

Pathological Study on Anencephaly (10 Autopsy Cases)

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INTRODUCTION

Anencephaly is the most common and the most serious congenital malformation which occurs spontaneously in man and other mammals and which is compatible with completion with the pregnancy but incompatible with life (Anderson et al., 1967).

In this common maldevelopment, the brain is either absent or rudimentary and there is an associated defect of the cranial vault and scalp (Urich, 1976). Frequently anencephaly is combined with other malformations such as anterior lobe of pituitary body unaccompanied by a posterior lobe and marked adrenal hypoplasia, while such features as harelip, cleft palate, spina bifida, hyperplasia of the thymus, hydronephrosis, hydroureter and abnormalities of major visceral arteries are present also in some cases (Vogel and McClenahan, 1952).

The frequency of the disease varies between approximately 0.5 and 2.0 per thousand births in the United States and most of Europe; it is locally higher in Britain and lower in Africa, Asia, and South America (Friede, 1976). In our country, many cases of anencephalic fetuses have been reported, too. The frequency of the anencephaly in our country is approximately 1.5 per thousand births (이명복 등, 1969). And another report show that the CNS malformations

comprise 17.3 percent of all abnormal births and anencephaly is 7 out of 53 cases of the CNS malformation (이제구 등, 1970). Although anencephaly have been reported for centuries, the underlying cause is still uncertain. In past years, several aspects of this anomaly have been studied, e.g., etiologic factors, and familial and genetic prevalence, complications, gross embryologic development, endocrine development and their interrelationships.

Recently we have experienced 10 cases of anencephaly during a period of 4 years, from 1977 to 1980. The current study is made to report 10 cases of anencephaly generally and to discuss the pathogenesis of anencephaly.

CLINICAL HISTORY

Only 3 of 10 anencephalic fetuses were female in our cases. Their ages varied from 34 weeks to 44 weeks while it was uncertain in case III. They were born during the last 3 months of pregnancy or later. They were still birth or died within the first 2 days. The history of pregnancy revealed that carbon monoxide poisoning had occurred in case II and herb medicine had been taken in case V both at about the third month of pregnancy. During the pregnancy, hydramnios were noted in case I and V. Birth rank showed that 4 cases were in first births, 2 in second and 1 in third, fourth, and fifth respectively. In 4 out of 9 cases the mothers had one or two previous abortions. Maternal ages varied from 23 to 32 years.

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Table 1. Clinical history of 10 anencephalics

Case No.	Sex	Gestational age (week)	Postnatal age	Remarks on maternal history		
				Age(yr.)	Para	Others
I (A-79- 15)	F	34	SB	30	1-0-2-1	hydroamnios
II (RCM 123)	M	35	?	22	0-0-1-0	CO poisoning(3)*
III (RCM 232)	M	?	?	?	?	
IV (A-78- 8)	F	40 ³	1 day	25	0-0-0-0	
V (A-79- 19)	M	41 ⁴	2 days	31	0-0-1-0	hydroamnios
VI (RCM 345)	M	42	SB	29	0-0-0-0	herb remedy(3)
VII (RCM 490)	M	42	SB	23	0-0-0-0	
VIII (RCM 201)	F	43	SB	32	3-0-0-0	
IX (RCM 170)	M	44	9 hours	25	0-0-2-0	
X (RCM 235)	M	44	?	23	0-0-0-0	

SB: Still birth, RCM: Registry of Congenital Malformation.

* A parenthesized number indicates the gestational month when pregnant woman was contact with each factor.

OBSERVATIONS

Gross Appearance

The cranial vault was invariably absent. And the cerebral hemispheres were replaced by red-purple amorphous mass. The absence of the cranial vault gave the face the characteristic appearance. The eyes were protruding. The ears

were unusually thick, laterally protruding and low-set, and the noses were flat or large based. Protruding tongues were noted in cases II and III. Furrowed palate in cases III and VII, and choanal atresia in case III were noted. The mandibles were prognathic from lateral radiographs in 6 cases(table 2).

