서울醫大學術誌 제20권 제 2 호
The Seoul Journal of Medicine
Vol.20, No. 2 June, 1979

Holotelencephaly (An autopsy case report)

Je G. Chi, M.D., Byoung Tae Kim, M.D.
Department of Pathology, College of Medicine, Seoul National University
Jin Yong Lee, M.D., Ho Suk Suh. M.D.,
Department of Obstetrics & Gynecology

Holotelencephaly is a malformation of the brain that is characterized by failure of division of cerebral hemisphere in association with midline facial defect.

The term holotelencephaly was first defined and classified under the name of "arrhinencephaly", implying agenesis of the rhinencephalon, by Kundrat in 1882. However, the term, arrhinencephaly has been criticized by Yakovlev (1959) because the praepiriform and hippocampal formations of the rhinic lobe of the telencephalon are always present. Based on serial sections of 10 brains of this type of malformation, Yakovlev(1959) claimed that the common denominator of these malformations is the failure of evagination of the secondary telencephalic vesicles and of cleavage of the prosencephalon. He subsequently proposed the term holotelencephaly instead of arrhinencephaly, and this term has been accepted and is in wide use.

The present report is a case of alobar holotencephaly found in a still-born baby.

REPORT OF A CASE

A female still-born baby was deivered in breech at the Seoul National University Hospital on Aril 2 1979, to a twenty-eight year old multiparous female after 41 weeks gestational period. There was no history of febrile illness or exposure to drugs during this pregnancy except for the antiemetics which she took for hyperemesis gravidarum at 4 months of gestation. She had a history of delivering a still-born baby at 8 months gestational age in 1977. Fetal heart tone was audible until the day of delivery. The mother presented a puffy face and pitting edema. VDRL was non-reactive. At the time of delivery the amniotic fluid was meconium-stained.

Autopsy was performed 8 hours after delivery. The body weighed 3520 gm; crown to heel length, 59 cm; the head circumference, 42.5cm and the chest circumference was 31.5 cm. Examination of the body revealed a large head and a peculiar face. The nose was rather small and stubby without alae nasi. Only one nostril was found in the midline and there was no nasal septum. The distance between two eyes was short. The ears were lower than usual site and tragi were obscured (Fig. 1). Neither median cleft lip nor cleft palate was noted. Cranial sutures were widely separated. Opening the thoracic cavity, the heart was normal in size and location. Aorta, pulmonary arteries, and their major branches revealed no abnormality. Lungs were not aerated. Hemorrhage was noted in the right lung. Both adrenals were small to weigh 0.2 gm in the right and 0.3 gm in the left. Opening the calvarium, the cranial cavity was largely filled with cerebrospinal fluid tinged with blood, which was estimated to be 1000 cc. The entire brain weighed 200 gm. The cerebrum was rounded and unpaired with no interhemispheric fissure. The gyri were flattened and sulci obliterated over the anterior half of the cerebrum. The

posterior half of the cerebrum consisted only of a thin-walled membrane without any discernible cerebral tissue (Fig. 3).

The Sylvian fissure was rudimentary and no insula could be identified. The temporal lobes were represented by short, truncated inferior extensions of the cerebrum. Relatively small optic nerves and chiasm were present. All of the cranial nerves were identified at the roots although very thin and slender.

The olfactory bulbs and tracts were completely missing along with olfactory sulcus. As seen in Fig. 2, all gyri were fairly large (macrogyric) and oriented vertically. Two internal carotid arteries were identified. Without forming typical Willis circle, they branch into many vertically going twigs representing two anterior cerebral arteries and probably bifurcated middle cerebral arteries. Vertebral-basilar artery system was normally formed. However, the posterior cerebral artery branches were not recognized except for those of perforating branches heading for the thalamic mass. Fine twigs were found to supply the root membrane.

