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Mammillo-hypophyseal Duplication (Diplo-Mammillo-Hypophysis)

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Summary. A first-time description is given of a unique combination of congenital deformities encountered in a female infant born in the 35th week of gestation and surviving for minutes only. The principal malformations comprised duplicity of the hypophysis cerebri and mammillary bodies, olfactory aplasia, agenesis of corpus callosum, Dandy-Walker syndrome, thoraco-lumbo-sacral rachischisis and hydromyelia, associated with palato-gnatho-cheilo-schisis, defects in the pericardium and cardiac interventricular septum and gross maldevelopment of the diaphragm. Of these cerebral anomalies, we have chosen to concentrate on the condition which we denominate "diplo-mammillo-hypophysis" (mammillo-hypophyseal duplication) as the object of this study. On grounds of embryonal development it is considered to have come about during the first half of the 2nd month of gestation. The likely genesis of the pathologic findings is discussed.

Key words: Mammillo-hypophyseal duplication – Congenital deformities – Cerebral anomalies

Introduction

Duplication of the pituitary is an extremely rare phenomenon, one until recently recorded in cases of partial twinning only (Ahlfeld 1880; Morton 1957; Warkany 1975). According to Ahlfeld (1880) this abnormality is due to a "partielle Spaltung" of the still undifferentiated hypophyseal anlage and presents in cases of "duplicitas anterior" and the more severe "duplicitas posterior". Hori recently described a complete double hypophysis associated with mid-ventral malformation of the skull, brain, and spinal cord, classifiable among the "median cleft face syndrome" (Hori 1983). He concluded that division of the pituitary anlage occurred during a developmental stage corresponding to that of the median cleft and regarded the two conditions to be morphogenetically and nosologically correlated.

An example is presently recorded of duplication of the hypophysis cerebri and mammillary bodies accompanied by other cerebral and extracerebral malformations in a premature neonate whose mother had been given meclizine at a critical phase in its development. The nature and likely genesis of the pathologic findings revealed by necropsy of this infant are described and the possible rôle of meclizine in their production is discussed.

Case Report

Clinical History

There was no family history of congenital malformation or hereditary disease. The mother, a 22-year-old primipara, gave no history of any illness since childhood, when she had undergone tonsillectomy and the repair of an inguinal hernia. Menstruation had been normal since the onset of menarche at the 14th year. In the 5th week of her pregnancy (timed from the presumed date of conception) she developed nausea and vomiting culminating in anorexia. During the ensuing 3 weeks she lost 8 kg in body weight. During the 6th, 7th, and 8th week of gestation she was given meclizine per rectum in daily 50-mg doses and for some days also belladonna alkaloids and phenothiazine derivatives orally at a low dosage. In her 9th week she was hospitalized because of persistent hyperemesis, when general and gynecologic examination plus routine laboratory tests revealed nothing abnormal. Treatment with benzodiazepine and levulose produced prompt remission of symptoms, increase in body weight and general improvement. The subsequent course of her pregnancy was unremarkable up to delivery at the end of the 35th week, when she was found to by hydroamniotic and gave birth to a multiple-malformed female baby which survived for just a few minutes. Three years later, the mother gave birth to a perfectly normal son.