The degree of cranial defect, especially dorsal cranial defect varied to some extent. Frontal

Table 2. Skeletal abnormalities seen in 10 anencephalics

Case No.	Cranium	Face ⁺	Spine	Other associated skeletal anomalies
I *	holoacrania	prognathic Mn	c. lordosis	hand and foot deformity
II *	holoacrania	prognathic Mn protruding tongue	rachischisis scoliosis absent c. vert.	deformity of hand and forearm
III *	holoacrania	prognathic Mn protruding tongue lt. choanal atresia furrow in palate	c. spina bifida c. lordosis	
IV *	meroacrania	prognathic Mn	c. spina bifida c. lordosis	
V	meroacrania	?	?	
VI *	meroacrania	prognathic Mn	c. lordosis	
VII	meroacrania	furrow in palate	?	
VIII	?	?	?	?
IX	meroacrania	?	?	
X *	meroacrania	prognathic Mn	c. lordosis scoliosis	

* : X-ray available
c. : cervical

⁺ : except eye, nose, ear changes
Mn: mandible

bones were not present above the supraorbital ridges and parietal bones were either entirely absent or present as only narrow edges of the most inferior portions. In some cases (IV, V, VI, VII, IX and X), the greater part of the occipital bone was present, but in other cases (I, II and III), all of the squamous occipital was missing. In case II, the dorsal cranial defect extended into thoracic vertebrae, characterized by an absence of the skin over a "V" shaped area that extended downwards from the acrania to the midthoracic region. The skin of the temporal and occipital bones turned over the base of the skull encircling the hemorrhagic formless mass attached to the base of the skull. There were associated spina bifida in cervical region in cases III and IV. The anterior cranial fossa was foreshortened with the narrow end located anteriorly. The middle cranial fossa was shallow anteriorly and the boundary between the middle and posterior cranial fossae was nearly perpendicular to the midline. The clivus was more vertical and the depth of the posterior cranial fossa was greatly increased, so the cranial floor angle was reduced.

The neck was extremely short or absent. In case II with craniorachischisis, the neck was absent and the anterior surface of the face and chest were fused and chin lied low over the sternum. In 5 cases out of 6 cases examined, cervical lordosis was present, and 2 cases (II and X) showed scoliosis. The cervical vertebrae were absent in case II.

The upper extremities were abnormally large and long when compared with the lower extremities(II, III, IV). Some cases were abundant in lanugo, especially the back region. Subcutaneous fat was generally increased.

Other associated skeletal anomalies are listed in table 2.

Central Nervous System

The cerebral hemispheres consisted of soft,

red-purple, irregular masses that varied in size and shape-discoid or bilobed, flattened or protruding. In cases IV and VI, the cerebral masses were formed of largely thin vascular channels distended with blood, interspersed by connective tissue and irregular nests or islands of malformed brain tissue, predominately glial as well as scattered neuronal elements in disordered arrangement. There were a number of cysts lined by ependyma or endothelium, sometimes with irregular papillary structures resembling choroid plexus.

Everywhere there were rich plexus of thin walled vascular channels that varied markedly in size and shape with scanty interspersed stroma. These vascular channels were characteristically devoid of muscular and elastic tissue. And individual thick walled arteries were also found. In other cases, discernible neurogenic structures were found and hemorrhagic areas were noted in the degenerative brain tissue. And these structures were sharply delineated from surrounding loose but highly vascularized connective tissue representing leptomeninges. In case II, thin, relatively well preserved neurogenous tissue was present, especially basally, and grossly found cavity was not lined.

These masses were covered with cornified stratified squamous epithelium, and in some areas with thin cuboidal epithelium. At the margins of these masses, the covering epithelium merged with the hair-bearing normal integument. Case I was not examined.

The spinal cords were available only in 4 cases (IV, V, VI and VII) which showed highly vascularized leptomeninges. In case VII heterotopic fibroglial nodule measuring $0.3 \times 0.2 \times 0.1$ cm was found near the filum terminale.

In cases VII and X, midbrain and cerebellum were relatively normally developed and thalami were identified as remnants.