The posterior view of the brain consisted of undivided strial eminence with subependymal veins converging upon it. Caudal to the striatum, the thalamic eminence and the meatus of the cerebral aqueduct were recognized. The large midline cavity was bordered by a broad transverse convolution in the form of a horseshoe with the two ends abutting laterally upon the strial eminence interposed between them. The roofing membrane was attached slightly above (lateral) to the inner lip of this transverse convolution along a ridge-like thickening. At the area of pituitary stalk an amorphous mass of meningovascular and medullary tissue was seen. No definite pituitary stalk was identified, and the pituitary fossa was obscured. The brainstem was of unusual shape, showing absence of pes pedunculi of midbrain and abnormal pyramids and inferior olives in the medulla. The pons was relatively small.

Microscopic study of the membrane covering the dorsal cyst showed a layer of modified flattened and stratified cells of an ependymal stock and of a layer of glia covered by the meningeal tissue. The section from anterior vertical gyri was represented by a typical six-layered isocortex that was comparable to that of about seven months of gestation.

Sections from other areas of macrogyric brain show irregular lamination of cortical layers, particularly layer II and III. Neuroglial tissue was often found beyond the limit of pia mater in the cerebral cortex. This phenomenon was particularly prominent in the region of brainstem. Cerebral aqueduct and posterior part of the third ventricle show ependymal stripping and glial shrubs protruding into the cavity. Focal calcification around small blood vessels was also seen in the cortical layers.

Sections from the amorphous mass at the region of pituitary stalk revealed irregular proliferation of heuroglial cells predominantly astrocytes and many capillaries. No nerve cells were seen in this area.

Sections of adrenal show depletion of fetal zone accounting for the thinness of the adrenal. However, the medullary tissue was prominent.

DISCUSSION

Absence of the olfactory bulbs and tracts is the most consistent anomaly in holotelencephaly. However, anolfactoria is by no means a critical element of this malformation. Either unilateral or bilateral anolfactoria is observed more often as solitary anomaly without any demonstrable abnormality of telencephalic development.

In all holotelencephalic brains a consistent antero-posterior gradient in the failure of

cleavage of the secondary cerebral vesicles is present. Anteriorly in the holosphere the failure of cleavage is total in all cases, however posteriorly, there is a great difference in extent of malformation in regards to postero-lateral outpocketing of single ventricular cavity, bilateral representation of hippocampi and amygdalae, bilateral representation of isocortex or distinctness of interhemispheric fissure and interlobar fissures. This led people (DeMyer et Zeman, 1963) to classify this anomaly into three types; alobar, semilobar and lobar holotelencephaly.

In lobar holotelencephaly the brain has well-formed lobes and may be of normal size. A distinct interhemispheric fissure is present. And olfactory bulbs and tracts may or may not be present. Many patients will not have obvious facial malformations, but may have hypotelorism. The patients will tend to survive infancy and childhood. Although most will be amented, some will have sufficient intelligence to live fully in society.

A spectrum of facial anomalies associated with alobar holotelencephaly includes, in order of decreasing severity, cyclopia, cebocephaly, median cleft lip without philtrum, and bilateral cleft lip. Facial defects associated with semilobar and lobar holotelencephaly are poorly documented. This case shows hypotelorism, low-set ears and a small nose with a median single nostril. Our nasal cavity was associated with agenesis of nasal septum and was of direct continuation to the pharynx. However, palatal structure was normal.

Extracephalic anomalies associated with holotelencephaly includes; ventricular septal defect, polydactaly, syndactyly, absence of the gall bladder and of bile duct, transposition of great vessels, gonadal agenesis (Toews & Janes, 1968), congenital absence of the pituitary (Edmonds, 1950), diaphragmatic hernia, bicornate uterus, megacolon and cystic ovary.

The adrenal hypoplasia seen in this case could best be explained by the absence of pituitary gland. Adrenal hypoplasia has been repeatedly seen in anencephaly where pituitary anterior lobe is often missing.

