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# Review of the embryologic development of the pituitary gland and report of a case of hypophyseal duplication detected by MRI

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**Abstract** We describe the clinical manifestations, associated abnormalities, MRI appearances and pathologic significance of a case of hypophyseal duplication. A 16-year-old girl presented with delayed sexual development and history of midline craniofacial anomalies. MRI revealed paired infundibula extending inferiorly to two small pituitary glands, a midline hypothalamic mass, and a midline cleft in the basisphenoid. Twelve cases of pituitary duplication have previously been described. The suggested pathogenesis is duplication of the prechordal plate and anterior end of the notochord during early embryologic development.

**Key words** Pituitary · Hypothalamus · Embryology · Abnormalities · MRI

## Introduction

We had the opportunity to study by MRI a case of duplication of the pituitary gland and infundibulum. A search of the literature revealed reports of 12 similar cases in man and 2 in experimental animals [1–13]. This unusual case motivated a review of the normal development of the hypothalamic-pituitary axis and address a frequent misconception that "the pituitary gland is derived from two ectodermal primordia that unite to form the composite structure". Neuroanatomical and embryological studies have proved that the hypophysis forms as a "single structure" from the surface and neural ectoderms, which are closely adherent to each other from the earliest stages of organogenesis, before any hypophyseal evagination appears. An embryological speculation of the probable chain of events leading to this disorder and its associated abnormalities is offered.

## Case report

A 16-year-old girl presented with delayed sexual development. She was the product of a normal term pregnancy of a 23-year-old woman. Delivery was vaginal and uncomplicated. The mother used hormone therapy during the first 3 months of pregnancy to induce menstruation. There was no family history of congenital malformation or hereditary disease, and the baby had normal chromosomes. Birth weight was 3240 g, head circumference 35 cm (85th centile), and Apgar scores 9 and 5 at 1 and 5 min, respectively. The baby was admitted to hospital immediately after delivery for respiratory difficulty and feeding problems, and was noted to be dysmorphic with a large central cleft palate and a soft tissue mass protruding from the anterior portion of the cleft. The tongue and mandible were slanted to the right inferiorly. The head was asymmetric, and the neck short.

At 7 weeks, the child underwent excision of the nasopharyngeal tumor. The mass originated at the posterior margin of the vomer, and protruded through the soft palate and posterior 2/3 of the hard palate. It was polypoid and appeared to be covered by mucous membrane. The base of the mass, 2.5 cm wide and 3 cm in length,