Eyes were grossly well developed. Microscopically only 3 cases (IV, VII and IX) could be

Table 3. Fetal growth and organ weights of 10 Anencephalics

	I	II	III	IV	V	VI	VII	VIII	IX	X
C.R. Length	18.5	18.0	*	28.0	28.0	25.5	30.0	28.0	18.0	*
C.H. Length	*	*	42.0	42.0	49.0	45.0	50.0	49.0	42.0	53.0
Body Wt.	845	830	1,560	2,120	2,620	2,300	2,860	1,950	3,000	2,700
Hypophysis	—	+	—	+	+	+	0.1	+	—	—
Thyroid	*	*	*	1.2	*	*	*	*	*	*
Thymus	5.8	6.0	6.3	25.5	21.1	15.5	22.9	13.0	16.2	27.8
Adrenal	1.1	+	1.9	0.5	0.6	2.0	0.3	1.0	1.9	1.2
Heart	*	*	6.2	20.0	15.8	16.0	21.9	14.4	24.2	*
Lung Lt	4.2	3.5	7.1	16.5	*	13.5	16.4	22.0	23.5	20.1
Rt	7.4	*	5.8	18.0	*	17.0	21.6	24.5	26.0	25.8
Liver	*	35.3	50.9	71.0	74.0	75.0	133.9	56.2	98.5	78.6
Spleen	3.7	2.2	14.1	9.6	10.3	8.0	7.0	13.0	10.5	11.8
Kidney Lt.	4.1	4.6	6.0	8.2	10.2	8.0	11.8	7.0	13.2	8.4
Rt.	4.1	5.9	5.2	8.0	9.6	8.0	11.8	11.6	13.5	8.1
Pancreas	2.6	0.7	1.2	2.5	1.2	*	4.1	*	4.5	*

*: not weighed or measured Unit; length-cm
 —: absent weight-gm
 +: microscopically present

examined. The retina was normal except the decrease in number of the 3rd neuron and ganglion cells in cases IV and IX. In case VII, optic nerves, measuring 1.5~2.0 cm ended blindly into adjacent soft tissue. Neither optic chiasma nor optic tracts was identified. Microscopic examination of serially sectioned optic nerves showed that at the site nearer to the retina, well developed central artery with abundant vascularity and poor myelinations in optic nerves and definite dural sheath were seen, and more centrally decreased vascularity and more severe neural degeneration were noted.

Pituitary Gland

Pituitary glands were identified in 6 cases. (table 3) All cases but case VII showed only adenohypophysis. In case VII, separated anterior and posterior lobes were found. Other 4 cases were not examined. All identified cases exhibited smaller size than normal. Fibrous capsules were found in case IV, V and VIII.

In cases VII and VIII, anterior pituitaries were

located on sella turcica and in cases II and IV, in area cerebrovasculosa. Microscopically cells were polygonal and poorly developed narrow cords were seen between numerous engorged sinusoids.

Adrenal Gland

Adrenal glands were extremely small without exception. Microscopically all examined adrenals showed common characteristics. Thinned cortex, almost complete absence of fetal zone and relative increase of definitive cortex were noticed. There were also sinusoidal dilatation and focal hemorrhage. In case II, cortical cells were not orderly arranged, and below them, extensively hemorrhagic area with numerous cell rest and hemosiderin laden macrophages was found without any features characteristic of adrenal medulla. Outside the gland, there was massive accumulation of ganglion cells representing ganglia. In case III, there found erythropoietic foci near the large arteries.

Thyroid Gland

In case IV and V, large follicles filled with

Table 4. Associated visceral anomalies of anencephalics

Case	Hypophysis	Thyroid	Thymus	Adrenal	Other Visceral Anomalies
I	*	Adult follicle	Hyperpl.	*	PDA, Acc. spleen
II	Ant. only	Unremarkable	Hyperpl.	Hypopl.	IAOAS, ASD, RVH, 2 Acc. S. hypopl. lung, bilat. undes. testis
III	*	Adult follicle	Normal	Hypopl.	
IV	Ant. only	Adult follicle	Hyperpl.	Hypopl.	PDA, Persist. FO, bilat. undes. testis
V	Ant. only	Adult follicle	Hyperpl.	Hypopl.	
VI	Ant. only	*	Hyperpl.	*	mediastinal emphysema
VII	Ant. & post. lobes	Adult follicle	Hyperpl.	Hypopl.	Persist. FO
VIII	Ant. only	*	Normal	Hypopl.	
IX	*	*	Hyperpl.	Hypopl.	2 Acc. S.
X	*	Adult follicle	Hyperpl.	Hypopl.	

* not examined PDA patent ductus arteriosus
 Acc. S. accessory spleen ASD atrial septal defect
 Bilat. undes. testis bilateral undescended testis

Persist. FO persistent foramen ovale
 RVH right ventricular hypertrophy
 IAOAS interrupted aortic arch syndrome

colloid, well developed like those of adult, were found at the periphery of the lobules. In cases I, III, VII and X, eosinophilic colloid accumulation in distended acini was found in entire lobules. In case II, neither adult type follicle nor colloid was present. Other 3 cases were not examined.