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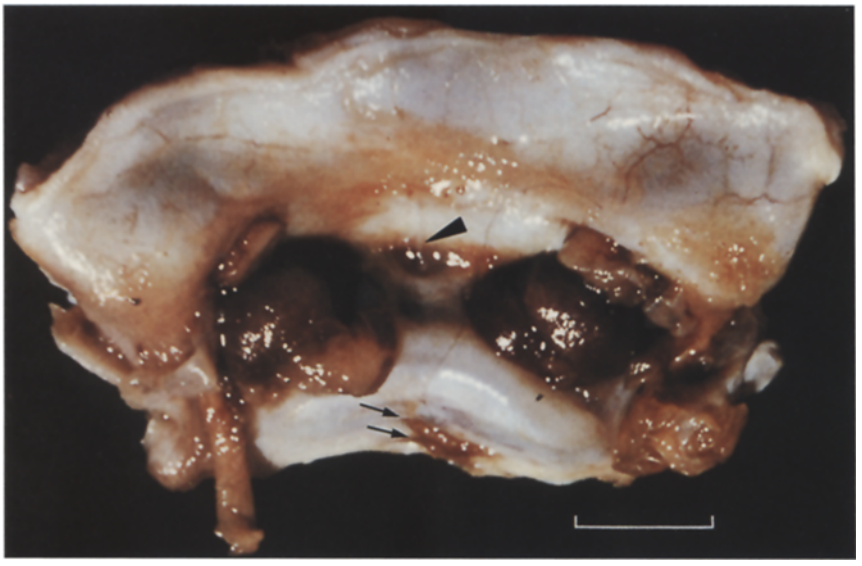

Fig. 1. Sella turcica with two hypophyses. Note the persistence of the craniopharyngeal canal (*arrowhead*) and the presence of two median foramina of the clivus penetrated by two anomalous arteries (*arrows*)

Necropsy Findings in Infant

The body weighed 2,100 g and was 42.5 cm long. Examination disclosed: (1) Palato-gnatho-cheiloschisis with longitudinal division of the uvula and tongue. (2) Sinistral maldevelopment of the diaphragm permitting intrathoracic herniation of the stomach, small bowel, proximal colon, left liver lobe, and spleen with consequent left-sided pulmonary atelectasis and dextral displacement of the mediastinal septum. (3) A defect of 15 mm diameter was present in the pericardium and a defect in the membranous interventricular septum. (4) Rachischisis affected the 7th thoracic to the 1st sacral vertebrae inclusively.

The placenta manifested a purulent chorioamnionitis.

Neuropathologic Findings

The Cranial Basis

The sella turcica was enlarged in the form of two symmetrical lateral recesses located posteromedially to the optic canals and separated by a rostral protrusion of the dorsum sellae (Fig. 1). Anterior to this protrusion a small, vascularized foramen represented the craniopharyngeal canal. The sella turcica recesses contained a pair of pituitary bodies, each some 6 mm in diameter and comprising a normally structured neuro- and adeno-hypophysis (Fig. 5a). On the clivus two median foramina transmitted a pair of anomalous arteries (1 mm in diameter) from the circle of Willis to the nasal cavity (Figs. 1, 3a). The posterior cranial fossa was distinctly shallow.

The Brain (1766/67)

Gross Anatomy. This organ weighed 300 g. Its leptomeninges were generally thin and transparent, save around the brain stem and cerebellum, where they were thick and highly vascularized. The circle of Willis was unusual in giving off two branches from the basilar artery which took a tortuous course to the clivus (Fig. 3a).

The cerebral hemispheres were normal in bulk and fairly symmetrical (Fig. 2a) with a tendency to polygyria. The dextral frontal convolutions ran radially from the longitudinal fissure to the lateral (Sylvian) sulcus which extended unduly toward the occipital pole (Fig. 2b). Below the frontal lobes there was no trace of olfactory bulbs, tracts, or trigona (Fig. 2c). The optic chiasm, appreciably widened transversely, formed the anterior limit of an extensive grayish, trapezoid area which extended posteriorly to the interpeduncular fossa, altering the configuration of the tuberomammillary region (Fig. 2c). This area was subdivided by a deep mesial, and a fainter transverse sulcus into two anterior and two larger posterior quadrants. From each of the anterior quadrants an infundibulum emerged, directed toward the ipsilateral hypophysis. The posterior quadrants, smooth of surface, have longitudinally divided by a superficial sulcus, receiving a fine artery from the abnormal branches of the basilar; they formed, therefore, four large tubercles with free caudal margins presumably representing the mammillary bodies (Fig. 3a, b).