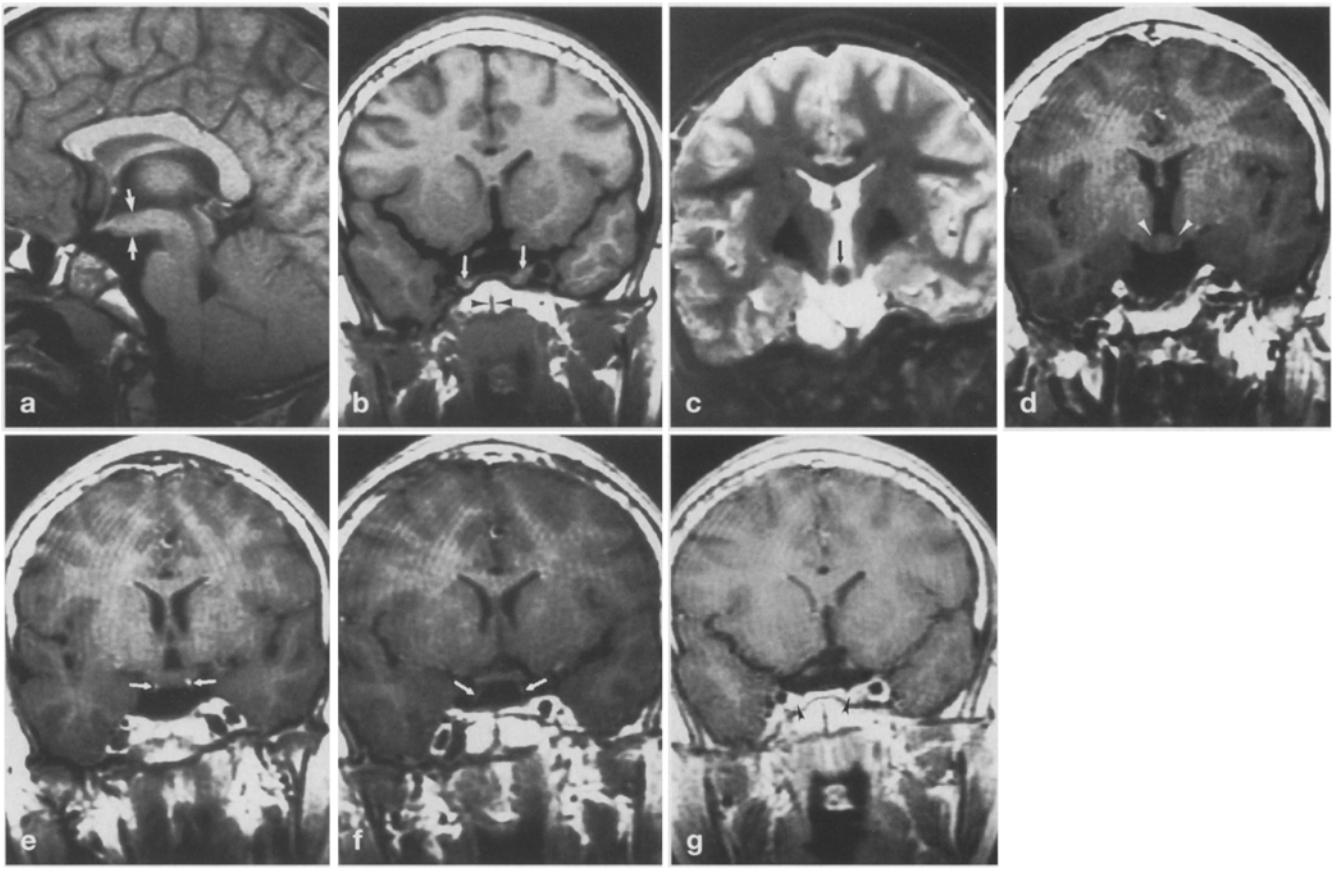



**Fig. 1** 16-year-old girl with duplicated pituitary gland. **a** Sagittal T1-weighted image, 500/12/4 (TR/TE/excitations), shows a prominent hypothalamic mass *(arrows)* extending along the floor of the third ventricle from the brain stem to the posterior aspect of the optic chiasm. **b** Coronal T1-weighted (600/12/2) image shows a broad, shallow sella turcica with two pituitary fossae *(arrows)*, and a midline cleft in the basisphenoid *(arrowheads)*. **c** Coronal T2-weighted (2500/100/1) image reveals the T2 shortening in the midline hypothalamic mass *(arrow)*. **d–g** Coronal contrast T1-weighted images (600/12/4) show two infundibular recesses separated by the nonenchancing midline hypothalamic mass *(white arrowheads)*, leading to two enhancing infundibula *(arrows)*, and two small enhancing pituitary glands *(black arrowheads)*

was attached to the sphenoid, which was irregular, with a spinous bony process projecting through the mass. The mass was a nasopharyngeal teratoma, whose surface consisted of stratified squamous epithelium; the stroma contained hair follicles, prominent sebaceous glands surrounded by adipose tissue, fibrous septa, cartilage, bone, and skeletal muscle.

At 16 months the midline cleft palate, about 1.8 mm in width, was repaired by island flap push-back technique.

The patient was seen at 8 years of age, when she had speech and swallowing problems. Examination showed a 3 cm midline mass extending posteriorly from the tip of the tongue, and midline splitting of the uvula. Neurological examination was normal, but significant velopharyngeal incompetence was demonstrated by a cine speech study. The patient underwent surgery, involving a posterior pharyngeal flap, repair of the bifid uvula, and excision of the tongue lesion, which extended from just anterior to the foramen cecum to within 0.5 cm of the tip of the tongue, and was approximately 1.5 cm in width and 5 cm in length. It consisted of a longitudinal roll of muscle fibers, covered by normal tongue epithelium, and was thought to result from a fusional development abnormality.

At 16 years of age, she was referred because of delayed sexual development. Her motor and developmental milestones were appropriate for age. There was no evidence of secondary sexual characteristics. Laboratory tests suggested either a luteinizing hormone releasing hormone deficiency and/or deficiencies in follicle-stimulating and luteinizing hormones. Karyotype, thyroid function tests, cortisol level, ACTH stimulation test, and antidiuretic hormone level were normal. MRI at 1.5 T revealed widening of the nasal cavity and interoptic nerve distance consistent with hypertelorism. A prominent nonenhancing mass, isointense with gray matter on T1-weighted images, ran along the floor of the third ventricle from the brain stem to the posterior aspect of the chiasm. On T2-weighted images the mass was hypointense similar to areas of normal iron deposition in the brain. On coronal images two infundibular recesses were noted, separated by the midline mass, leading to two infudibula and two small pituitary glands. The sella turcica was broad, shallow, and divided into two fossae by a midline osseous ridge. A midline cleft was present in the basisphenoid (Fig. 1).

The clinical diagnosis was isolated hypogonadotrophic hypogonadism secondary to abnormal development of the hypothalamus, infundibulum and pituitary gland. The patient was prescribed estrogen replacement therapy, and on follow-up examination showed early signs of estrogenization.

## Discussion

Although neuroendocrine dysfunction is frequent with congenital malformations, especially of the midline craniofacial structures (cleft lip and palate, hypertelorism, septo-optic dysplasia, holoprosencephaly, basal encephaloceles, callosal agenesis), only scattered reports concern congenital morphologic abnormalities of the pituitary gland and hypothalamus. The incidence of these abnormalities is probably underestimated, as they are often associated with severe developmental errors incompatible with life, and therefore identified as incidental findings only at autopsy. Congenital abnormalities involving the hypothalamic/pituitary axis include agenesis and hypoplasia of the pituitary gland, pituitary dystopias, persistence of the craniopharyngeal canal, congenital pituitary cysts, congenital teratomas of the pituitary region and pituitary duplication [14].

