly inside the canal and fibrous tissue connected the SP and PhP, suggesting a transitory or frust form of pharyngosellar pituitary. In every anencephaly case examined, a PhP was found (although dislocated due to cranial base anomaly), while SP was flattened, reduced in volume, or contained proliferating vessels, suggesting an "area pituitovasculosa". An early quantitative study on PhP in fetuses [25] showed a decreased SP volume and an increased PhP volume in anencephalics as compared to normal fetuses. These facts suggest that the pituitary gland may be destroyed secondarily due to dysraphism, as is the case in area cerebrovasculosa, and that PhP may develop reactive (compensatory) hypertrophy. This confirms the opinion that agenesis of the pituitary gland in anencephaly may be a myth. The hormone production of PhP in three out of four anencephalies in our study (17–18 weeks of gestation) did not seem to differ from that of the normal group.

A complete agenesis of SP as well as PhP was ascertained in a case of Pallister-Hall syndrome with a large congenital hypothalamic ganglionic hamartoma. Fifty percent of pathologically examined cases of Pallister-Hall syndrome described agenesis of the pituitary gland. This suggests that the time of occurrence of the ganglionic hamartoma may be almost the same as pituitary ontogenesis. Only the trivial time difference in the occurrence of the ganglionic hamartoma may decide the successful or failed pituitogenesis. (Details will be discussed in a different paper; in preparation.) In conclusion, there was no relationship between the craniofacial anomalies and PhP developmental anomalies except in cases of trisomy 18. Malformation of PhP itself was very rare.

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