The pons was hypoplastic and the medulla oblongata deformedly carinate. The cerebellum manifested agenesis of the vermis and hypoplasia of the

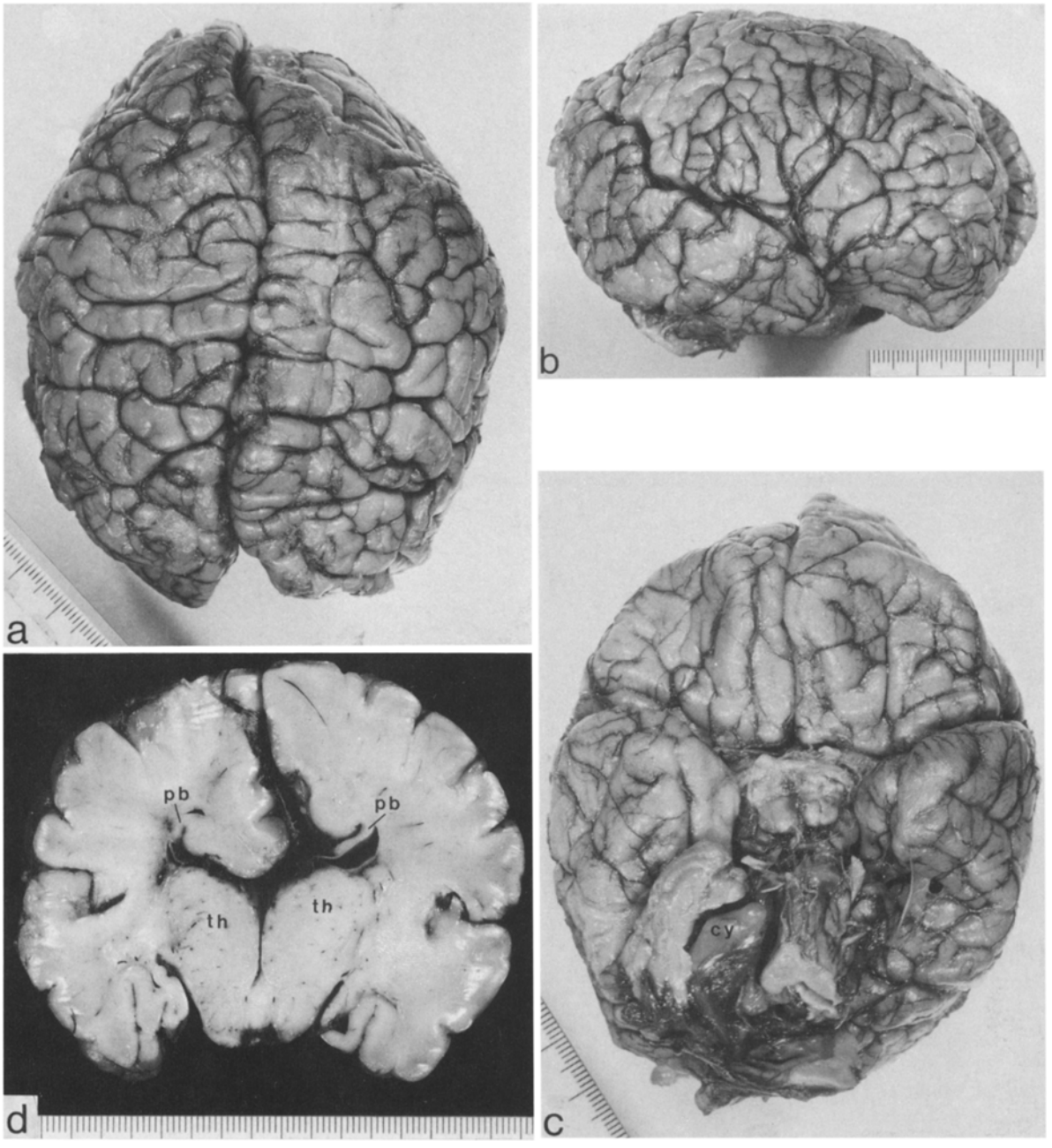

Fig. 2. a, b Dorsal and right lateral view of the brain. Note the tendency to polygyria and the anomalous convolutional pattern of the right hemisphere. **c** Base of the brain. Olfactory aplasia, maldevelopment of the tuberomammillary region and cerebellar hypoplasia with cystic formation (*cy*) at the base of the right hemisphere. **d** Coronal section through the thalamus (*th*). Note the agenesia of the corpus callosum, with presence of two prominent Probst bundles (*pb*)