Thymus

All cases except one showed increased weight in relation to the total body weight. They varied in size and shape, often enlarged. In case VII, intrathyroid thymic tissue was found. Histologically 8 cases showed hyperplasia, evidenced by unusually large cortical areas packed with small lymphocytes.

Other Visceral Organs

Other visceral organs showed generally congested features in some cases. In case II, both lungs were hypoplastic. Kidneys in cases I and II showed subcapsular nephrogenic zone with immature tubules in addition to congestion. Hepatic hemopoietic cells seemed to be generally increased. And accessory spleen(s) were noted in cases I, II and IX. Heart and great vessel

anomalies were enlisted in table 4. Cases II and IV showed bilateral undescended testis.

DISCUSSION

In review of literature in our country, 19 cases out of 31 cases were male. Our cases also present male preponderance, while many reports of other countries revealed overwhelming female preponderance. Coffey et al. (1957) reported that the percentage of males with anencephaly varied from 19.5 to 48.4. However, the preponderance of females diminished in the more mature infants and the sexes were equally represented among infants born alive or neonatally dead who weighed 2,000 gm or more. Further studies are needed to elucidate the discrepancy in sex ratio between our country and others.

The association between anencephaly and birth order is most readily described as U-shaped. However, Elwood et al. (1978) reported that the frequently noted U-type relationship of anencephalus risk with maternal parity was

produced by a combination of two influences, i.e., a decrease in risk with previous live born 'healthy' pregnancies and an increase in risk with previous 'unhealthy' pregnancies as still births or infants deaths. They also reported that the association with maternal age was at least in Canadian data, a secondary effect of the association with parity. In our cases, 4 with previous abortion and 4 in first births rank were noted.

The hydramnios in anencephaly could be explained by increased output of urine or impaired deglutition, coupled with a deficiency of antidiuretic hormone (Nakano, 1973).

The pathogenesis of anencephaly has been the subject of many studies. Theories proposed for the formal pathogenesis of anencephaly include; failure of neural tube closure, reopening of the neural tube after its closure, arrest of cerebral development because of abnormal angiogenesis or mechanical trauma in utero. There is no doubt that part of the malformation is due to a disintegration of preformed portions of the brain, since in many specimens the eyes were normal though there may be no trace of the optic nerves (Urich, 1976). In our cases, eyes were grossly well developed and the retina was relatively well preserved. In case VII, optic nerves were identified but had no central connection. These findings suggest that the diencephalon be properly formed through the 7th or 8th week of fetal life and the developing brain be affected thereafter.

Concentrating on the 'area cerebrovasculosa', the findings of our cases were similar to those previously reported on anencephaly. (Vogel and McClenahan, 1952; Friede, 1976; Bell et al., 1981) There were an apparently disorganized mass of neural tissue, choroid plexus and hypervascular meninges. Discernible or disorderly arranged neural tissues were noted but they seemed not to be associated with the extent of

the neural defect. Spinal leptomeninges were also hypervascular in examined cases. The dense vascularity that gave the area cerebrovasculosa its name is most noticeable in association with anencephaly. But this type of increased vascularity is a nonspecific trait often seen in other malformations such as encephaloceles and myelomeningoceles. (Friede, 1976) It represents persistence of embryonal meningeal vascularization, characterized by dense plexus of sinusoid capillaries at the pial surface. Vogel (1952, 1958, 1961, 1980) suggested that in anencephaly, normal development probably occurred through the 7th or 8th week of life and then was impaired perhaps by a selective interference in angiogenesis. In support of this theory the blood vessels in the cerebral mass did not have smooth muscle, and also the mass on occasion contained extramedullary hemopoiesis, suggesting persistent anoxia. In our cases both characteristics supporting this theory were found. However, it still remains uncertain whether these vascular abnormalities precede or are secondary to the cerebral defect.

It has also been suggested that anencephaly, as well as other cranial or spinal dysraphism, results from nonclosure of the neural tube, which was supported by demonstrating the occurrence of a complete cranial and spinal dysraphism in a human embryo of less than four weeks of gestation (Dekaban, 1963), and the association between anencephaly and spina bifida in certain families (Nakano, 1973).