Duplication of the pituitary gland gives rise to two morphologically normal glands (with anterior and posterior lobes), lying on either side of the midline, in an appropriately compartmentalized sella turcica. In 1880 Ahlfeld [1] described hypophyseal duplication in association with partial duplication of the brain and considered it as the first degree of twinning of the anterior part of the body, due to a "partielle Spaltung" of the hypophyseal anlage. Morton [2] suggested that the primary factor is duplication of cells of the precordal plate and anterior end of the notochordal process, at about the 15–16th gestational day, due to a teratogenic influence, which leads to duplication of the stomatodeal region and hypophyseal anlagen. Bacsich et al. [14], considered hypophyseal duplication a less advanced form of the split-notochord syndrome. Hori [6] reported a case of pituitary duplication associated with malformations confined to the ventral midline and suggested a unique variant of the median cleft face syndrome. Tagliavini and Pilleri [9] described pituitary duplication with duplication of the hypothalamus and mamillary bodies and proposed the descriptive term "diplo-mamillo-hypophysis". They also considered that morphogenesis of the malformation may vary depending on the timing and nature of the teratogenic influence.

Table 1 summarizes the findings in 13 human cases in the literature, including our own. Associated malformations consisted of facial dysmorphism ranging from hypertelorism to complete duplication of the mouth (10/13), abnormal development of the tuberomamillary region with thickening of the hypothalamus and 2 infundibular recesses separated by the hypothalamic mass (9/13), cleft palate (7/13), developmental anomalies of the tongue (7/13), pharyngeal masses attached to the cleft palate and protruding into the oral cavity (6/13), agenesis of the corpus callosum (6/13), spinal abnormalities ranging from duplication of the anterior median fissure to diplomyelia and myelomeningocele (6/13), posterior cranial fossa abnormalities (4/13), absence of the olfactory bulbs and tracts (3/13), absent anterior commissure (3/13), hydrocephalus (3/13) and abnormalities of the circle of Willis (2/13). Anomalies outside the CNS, present in 6 cases, varied from notched epiglottis and low set ears to severe cardiac, genitourinary and gastrointestinal defects.

### Normal embryological development of the pituitary gland (Fig. 2)

It has long been believed that the hypophysis is formed from a craniopharyngeal evagination from the roof of the oropharyngeal membrane growing upward toward the neural tube and a neuroectodermal evagination growing downward from the floor of the diencephalon, which approach each other and fuse, forming respectively the anterior (adenohypophysis) and posterior (neurohypophysis) lobes of the pituitary gland. Gilbert [15] showed in 1934 in laboratory animals and humans that the hypophysis forms as a single structure. It arises from the surface and neural ectoderms, which are closely adherent to each other from the earliest stages of organogenesis, in a small area on the ventral surface of the head, before any hypophyseal evagination appears. This original neuroectodermal adherence is maintained throughout formation of the hypophysis and together with the tissue changes in the adjacent structures and in the entire embryo, is a primary factor in early hypophyseal development.

The primordium of the adenohypophysis can be distinguished, at Carnegie stage 10 (22 days of gestation), although its material may be already present in stages 8 (18 days) and 9 (20 days). It is represented by a small area of ectoderm immediately rostral to the oropharyngeal membrane, in close contact with the overlying neural plate, in the median plane. The 3 major subdivisions of the brain (forebrain, midbrain and hindbrain), are already present from stage 9. In the median plane of the diencephalon two areas can be distinguished: D1, which comprises the chiasmatic plate, and D2, which represents the future neurohypophysis and mamillary region [16].

At stage 12 (26 days of gestation) the oropharyngeal membrane ruptures and the stomodeum merges with the foregut. The telencephalon begins to expand rostrocaudally. An indication of a infundibular recess may be present in the floor of D2, in the area that remains in contact with the adenohypophyseal primordium [17].

At stage 13 (28 days of gestation) the adenohypophyseal pocket (Rathke's pouch) is forming. The term "craniopharyngeal" is imprecise since this invagination probably does not involve any pharyngeal epithelium. This adenohypophyseal pocket wraps around the infundibular area at the base of D2. The basement membrane of its rostral wall is firmly adherent to that of the

**Table 1** Reported cases of pituitary duplication (*C* cervical, *T* thoracic, *L* lumbar, *S* sacral, *N* normal, *ant* anterior, *vent* ventricle, *CNS* central nervous system)