hemispheres, the left of which was represented by some few folia only (Fig. 2c). The fourth ventricle was the seat of cystic enlargement, its tectum being formed by a grayish opaque membrane underlying a thick vascular web, and continued over the dorsomedial aspect of the cerebellar hemispheres. The base of the right cerebellar hemisphere exhibited a comparable cystic formation, in the shape of an extensive, smooth-walled cavity communicating with the fourth ventricle (Fig. 2c).

On coronal sections of the brain, a corpus callosum was wanting. Bilaterally, a substantial Probst bundle was identifiable, delimiting the lateral ventricles dorsally (Fig. 2d). The two moieties of the fornix body were separated and displaced laterally in close connection with the Probst bundles. The cingulate gyri, par-

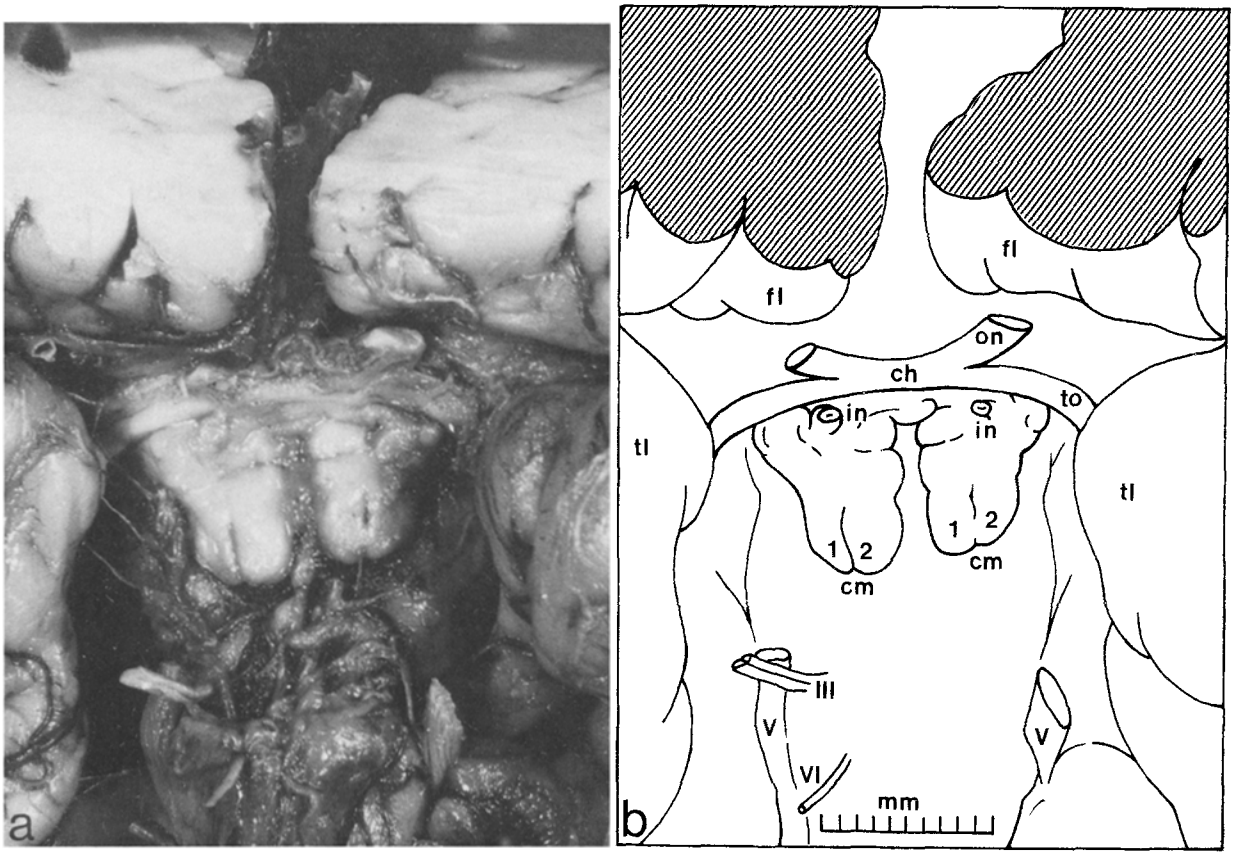

Fig. 3a, b. Detail of the tuberomammillary region (**a**) with diagram (**b**) showing the duplication of the infundibula (*in*) and the mammillary bodies (*cm*). *ch* chiasma opticum; *cm* corpora mammillaria; *fl* frontal lobe; *in* infundibulum; *on* optic nerve; *tl* temporal lobe; *to* tractus opticus; *III, V,* and *VI* third, fifth, and sixth cranial nerves

ticularly the left-sided, were rotated mediolaterally. The lateral ventricles were of bat-wing configuration; centrally, the ventricle roof was formed medially by a thin lamina continuous laterally with the fornix and the Probst bundles. The ventricular occipital horns were enlarged. The thalami, though normal in size and structure, were mutually fused. The basal ganglia, the amygdaloid nuclei, and the Ammon's horns appeared normal.

Histological Findings. Blocks of the whole brain were celloidin-embedded and serially sectioned at a thickness of 20 μm. At 600-μm intervals sections were stained by the Nissl, Heidenhain-Woelcke, and hematoxylin-eosin (HE) techniques.