Vogel (1980) questioned the concept that anencephaly is a dysraphic process, for following reasons; the presence of eyes and cranial ganglia and choroid plexus existed in the cerebral mass in anencephaly. Choroid plexus is formed when the hemispheres fold inward and the pia comes in contact with ependyma, and the tela choroidea of the choroid plexus is pial in origin and the epithelium is derived from ependyma. This

indicated closure of the hemispheres. And he explained that the association between anencephaly and spina bifida was not a close one because, although closure of the cephalad and caudad ends of the neural tube occurred at closely related times in embryonic development, classic spina bifida in the lumbar area was very rare association of anencephaly.

The craniofacial skeleton in our cases showed calvarial defect and morphologic changes of the cranial floor and facial skeleton. In cases VII and X relatively small size of the calvarial defects were associated with the presence of the cerebellum and brainstem. Detailed study of the craniofacial skeleton in anencephalic human fetuses (Fields et al., 1978 a;b;c) indicated that the morphologic alterations of the anencephalic cranial floor were due to the altered size, form or duration of the neural functional matrix, which in turn influence adaptive changes in the membranous bones of the neurocranium and the facial skeleton. And in general the degree of maldevelopment was proportional to the extent of the dorsal cranial defect in anencephaly. Calvarial defect in anencephaly showed that the critical time for anencephaly could not be later than the 9th week (Warren, 1951)

Anencephaly is frequently associated with defect in many of the endocrine glands. Our cases showed that anterior pituitary glands were invariably present in examined cases, but posterior in only one case. Hypoplasia of the adrenals, hyperplasia of the thymus and thyroid with adult follicles were also noted. Angevine (1938) reported that the anterior lobe of the pituitary can always be found in the deformed base of the skull, but the posterior lobe is often absent, depending on the cranial defect. Electro microscopic study of the pituitary gland of the anencephaly demonstrated differentiation of cells apparently in absence of secretory activity although hypothalamus was absent, which meant

that the influence of hypothalamic neurosecretory activity of the adenohipophysis was not required for differentiation of most cell types (Salaazar et al., 1969).

Hypoplasia of the adrenals, having been described in the 19th century, is known to be caused by premature involution of the fetal zone of the adrenal cortex. Benirschke (1956) observed that by the 20th week of gestation the fetal zone was present even in anencephaly, and after this critical period the fetal zone atrophied. He explained that the fetal zone of the adrenal gland was governed in early gestation by chorionic gonadotrophin, and the atrophy of the adrenal in anencephaly resulted from absence of fetal luteinizing hormone secondary to a defective hypothalamus, and partially from reduced ACTH production. Recently Gray et al. (1980) observed that the involution of fetal adrenal began well before 20th week gestation.

Thymus has been reported as normal or enlarged. Thymus hyperplasia found in anencephalic fetuses may be due to the loss of the normal inhibitory activity of the fetal pituitary-adrenal axis on thymus growth. (Bearn, 1967)

About thyroid-pituitary axis, it has been reported that in anencephaly both pituitary TSH secreting cells and the thyroid gland do develop despite the absence of the hypothalamus and are able to function if adequately stimulated (Benirschke, 1952; Grasso et al., 1980).

In anencephaly other malformation are said to be rare. In our cases multiple skeletal anomalies, spina bifida, furrowed palate, choanal atresia, interrupted aortic arch syndrome, congenital heart anomalies and hypoplastic lung were noted.

Despite intensive investigation the causation of prenatal malformations including anencephaly in man remains largely undetermined. The problem is complicated by the fact that the same type of structural anomaly may be produced both

by genetic and exogenous causes(Urich, 1976). They can be induced readily by means of anoxia, irradiation with X-rays, and by alterations in the thermal, osmotic or ionic environment of the developing embryos(Vogel and McClenahan, 1952). Furthermore, the nature of the induced malformation seems to depend more upon the stage of embryonic development at the time of the experiment than it does upon the means by which the injuries are induced. In our case II, a history of carbon monoxide poisoning at the third month was present and the fetus exhibited anencephaly with multiple anomalies. It has been reported that malformation or intrauterine death resulted from accidental carbon monoxide poisoning (Muller and Graham, 1955; Ingalls and Philbrook, 1958). And Ingalls induced anencephaly with multiple skeletal anomalies by hypoxia in animal experiment (Ingalls et al., 1952). A history of herb medicine at the third month was also noted in our case. These factors should be studied further especially because fetuses in our country, have more chances to be exposed to these factors.