The pathology of this entity is best described by Yakovlev (1959). He presented 10 cases representing different parts of the spectrum and then described the morphology of the brain in detail, common denominators being prosoporhinal malformations, failure of evagination of secondary telencephalic vesicles, failure of cleavage of prosencephalon, hippocampal formations and prespyriform area of rhinic lobe, and absence of supralimbic lobe crowning the hemispheres above the limbic lobes of Broca and the Island of Reil.

The cause of holotelencephaly in man is unknown. It has occured in association with maternal disorders, such as diabetes mellitus (Dekaban, 1959), syphilis (Yakovlev, 1959), toxoplasmosis, and cytomegalic inclusion disease. It has been noted with the following chromosomal types; normal (DeMyer & Zeman, 1963), deletion of short arm of 18 (Uchida, et al., 1965) and trisomy 13-15 (Kakulas & Rosman, 1955; Miller, et al., 1963). It seems that there are at least 2 types of holotelencephaly, one type having 13-15 trisomy associated with multiple extracephalic anomalies and the other type being a 46-chromosome karyotype. Unfortunately our case was not studied for the chromosome anomaly. However, in view of absence of significant extracephalic malformations, it appears less likely that our case had chromosome anomaly. In lower mammals, etiologic factors are somewhat understood. Alobar holotelencephaly is hereditary in strain 13 guinea pigs(Wrights, 1965). Extrinsic pathogen, Veratrum californicum,

is responsible for alobar holotelencephaly in sheep of Idaho grazing areas (Binnes, et al., 1962).

SUMMARY

An autopsy case of a typical alobar holotelencephaly in a still-born female baby to a 28 year old woman was reported. The facial anomalies of this case consisted of single midline nostril and hypotelorism. Low-set ears with abnormal were tragi also seen. The brain weighed 200 gm, and was represented by complete failure of cleavage with no anterc-posterior gradient(a lobar holotelencephaly).

》國文抄錄《

無葉性 前腦發達異常症
——1剖檢症例報告——

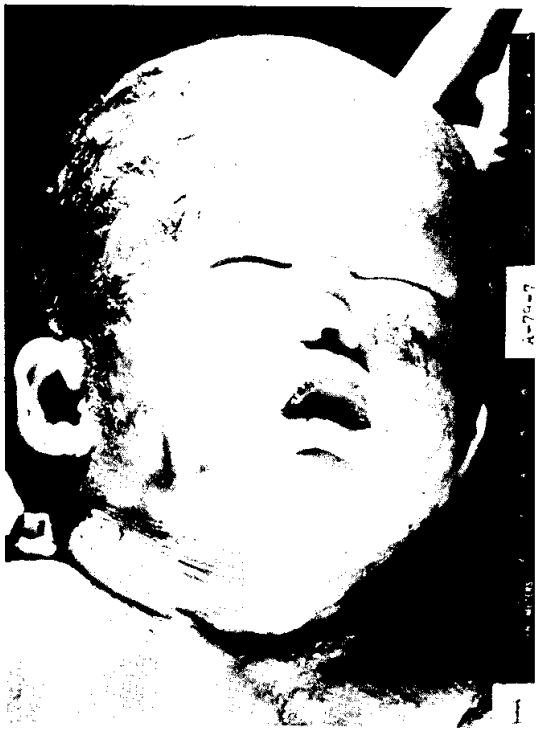
서울大學校 醫科大學 病理學敎室
池 堤 根·金 柄 泰
産婦人科學敎室
李 珍 鎬·徐 浩 錫

著者들은 姙娠 41週만에 死産된 女兒를 剖檢한 結果 無葉性 前腦發達異常症과 이에 隨伴된 顔面畸形을 觀察하고 이를 報告하였다.