| | Ahlfeld [1] | Morton [2] | Bainborough and Hase [3] | Bacsich et al. [4] | Bale and Reye [5] (two cases) | |
|---|---|---|---|---|---|---|
| | | | | | Case 1 | Case 2 |
| Sex, age[a] outcome | – | M, 3 days, died | F, 26 years, died (Addisonian crisis) | F, 11 days, died (bronchopneumonia) | F, 6 h, died (respiratory arrest) | 24 h, died (respiratory arrest) |
| Family history | – | 1st child | – | – | 5 siblings alive and well | – |
| Pregnancy | – | Uterine bleeding 1st month | – | – | Loss amniotic fluid 6th wk | Hydramnios |
| Gestation | – | 38 weeks | – | Full term | 37 weeks | 38 weeks |
| Pituitaries | 2 glands each with stalk | 2 glands each with stalk; (N histology); pharyngeal pituitaries | 2 glands with "Y" shaped stalk (N histology) | 2 glands each with stalk | 2 small glands each with stalk (N histology) | 2 small glands each within stalk (N histology; probable pharyngeal hypophysis) |
| Sella turcica basisphenoid | – | Broad sella with 2 pituitary fossae; midline gap with vessels in basisphenoid communicating with interior of skull | 2 separate pituitary fossae | Broad sella | Borad sella with 2 pituitary fossae | Broad sella with 2 pituitary fossae |
| Hypothalamus | – | wide, thick hypothalamus; 2 infundibular recesses | – | – | Mamillary bodies 1 cm apart | Wide tuber cinereum |
| Eye anomalies | – | optic nerves widely separated | Hypertelorism | Hypertelorism | Hypertelorism | Hypertelorism |
| Corpus callosum | – | Present | – | – | Absent | Absent |
| Olfactory bulbs/ tracts | present | absent | N | – | Present | Present |
| Mouth nasopharynx | – | Wide; 2 lower lips, 2 frenula, bifid tongue and uvula; 2 mandibles with common medial ramus (bar of tissue from roof to floor of mouth); soft, hairy mass extending from nasal septum; bilateral cleft palate; epignathus | – | 2 months left N: tongue and mandible, cleft palate communicating with the nasal cavity; right: no tongue, hypoplastic mandible | Epignathus projecting from hard palate through mouth | Epinathus projecting from hard palate through mouth; trifid tongue; wide lips and mandible |
| Posterior fossa | – | N | N | – | Cerebellar hypoplasia | N |
| Other cranial and brain anomalies | Partial duplication of brain | No | No | No | Absent ant. commissure, absent septum pellucidum; right choanal atresia, wide cribriform plate | Absent ant. Commissure, absent septum pellucidum; fornix; right choanal atresia, wide cibriform plate; central nasal groove; wide sutures |
| Spine | – | N | N | Partially duplicated C spine | – | – |
| Anomalies outside CNS | – | Notched epiglottis | Addison's disease; tuberculous destruction of renals | No | Low set ears; small thyroid isthmus | Low set ears; absent thyroid isthmus |

[a] At death or MR imaging

| Hori [6] | Bagherian et al. [7] | Roessmann [8] | Tagliavini and Pilleri [9] | Il'ina and Lasiuk [10] | Ryals et al. [11] | Kollias et al. |
|---|---|---|---|---|---|---|
| F, 26 days, died (respiratory distress) | F, 8 days, died (cardiac arrest) | F, 12 days, died (cardiorespiratory arrest) | F, died soon after birth | Died soon after, birth | M, 34 months developmental delay | F, 16 years, alive delayed sexual development |
| 1 sibling alive and well | Parents dysmorphic | 1st child | 1st child | 1st child | Not revealing | 2 siblings alive and well |
| Surgery for hernia early in pregnancy | Vaginal herpes 2–3 months, digoxin for tachycardia | N pregnancy | Meclizine 6–8 weeks | Hormone treatment 1st trimester | Uncomplicated | Hormone treatment 1st trimester |
| – | – | 38 weeks | 35 weeks | 36 weeks | Full term | Full term |
| 2 glands each with stalk (N histology) | 2 small glands | 2 glands each with stalk | 2 glands each with stalk (N histology) | 2 glands each with stalk | 2 glands each with stalk | 2 small glands each with stalk (N morphology) |
| Broad sella with 2 pituitary fossae; midline defect in short clivus with small penetrating artery and stalk of connective tissue | Broad sella with 2 pituitary fossae | Broad sella with 2 pituitary fossae | Broad sella with 2 pituitary fossae; persistent craniopharyngeal canal; 2 median clival foramina with anomalous arteries | – | Broad sella with 2 pituitary fossae | Broad sella with 2 pituitary fossae; cleft in basisphenoid |
| Hyperplastic gray-matter mass between mamillary bodies | Wide hypothalamus | Wide, thick hypothalamus; 2 infundibular recesses | Hyperplastic gray-matter mass in hypothalamus (diplo-mamillo-hypophysis) | – | Hyperplastic gray-matter mass between mamillary bodies | Hyperplastic gray-matter mass in hypothalamus; 2 infundibular recesses |
| Hyperteolorism | Hypertelorism wide optic chiasm | – | Optic nerves widely separated | – | hypertelorism | Hypertelorism |
| Absent | Absent | – | Absent | Absent | Present | Present |
| Widely apart | Present | – | Absent | Absent | N | – |
| Tongue fixed by a persisting frenulum; cleft palate with polypoid tumors inside cleft; retrognathia | Cleft lip and palate; hairy mass extending from cleft, thick frenula, trifid tongue; hairy mass from lips over alveolar ridges; inward deviation mid-mandible | – | Bifid tongue; bifid uvula; palato-gnathocheilo-schisis | – | Mild micrognathia | Midline tongue mass; bifid uvula; cleft lip; wide cleft soft and hard palate with protruding hairy mass |
| N | Shallow post. fossa; hypoplastic cerebellum | Cerebellar hypoplasia | Shallow post. fossa; cerebellar hypoplasie; cystic 4th vent. | – | N | N |
| Abnormal circle of Willis; heterotopias at midbrain-pons-medulla; absent ant. commissure; split at the top of the nose | Absent ant. falx; migrational anomalies; fused thalami,hydrocephalus; two aqueducts | Microcephaly; craniolacunae | Abnormal circle of Willis; hypoplastic pons; carinated medulla; fused thalami; hydrocephalus | Hydrocephalus | – | No |
| Duplicated ant. median fissure of C-T spinal cord | Sagittal clefts C-T vertebral bodies | C-diplomyelia; myelomeningocele | T-L-S rachischsis | Rachischsis C1-T6 | – | N |
| Varus deformity of the right foot; low set ears; "V" shaped hair line | 11 ribs; genitou rinary anomalies; low set ears; "V" shaped hair line | – | Cardiac anomalies; maldeveloped diaphragm | Diaphragmatic hernia; cardiac, urinary anomalies; colorectal atresia; hip dysplasia | "V" shaped hair line | No |