Examination of the sections revealed the persistence of a fetal vascularization pattern within the leptomeninges of the brain stem and cerebellum.

Both neocortex and archicortex showed an architecture normal for their age. No subcortical heterotopic masses of gray matter were observable, and no cortical field exhibited microgyri. The undersurfaces of the cerebral frontal lobes showed obvious inflammatory changes in the shape of slight, diffuse, subpial, subependymal, and perivascular infiltration by lymphogranulocytes.

The development of the thalami, the basal ganglia, the amygdaloid nuclei, and the nuclear formations of the midbrain, pons, and medulla were normal for their age, save for a pronounced hypoplasia of the inferior olivary nuclei. Myelination and involution of periventricular matrix-tissue likewise agreed with age in their degree of development.

The upper angle of the lateral ventricles extended upward, and fusion of its walls produced cavities lined by ependymal canaliculi and apparently isolated from the ventricles. The septum pellucidum comprised two thin laminae displaced laterally between the fornix and the Probst bundles. An anterior commissure was developed but very imperfectly. The area between the optic chiasm and the interpenduncular fossa consisted largely of an overdeveloped mass of small tightly packed nerve cells interspersed by glial cells.

Within this diffuse gray area there were identifiable scattered medium-sized neurons (Fig. 5b) and groups of larger nerve cells corresponding in structure to the tuberal nuclei. The hypophyseal stalks issuing from the anterior pair of quadrants appeared to be normal