SUMMARY

Ten cases of anencephaly are presented with clinical and pathologic findings. This series showed male preponderance. Although most anencephalics did not accompany extraneural malformation, one case with craniorachischisis had multiple anomalies. The morphologic features of our cases are in agreement with the view of secondary degeneration and not with primary neural defect for the pathogenesis of anencephaly. A brief review of pathogenesis and etiology was also done.

==國文抄錄==

무뇌증의 병리학적 검색(10부검증례)

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1977년부터 1980년까지 4년 동안 서울대학교 의과대학 병리학교실에서 부검하였던 무뇌증 10예를 대상으로 병리학적 검색을 하였다. 이들은 남성 7예, 여성 3예로 구성되었고 재태기간은 34주에서 44주였다. 대부분이 사산되었으나 2일 생존한 예도 있었다. 한 예에서 연탄가스중독 또 한 예에서 한약을 각각 임신 초에 경험하였거나 복용하였던 과거력을 가졌었다.

신경병리학적 검사에서 모든 예에서 안구의 발달은 정상이었으나 시신경은 가늘고 변성이 심하였고, 관찰한 모든 예에서 교차를 형성하지 않았다. 하수체는 6예에서 존재하였고 1예를 제외하고는 선하수체로만 구성되었다.

무뇌증에 있어서의 각 장기의 중량을 측정한 결과 부신의 저형성과 흉선의 과형성이 모든 예에서 현저하였으며 특히 부신피질은 태역의 소퇴가 특징이었다.