infundibular area throughout development, despite the fact that increasing amounts of mesenchyme accumulate between the ectoderm and the neural tube in more lateral areas [18]. In fact, this overgrowth of mesenchyme around a limited median area of persisting neuroectodermal adhesion, and the rapid growth of the embryonic head in a dorsoventral direction, around the apex of the foregut, are the primary factors in the formation of the adenohypophyseal pocket [15]. Without the influence of the hypothalamic floor and the accumulation of mesoderm on each side of the neuroectodermal adherence, the adenohypophysis does not develop [18].

During stages 14 and 15 (32 and 33 days of gestation) changes in the diencephalon lead to the formation of five longitudinal zones (epithalamus, dorsal thalamus, ventral thalamus, subthalamus, hypothalamus) and appearance of the first diencephalic nuclei (hypothalamic cell cord, habenular, mamillary, subthalamic). The floor of the diencephalon in the median plane corresponding to the infundibular area, has a characteristically low mitotic activity [19].

At stage 16 (approximately 37 days of gestation) evidence of the infundibular recess indicates the outgrowth of the neurohypophysis [20]. Three-dimensional reconstructions of the pituitary gland in late 16th stage show an "open wing" configuration to the left and right of the adenohypophysis, indicating the primordia of the lateral lobes (tuberal processes) which will differentiate into the pars tuberalis [21]. Mesenchyme accumulating between the lateral lobes and hypothalamic floor will later differentiate into blood vessels serving the pituitary gland.

At stage 17 (approximately 41 gestational days) the infundibular recess is a readily evident external feature. The communication of the adenohypophysis with the oral cavity becomes narrower, forming a slender stalk between the adenohypophyseal pouch and the roof of the pharynx. Both lateral lobes of the adenohypophysis are partially wrapped around the infundibulum [21].

During stages 18–20 (7th gestational week) the walls of the neurohypophyseal evagination become folded. This is not an active process, since mitotic activity in this area of the diencephalon is very low, but the result of pressure exerted by the adjacent rapidly growing regions (chiasmatic plate ventrally and rapidly elongating premamillary region dorsally) on an area of inactive tissue which is intimately adherent to the apex of the adenohypophyseal pouch [15]. The region of contact between the diencephalon and the adenohypophyseal pouch moves from the anterior wall to the posterior wall of the latter [21]. Capillaries develop between the adenohypophysis and the caudal wall of the hypothalamus [22]. Development of the cartilage of the primordial sphenoid bone around the adenohypophyseal stalk reduces the connection of the pouch with the oral cavity to an epithelial strand and interrupts the communication with the oral cavity. The adenohypophyseal lobe is confined into a small space formed by the basal cartilage of the skull which eventually will form the sella turcica. Marked mitotic activity in the adenohypophyseal lobe results in thickening of its walls and changes in the shape of its lumen. The portion of the adenohypophyseal epithelium in close approximation with the infundibulum remains thin and represents the primordium of the pars intermedia which, together with the neural lobe, makes the posterior lobe of the pituitary. The remainder of the adenohypophyseal lobe (except the pars intermedia and pars tuberalis) represents the pars distalis of the anterior lobe [23].

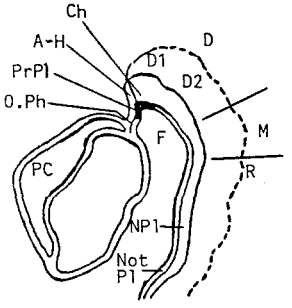
During stages 21–23 (8th embryonic week) the adenohypophysis is completely separated from the oral cavity and only a small remnant of the adenohypophyseal stalk persists in the posterior nasopharynx, throughout life, as the pharyngeal pituitary. The cells that form the anterior portion of the adenohypophysis proliferate rapidly, resulting in thickening of the pars distalis. Laterally the tuberal processes almost totally surround the infundibulum, which increases in size and deepens its folding, and they come to invest the median eminence of the tuber cinereum [23].

During the remainder of the gestational period the infundibulum differentiates into a thin stalk region and a roundish posterior lobe [21]. The pars tuberalis fuses with the median eminence. Blood vessels penetrate the pars tuberalis and pars distalis which become glandular tissue. The residual lumen between the pars distalis and the pars intermedia reduces in size becoming a narrow cleft (Rathke's cleft) between the anterior and posterior lobes. The pars intermedia attenuates and the infundibulum elongates downward and backward forming an angle of 20° relative to the third ventricle. This infundibular angle gradually increases as the gland deepens into the sella turcica and becomes nearly perpendicular at the time of birth [23].

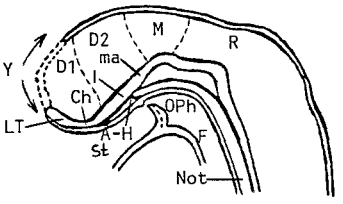
## Pathogenesis of pituitary duplication

The basis of organ duplication resides in the regulative capacity and plasticity of the primordium of the organ. Portions of a primordium, for a specific time during development, are able to produce a whole which may approach or achieve structural normality. If the organ is formed from two embryonic plates which fuse in the midline and this fusion is prevented, the two primordia tend to produce two separate organs. Organs arising from a single primordium can duplicate as a result of a specific insult, at a specific period of time during embryogenesis, which causes division of this primordium [24].