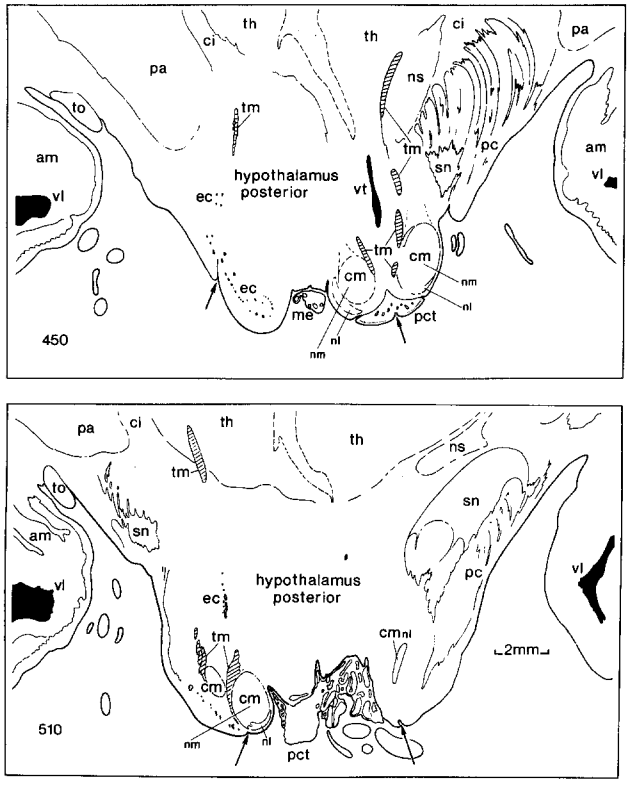

Fig. 4. Diagram of serial frontal sections through the mammillary bodies. Numbers refer to individual slices of a series. *am* amygdala; *ci* capsula interna; *cm* corpora mammillaria, *nl* nucleus lateralis, *nm* nucleus medialis; *ec* ependymal channels; *me* meninx; *ns* nucleus subthalamicus; *pa* pallidus; *pc* pedunculus cerebri; *pct* pars caudalis tuberis; *sn* substantia nigra; *th* thalamus; *tm* tractus mammillothalamicus; *to* tractus opticus; *vl* ventriculus lateralis; *vt* ventriculus tertius; *broken line* adhaesio interthalamica

in structure; the four posterior tubercles proved to be four large mammillary bodies, each with a medial and a lateral nucleus, immersed in luxuriant gray tuberal matter and surrounded ventrolaterally with multiple small ependymal channels (Figs. 4, 5c).

Canonic hypothalamic formations proved identifiable and not appreciably different from those of a control specimen of corresponding age.

The cerebellar cortex, though macroscopically hypoplastic, was histologically normal; the right dentate nucleus was well developed, the left appreciably reduced in size; the cerebellar peduncles (particularly the left-sided) were hypoplastic. The wall of the cerebellar cystic cavity presented an internal layer of ependymal cells and an external leptomeningeal stratum.

The Spinal Cord

The central canal of the 13-cm-long spinal cord was remarkably dilated, with an incomplete ependymal lining replaced, where absent, by thickened, subependymal glial tissue. Regressive changes were present in the anterior and posterior horn cells.

Discussion

The term suggested as descriptive of the relevant cerebral anomaly herein reported for the first time is "diplo-mammillo-hypophysis". The pathologic significance of the pituitary duplication is unquestionable, that of the mammillary duplication more obscure. An accessory mammillary tubercle alongside the main structure is constant in some carnivores and rodents and occurs in some 10% of humans (Staurenghi 1893). Moreover, it is well known that the tuber cinereum is more developed in the lower mammals than in man. The duplication of the mammillary bodies and the tuberal changes might therefore be considered an atavism, the result of pathogenic hyperdysplasia.

Present neuropathologic findings differ from those in previously reported cases, wherein a double hypophysis formed part of a more or less complex partial twinning (Ahlfeld 1880; Morton 1957; Warkany 1975) or was associated exclusively with manifestations of the median cleft face syndrome (Hori 1983). In fact, they combine duplicity of the pituitary and corpora mammillaria with the absence or the maldevelopment of both structures of the ventral an dorsal midline and bilateral formations, such as the olfactory bulbs, tracts and tigona, and the cerebellar hemispheres. This suggests that duplicity of the hypophysis may occur at different embryonal phases and that morphogenesis of the malformation may vary from case to case depending on the stage of development attained by that organ when the teratogenic factors become operative and dependent upon the characteristics of these factors.