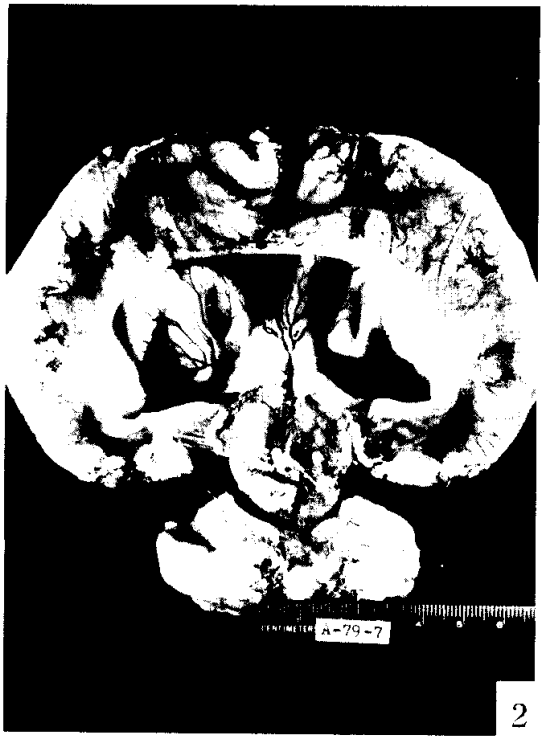
顔面畸形은 鼻中隔 欠損을 同伴한 한 개의 中央鼻腔을 가진 작은 코와 좁아진 兩眼間의 거리였다. 귀도 正常보다 낮은 位置였으며 耳輪은 뚜렷하지 않았다. 한편 腦全體 무게는 200gm으로 大腦半球間溝는 없었고 大腦回轉은 그 數가 減少되면서 크고 그 方向이 垂直이었고 側頭葉의 發達이 아주 不良하였다. 大腦後半은 거의 形成되지 않고, 얇은 膜으로 構成되었고, 腦室은 分離되지 않고 中央部에 커다란 空間으로 되어 있으면서 馬蹄形의 海馬葉으로 境界되어 있었다. 中腦의 大腦脚底는 없었으며 錐體와 下卵形突起의 異常을 보였다.

REFERENCES

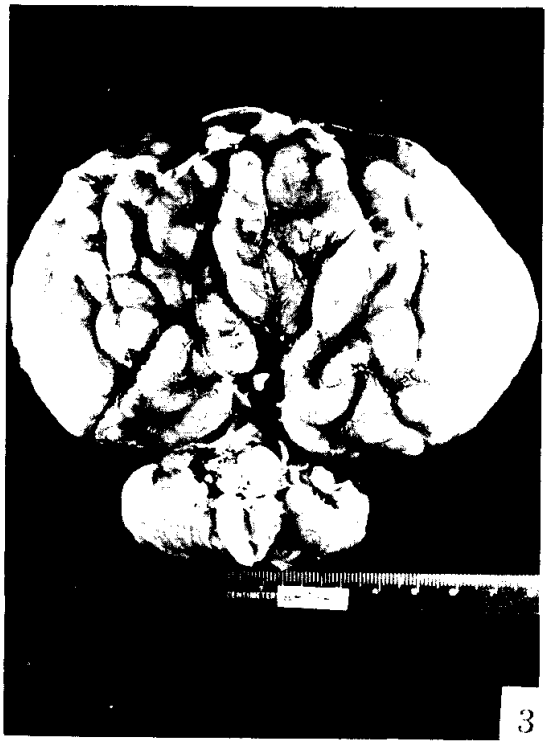
1. Binns, W., James, LF., Shupe, JL., et al.: *Cyclopian Type Malformation in Lambs. Arch Environm Health*, **5**:*106, 1962.*
2. Dekaban, A: *Arhinenephaly in an Infant Born to a Diabetic Mother. J Neuropath Exp Neurol.*, **18**:*620, 1959.*
3. Demyer, W., Zeman, W.: *Alobar Holoprosencephaly (Arrhine cephaly) with Median Cleft Lip and Palate. Clinical, Electroencephalographic, Nosological Considerations. Confin Neurol.*, **23**:*1, 1963.*
4. DeMyer, W., Zeman, W., Palmer, CG: *The Face Predicts the Brain: Diagnostic Significance of Median Facial Anomalies for Holoprosencephaly (Arrhinencephaly). Pediatrics*, **34**:*256, 1964.*
5. Edmonds, HW.: *Pituitary, Adrenal and Thyroid in Cyclopia. Arch Path.*, **50**:*727,* 1950.
6. Kakulas, BA, Rosman, NP.: *13—15 Trisomy in 8 Cases of Arrhinencephaly. Lancet*, **2**:*717, 1955.*
7. Kundrat, H.: *Arhinencephalie als typische Art von Mißbildung. Graz: Leuschner and Lubensky 1882.*
8. Miller, JQ, Picard, EH., Alkan, MK., et al: *A Specific Congenital Brain Defect (arrhinencephaly) in 13—15 Trisomy. New Eng. J Med.*, **268**:*120, 1963.*
9. Toews, HA., Jones, HW.: *Cyclopia in Association with D-trisomy and Gonadal Agenesis. Amer J. Obstet. Gynec.*, **102**:*53, 1968.*
10. Uchida, IA., McRae, KN., Wang, HC., Ray, M.: *Familial Short Arm Deficiency of Chromosome 18 Concomitent with Arrhinencephaly and Alopecia Congenita. Amer J Human Genet.*, **17**:*410, 1965.*
11. Wrights: *The Genetics of Vital Characters of the guinea Pig. J Cell Comp Physiol.*, **56**:*123, 1960.*
12. Yakovlev, PI.: *Pathoarchitectonic Studies of Cerebral Malformations: III. Arrhinencephalies (Holotelencephalies). J Neuropath Exp Neurol.*, **18**:*22, 1959.*