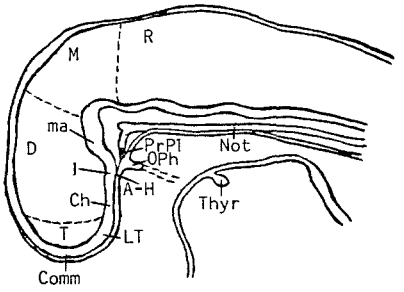
The primordium of the pituitary gland is the area of neuroectodermal adhesion, is present from the earliest stages of organogenesis. Any explanation of its abnormal development must therefore be based on the anal-



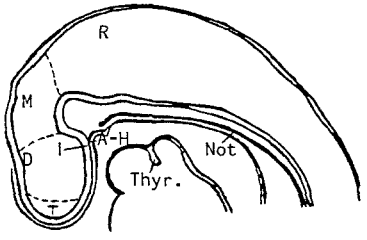

Stage 10 (22 days)



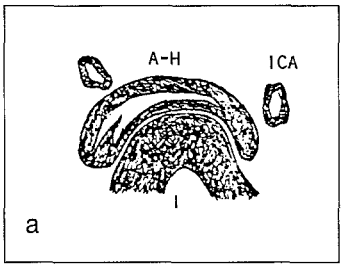

Stage 11 (24 days)

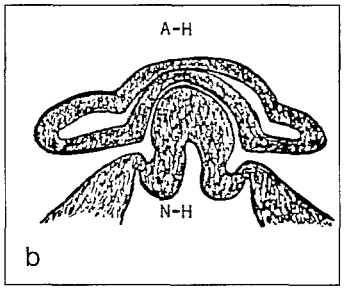


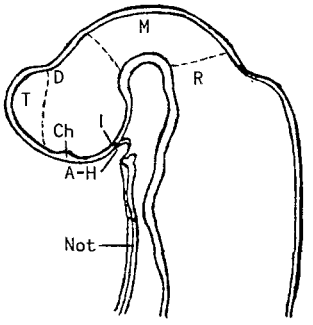

Stage 12 (26 days)



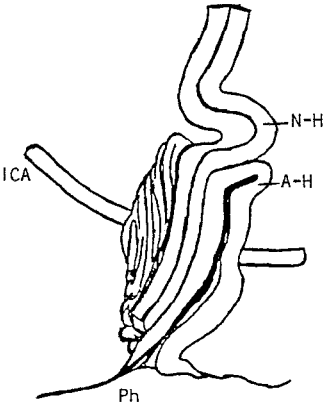

Stage 13 (28 days)



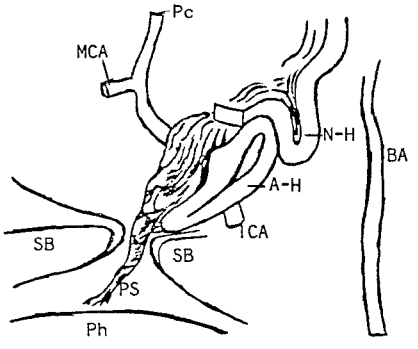



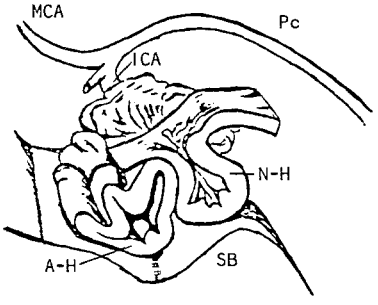

Stages 14–15 (33 days)



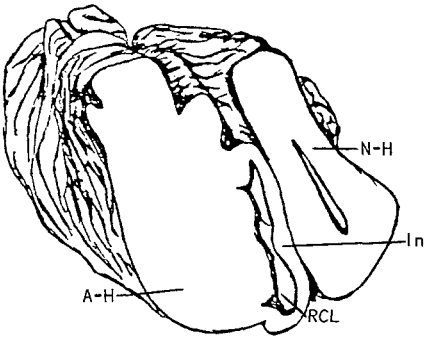

Stages 16–17 (6 weeks)




Stages 18–20 (7 weeks)




Stages 21–23 (8–9 weeks)




13 weeks

ysis of the factors that influence the morphological development of this region. According to epigenic interpretation of development, many organs do not appear because of inherent potencies of development of the embryonic primordia, but rather as a result of changes in the adjacent structures and entire embryo [15]. The normal formation of the hypophysis is the result not of predetermined potencies of development, but of the reaction of the embryonic primordium with the normal configuration of materials and growth processes in the prechordal region of the head [15]. An explanation of pituitary duplication and the complex associated abnormalities should be targetted at structures in close relation with the pituitary primordium during early embryonic period, abnormal development of which would potentially influence the hypophysis. The prechordal plate and the notochord are two such structures (Fig. 2).