In the present instance, the presence of a single craniopharyngeal canal indicates the onset of hypophyseal duplicity subsequent to the development (at the end of the 3rd week of gestation) of Rathke's pouch and its extension toward the brain floor. On the other hand, the modalities of development and the "teratologic termination periods" of the other cerebral and extracerebral structures involved both suggest that the malformation had established itself by the first half of the 2nd month of gestation (Schwalbe 1906; Chiarugi 1944; Warkany 1975; Friede 1975).

In this connection it may be recalled that during the 6th week of gestation the medial nasal processes unite to form the central portion of the upper lip, the septation of the cardiac ventricles is usually completed, the evagination of the olfactory bulbs from

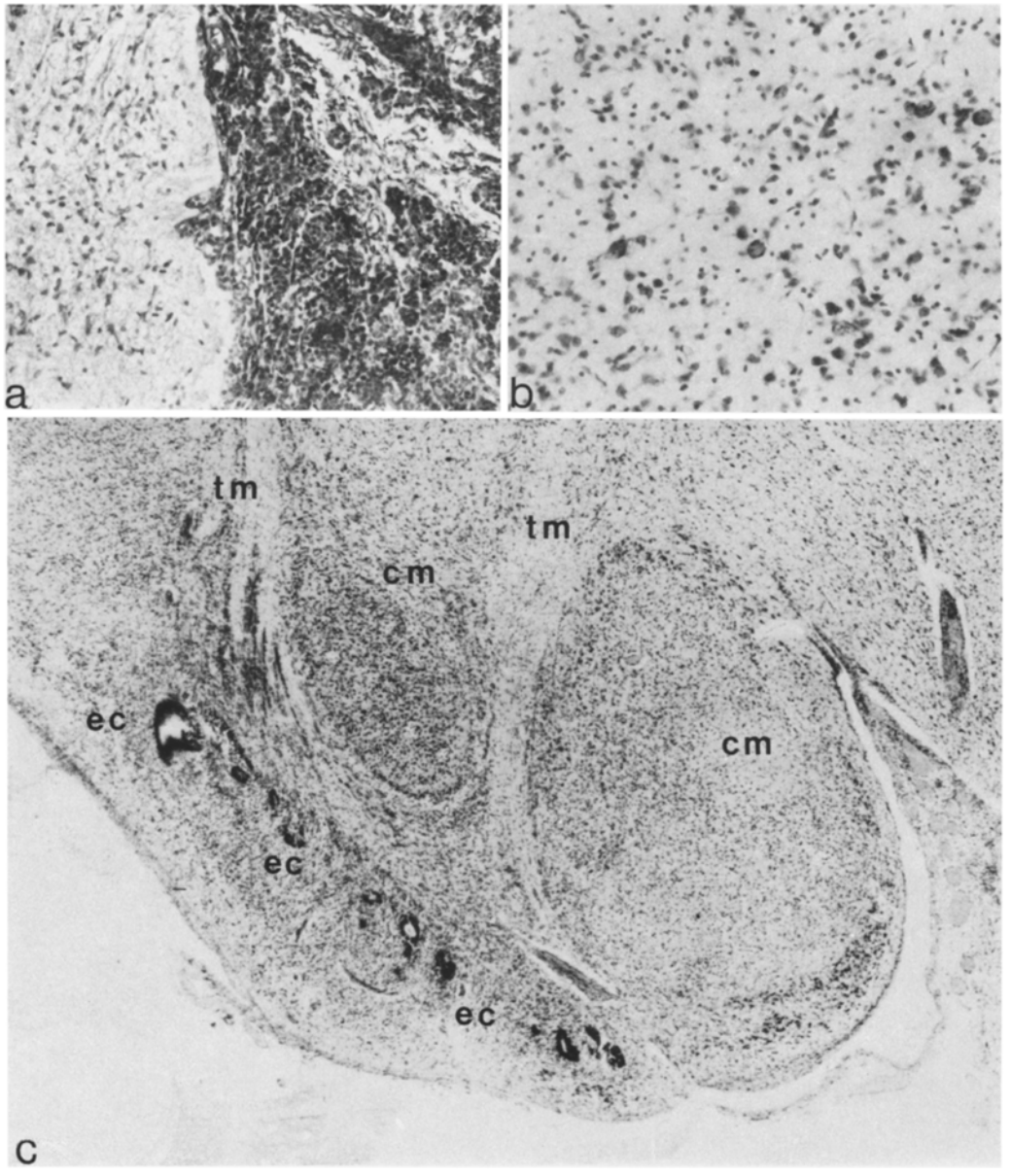

Fig. 5. a Histological structure of the right hypophysis. Mallory-Azan, ×300. **b** Glioneuronal hyperdysplasia of the tuberal region. Nissl, ×300. **c** Histological structure of the left mammillary bodies. Nissl, ×30

the cerebral hemispheres begins, and the commissural plate of the lamina terminalis (the developmental bed of the corpus callosum) is well-formed by the end thereof. During the 7th week, the diaphragmatic components unite, and the definitive palate is formed at its end. During the 2nd month, the rhombencephalic segments of the alar laminae merge to form the single cerebellar lamina from whose mesial portion the vermis develops.

As noted, the mother of the subject was given meclizine from the beginning of the 6th to the end of the 8th week of gestation – an antihistamine drug commonly employed to control the nausea and vomiting of pregnancy. In 1962, suspicion was first expressed that meclizine was capable of producing developmental abnormalities in the human fetus (Watson 1962), a suspicion which evoked conflicting opinions from others (for review see Sadusk and Palmisano 1965) and was strengthened by experimental demonstration of this drug's teratogenic properties in the rat (King 1963). In animal fetuses high dosage of this drug does produce 100% incidence of abnormalities of the tongue, palate, mouth, mandible, vertebrae, and limbs (King 1963). However, successive studies of