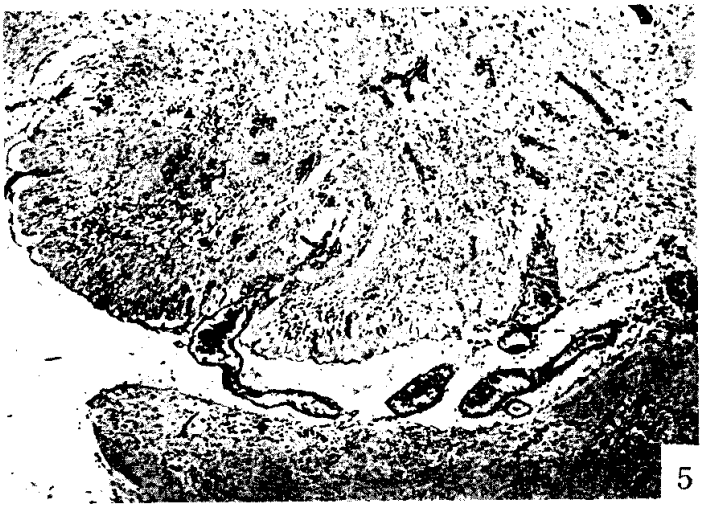
1



2



3



5

6

LEGENDS FOR FIGURES

Fig. 1. The face shows single midline nostril, hypotelorism and low-set ears with obscured tragi. The head circumference was 42.5cm.

Fig. 2. Anterior view of the brain, showing flattened, vertically oriented large gyri and obliterated sulci. Temporal lobes are represented by short truncated inferior extensions of the cerebrum. The olfactory bulbs and tracts are completely missing along with olfactory sulcus.

Fig. 3. The posterior half of the cerebrum consists of a thin-walled membrane without any discernible cerebral tissue. A single midline horseshoe-shaped cavity represents unpaired holosphere.

Fig. 4. Low power photomicrograph of the membranous structure that covered the dorsal cyst of the holosphere. H&E×60

Fig. 5. Photomicrograph of the amorphous mass at the region of the pituitary stalk. This consists of irregular overgrowths of glial cells and capillaries. H&E×100

Fig. 6. Photomicrograph of posterior third ventricle, showing stenosis and ependymal stripping along with nodular glial overgrowth.