Notochordal abnormalities have been implicated as the underlying cause for a variety of visceral, skeletal and neural malformations [25, 26]. The neural groove, from the time of its appearance (stage 8), is related not only to the length of the notochordal process but also to its shape [27]. From stage 10 (first visible indication of the adenohypophysis) to stage 14 the notochordal plate, and later the notochord, comes into intimate contact with the hypophyseal primordium through the prechordal plate. The latter has an inductory role in the prosencephalon and at stage 10 is seen to take part in the formation of the oropharyngeal membrane [17]. Defects in it have been proposed as the pathogenetic mechanism of prosencephalic midline abnormalities such as holoprosencephaly and agenesis of the corpus callosum [28]. Faulty interaction between the notochord, prechordal plate and surface ectoderm may result in various craniofacial abnormalities [23]. The adenohypophyseal pouch derives from material immediately rostral to the oropharyngeal membrane. From these early embryonic relationships it seems logical that duplication of the tip of the rostral end of the notochordal plate or notochord may act as the primary factor which leads to duplication of the pituitary primordium (area of neuroectodermal adherence), with formation of two morphologically normal glands, and initiate the complex associated abnormalities. Morton [2] must be credited with focusing attention on the role of the prechordal plate and the notochordal process. The majority of notochordal clefts involve the rostral end of the notochord. The fact that this end develops first and subsequently extends caudally suggests that splitting occurs at an early (presomite) stage and supports the observation that developmental disturbances to an organ are most likely to occur during the sensitive period of its inception [26].

The underlying initiating factor for notochordal splitting is unknown. Numerous factors, such as maternal exposure to physical and chemical teratogenic factors or ill health during the sensitive period of organogenesis, are influential in the production of a wide variety of congenital abnormalities. Uterine bleeding in the first month of pregnancy [2], loss of amniotic fluid at the sixth gestational week [5], surgery early in pregnancy [6], intrauterine infection [7], and medication at the first trimester [7, 9, 10], may have a causal relationship to pituitary duplication.

## Associated abnormalities

A midline hypothalamic mass along the floor of the third ventricle, separating the two infundibular recesses, was the most common associated abnormality, present in nine cases and not excluded in two other. Histologic examination of these masses revealed nerve cells without evidence of definite formation of hypothalamic nuclei [2, 8], or a mixture of neurons with irregular myelinated nerve fibers [6]. A large hypothalamic mass, which extended from the optic chiasm to the interpeduncular fossa, showed medium size neurons and groups of larger neurons, similar in structure to tuberal nuclei, dispersed in a diffuse gray area of tightly packed nerve cells and glial cells. More posteriorly, four tubercles corresponded histologically to four large mamillary bodies, each with a medial and lateral nucleus [9]. The presence of this hypothalamus mass can also be attributed to splitting of the rostral tip of the notochord. The hypothesis relies on the inductive role of the notochord and mesoderm on ependymal differentiation. Stimulatory and inhibitory effects of the notochord on the interkinetic cell cycle are demonstrated by thinning of the ventral neural tube ependyma adjacent to the notochord, and thickening of the lateral ependyma adjacent to somites. Two areas of ventral thinning were observed in experimentally produced cases of duplication of the notochord [23]. The early development of the diencephalon can be divided into major longitudinal and transverse components. Longitudinally, the gernninal matrix, along the floor of the embryonic third ventricular neuroepithelium, is divided into five parts (preoptic area, anterior hypothalamus, ventral region of the posterior hypothalamus, dorsal re-

**Fig. 2** Diagram showing development of the pituitary gland. *A–H* adenohypophysis; *BA* basilar artery; *Ch* chiasmatic plate; *D* diencephalon; *F* foregut; *ICA* interal carotid artery; *In* intermediate lobe; *LT* embryonic lamina terminalis; *M* mesencephalon; *ma* mamillary area; *MCA* middle cerebral artery; *N–H* neurohypophysis; *Not Pl* notochordal plate; *N Pl* neural plate; *O–Ph* oropharyngeal membrane; *PC* pericardial cavity; *Pc* posterior communicating artery; *Ph* pharynx; *Pr Pl* prechordal plate; *PS* pharyngohypophyseal stalk; *R* rhombencephalon; *R Cl* Rathke's cleft; *SB* sphenoid bone; *St* stomodeum; *T* telencephalon; *Thyr* thyroid primordium; *Y* rostral neuropore. *Insets:* Axial sections through the adenohypophyseal pouch at stages 13 **(a)** and 18–20 **(b)**. Reprinted with permision from Muller and O'Rahilly [16–20, 22] and Ikeda et al. [21].

gion of the posterior hypothalamus, and mamillary bodies). The vertical division is based on the distinction of three successive waves of migratory neurons from the midline neuroepithelium, which from medial to lateral form the midline (or hypophysiotropic), core, and reticular hypothalamus. In this medial-to-lateral migration, neurons derived from specific neuroepithelial zones form specific nuclei. The glial cells of the hypothalamus derive from dispersed, multiplying cells that proliferate intensely after neurogenesis is completed [29]. Given the inductive role of the notochord on ependymal differentiation and cell migration, it seems reasonable to hypothesize that duplication of the notochord is the initiating factor for the formation of two areas of low mitotic activity in the floor of the diencephalon, which correspond to two median eminences. The interposed abnormal mass consists of arrested cells that normally migrate laterally to form the hypothalamic nuclei. Posterior extension of this splitting, due to more extensive splitting of the notochord, would presumably lead to duplication of the floor of the third ventricle and eventually duplication of the aqueduct as reported in one case [7]. The T2 shortening seen in the hypothalamic mass in our case can be explained by the presence of myelinated nerve fibers, or increased deposition of iron. Studies on animals and humans have shown preferential accumulation of nonheme iron in certain hypothalamic structures [30].