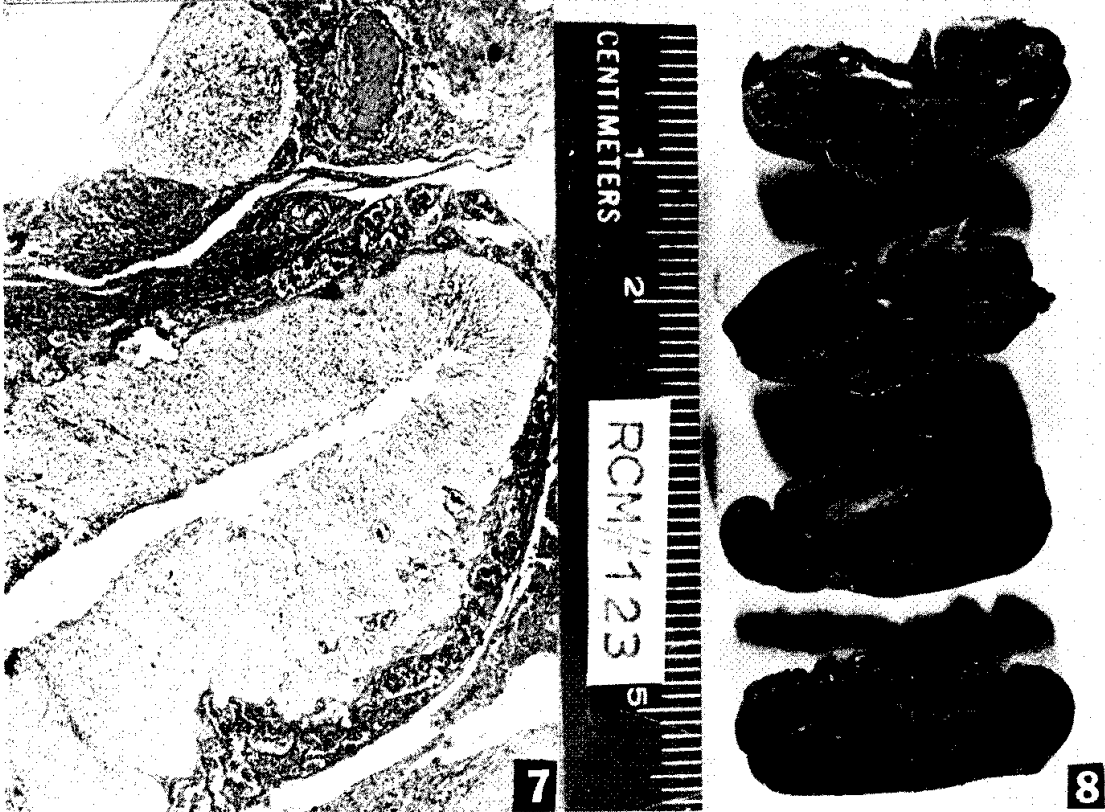
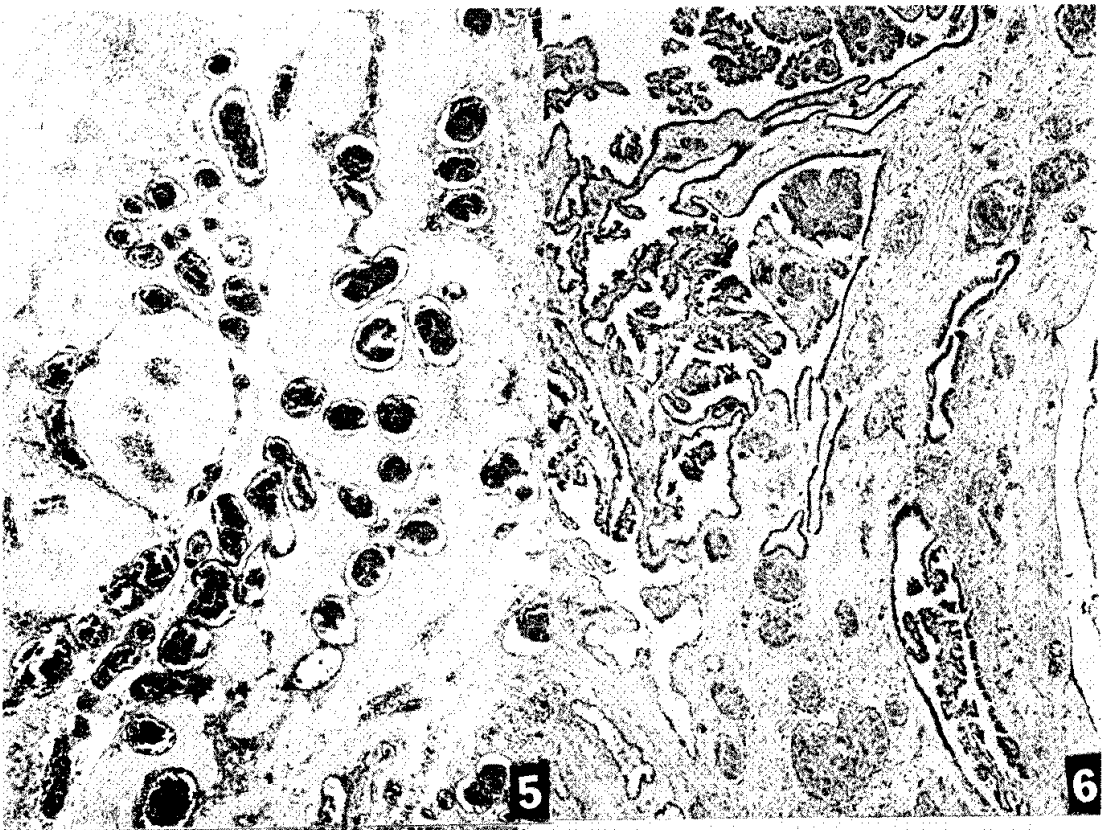
기타 무뇌증에 합병된 변화 및 기형을 기술하였으며 더불어 무뇌증의 발생기전을 고안하였다. 본 검색결과 무뇌증은 일차적 신경결손이라기보다는 어느 정도 발달하다가 이차적 변성에 의하여 발생될 것이라는 사실을 알게 되었다.