large numbers of pregnant women have not revealed any significantly greater frequency of congenital anomalies in the offspring of women treated with meclizine than in the offspring of women not so treated (Yerushalmy and Milkovich 1965; Lenz 1971), so that the drug is currently regarded as safe if administered in small doses (Warkany 1975).

Present observations have revealed no evidence of the action of alternative factors in the production of congenital anomalies in a particular infant, though chromosomal defect could not be tested for. For this reason, we think that it may be useful to point out the close time-correlation between the administration of meclizine to the mother in this case and the embryonal age at which organ malformations occurred presumably.

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References

Ahlfeld F (1880) Die Mißbildungen des Menschen. Grunow, Leipzig

Chiarugi G (1944) Trattato di embriologia. Società Editrice Libraria, Milano

Friede RL (1975) Developmental neuropathology. Springer, Wien New York

Hori A (1983) A brain with two hypophyses in median cleft face syndrome. Acta Neuropathol (Berl) 59:150–154

King CTG (1963) Teratogenic effects of meclizine hydrochloride on the rat. Science 141:353–355

Lenz W (1971) How can the teratogenic action of a factor be established in man? South Med J [Suppl 1] 64:41–47

Morton WRW (1957) Duplication of the pituitary and stomatodeal structures in a 38-week male infant. Arch Dis Child 32:135–141

Sadusk JF, Palmisano PA (1965) Teratogenic effect of meclizine, cyclizine, and chlorcyclizine. JAMA 194:139–141

Schwalbe E (1906) Die Morphologie der Mißbildungen des Menschen und der Tiere. Fischer, Jena

Staurenghi C (1893) Corpi mammillari laterali nel cervello umano. Atti Assoc Med Lombarda 2:115–122

Warkany J (1975) Congenital malformations. Year Book Medical Publishers, Chicago

Watson GI (1962) Meclozine ("Ancoloxin") and foetal abnormalities. Br Med J 2:1446

Yerushalmy J, Milkovich L (1965) The evaluation of the teratogenic effect of meclizine in man. Am J Obstet Gynecol 93:553–562

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