The time of induction of the teratogenic influence, and the extent of the notochordal abnormality, may be variable and respond for the wide spectrum of associated facial abnormalities. An early insult, with duplication of the prechordal plate at the time the latter takes part in the formation of the oropharyngeal membrane, would presumably lead to duplication of the floor of the stomodeum, and abnormal development of the mesenchyme that forms the facial structures around the stomodeum. The mandibular processes are the first to develop in the embryonic face, and the maxillary processes are already identifiable at stage 11, on each side of the rostral end of the notochordal plate [24]. Forking of the rostral notochord would result in duplication of the floor of the stomodeal invagination and accumulation of mesoderm between the branches of the notochordal cleft, capable of differentiating into mandibular processes around the duplicated primitive oral cavities. This differentiation depends on the amount of available mesoderm in the medial sides of the notochordal fork. Formation of two medial mandibular processes, which fuse with the corresponding lateral mandibular process on each side, would lead to the formation of two mandibles and two oral lips, as it is seen in cases of Morton [2] and Bacsich et al. [4]. Duplication of the oral opening, as seen in the latter, can be explained only by formation of two medial maxillary processes that merge with duplicated nasomedial processes to form two upper lips and gums. These processes fuse with the lower lips and gums which are formed by the duplicated mandibular processes. Lack of available medial mesoderm to form complete, or almost complete structures will lead to formation of a nasopharyngeal mass, which prevents the normally formed lateral structures fusing in the midline and results in a true midline cleft. The extent of this cleft depends on the extent and the size of the midline abnormal mass. Interposition of the mass between the developing lateral palatine processes will presumably lead to a cleft in the hard and soft palate and splitting of the uvula. Failure of the palatine processes to unite with each other and with the nasal septum leads to abnormal communication between the nasal and oral cavities [24]. Broadening of the nasal cavity due to abnormal development and fusion of the nasomedial and maxillary processes results in hypertelorism. This abnormal mass is the derivative of normal mesenchyme in abnormal location. Such masses, present in half of the cases reviewed here, including our own, were composed of mesodermal derivatives including bone, teeth, cartilage, and ectodermal derivatives including squamous epithelium and hair follicles. The presence of abnormal mesoderm on the medial side of the duplicated oropharyngeal membrane can also result in failure of fusion of the lateral swellings of the mandibular processes (that normally unite to form the body of the tongue), leading to a bifid tongue, or of the lateral processes and the tuberculum impar, leading to a trifid tongue. A midline mass covered by normal tongue epithelium, as in our case, can be explained by differentiation of the excessive medial mesoderm into normal tongue tissue that fuses with the lateral processes and contributes to the formation of the body of the tongue. The presence of a single root in all reported cases indicates that only mesoderm from the first pharyngeal arch, closely related to the normal shape and development of the stomatodeum, is involved [24].

The cartilage of the primordial sphenoid bone is seen during stages 18–20 to develop around the adenohypophyseal lobe, eventually forming the pituitary fossa, and represents the closest relationship seen between the brain and the basal chondrocranium [22, 31]. In the presence of two adenohypophyseal lobes the cartilage surrounds each lobe, resulting in a broad fossa or two complete fossae. The presence of a broad or duplicated sella in all cases reviewed indicates that hypophyseal duplication occurred before stages 18–20 (7th gestational week).

An explanation of the association with agenesis of the corpus callosum can also be proposed. The corpus callosum develops from the commissural plate, a thickening of the upper portion of the "adult" lamina terminalis. The primordium of the lamina terminalis and commissural plate prior to the closure of the rostral neuropore (stage 11), is not midline, but lies lateral to the diencephalic floor [32]. We suspect that faulty in-

teraction between the abnormally divided notochordal plate and the neural plate, before stage 11, when the material for the lamina terminalis and the commissural plate lies just lateral to the diencephalic floor, may result in faulty formation of the lamina terminalis and agenesis of the corpus callosum.

A similar pathogenetic mechanism can be suggested for olfactory aplasia. There is a close topographic relationship between the olfactory area (the primordium of the olfactory bulbs) and the lamina terminalis and commissural plate (the primordium of the corpus callosum). This topographic approximation of these primordia during early development may be the reason for the association of olfactory aplasia with agenesis of the corpus callosum [32]. The same factors that act on the lamina terminalis, inhibiting the normal formation of the commissural plate and eventually the corpus callosum, may have an inhibitory action on the adjacent olfactory area.

Spinal abnormalities were present in half the cases reviewed. A split notochord has been proposed as the etiological factor in the production of a wide spectrum of spinal abnormalities, ranging from slight widening of the vertebrae to complete anterior and posterior spina bifida [33, 34]. Vertebral defects most frequently involve the cervical and cervicodorsal region, suggesting an insult at an early stage of development.

Branches of the internal carotid arteries to the adenohypophyseal primordium develop during stage 13 and represent the earliest arteries to the forebrain [18]. Abnormal development, with duplication of the hypophyseal primordium, may result in abnormalities of the circle of Willis, as reported in two cases [6, 9].

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