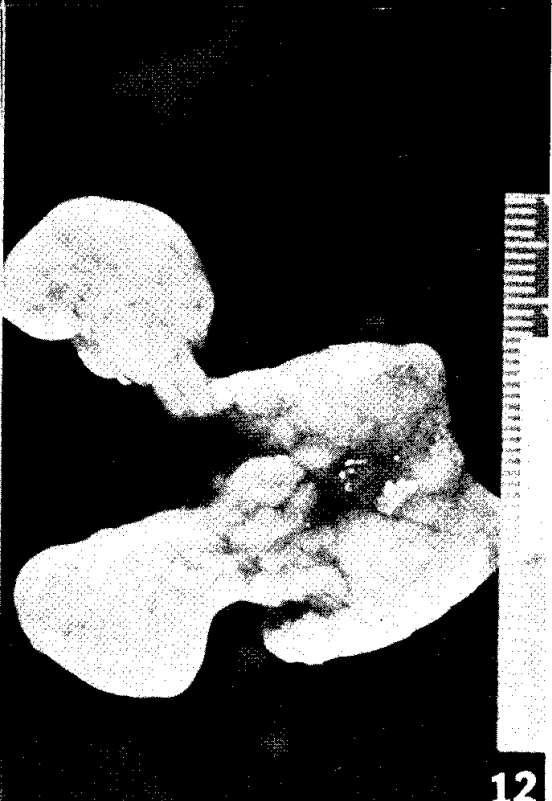
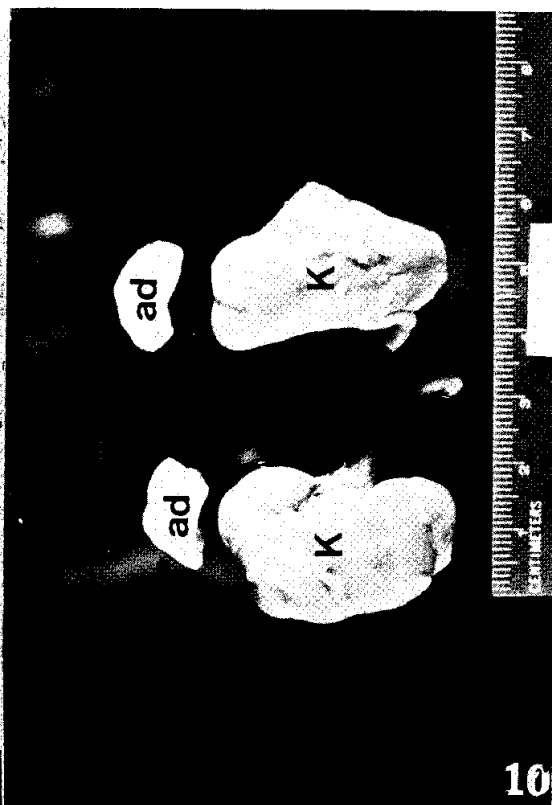
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LEGENDS FOR FIGURES

- Fig. 1.** Anterior aspect of anencephaly (case III) showing absent calvarium, marked proptosis, flat nose, protruding tongue, low-set laterally protruding ears and short neck.
- Fig. 2.** Lateral aspect of anencephaly (case V) showing crown like cerebral mass with thick, low-set ear.
- Fig. 3.** Hemangiomatic soft tissue on the top of the cranium showing lobating irregular surface (case V).
- Fig. 4.** Skull base in case II after complete extirpation of the hemangiomatic mass, showing foreshortened ant. cranial fossa, shallow middle cranial fossa with malformed sphenoid bone, almost perpendicular petrous ridge and more vertical clivus.
- Fig. 5.** Coronal sections of the hemangiomatic mass which show large cavity and remaining structure basally (Case II).
- Fig. 6.** Relatively well preserved neurogenous tissue, sharply delineated from surrounding loose but highly vascularized connective tissue, and isolated neural island ($\times 40$) (case II).
- Fig. 7.** Choroid plexus structures are formed in area cerebrovasculosa, in case IV.
- Fig. 8.** Neural islands composed of glial and scattered neural elements among the thin walled vascular channels (case IX).
- Fig. 9.** Pituitary gland in case VIII showing cord-like arranged cellw with distended sinusoids.
- Fig. 10.** Adrenal glands (Ad) in case VI, showing markedly reduced size. K represents kidneys.
- Fig. 11.** Adrenal gland in case III which show thinned cortex with complete absence of fetal zone and hemopoietic cells near large blood vessel.
- Fig. 12.** Bicornuated thymus in case II.
- Fig. 13.** Hypoplastic lungs in case II showing markedly reduced size without lobation.
- Fig. 14.** Heart in case II showing interrupted aortic arch syndrome. In addition to this anomaly there were ASD, PDA, RVH.
- Fig. 15.** Skeletal anomalies in case II, which show face and chest fusion, right elbow joint fusion, lack of radius and 4 digits on right side and left thumb varus.
- Fig. 16.** Bean-shaped small nodule near the tip of the filum terminale, proven to be a heterotopic fibroglial tissue.