

Bilateral Cleft Palate and Holotelencephaly with Multiple other Anomalies Consistent with 13 Trisomy Syndrome (An Autopsy Case)

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It is now recognized that multiple congenial anomalies may be associated with certain human chromosome defects. One of such chromosome abnormality is known as 13 trisomy, which is also known as Patau syndrome (Patau et al., 1960; Smith et al., 1963). The findings noted in most cases of 13 trisomy syndrome are fairly stereotypic. And some of them are cleft palate and/or cleft lip, eye defects, polydactyly, cardiac malformation, and brain defect (Warkany, 1966; Warkany, 1971). However, in the absence of karyotyping it is difficult to be sure of the diagnosis.

The case we describe here is a deadborn infant to a 26 year woman, born after 41 weeks gestational period. This infant showed almost all abnormalities described in 13 trisomy syndrome. Unfortunately blood sampling for chromosome study did not yield any viable cells, probably because of prolonged period of intrauterine fetal death.

In the paucity of Korean literature on autopsy findings of chromosome anomalies and also for reporting a very unusual anomaly, namely intrasplenic pancreatic tissue, we describe this case.

REPORT OF A CASE (RCM #331)

The mother of this patient was a 26 year old primigravida who delivered a dead-born female baby on August 8, 1979 at a local Obs. & Gyn. Clinic. Her last menstruation period was October 28, 1978. And EDC was August 5, 1979. The

gestational period was 41 weeks. After noticing multiple congenial anomalies the physician referred this case to Department of Pathology, College of Medicine, Seoul National University.

At autopsy this female baby weighed 1,950 gm and was measured 29 cm in crown-rump length and 47 cm in crown-heel length, respectively. Externally the head was obviously small (microcephalic), the head circumference being 26 cm (less than 10 percentile for gestational age, body weight, and body length: Colorado Intrauterine growth chart). The small head showed sloping forehead and wide sagittal sutures and fontanelles (Fig. B). A small patch of epithelium was lacking in an area, 1.5×0.7 cm, of the scalp over the vertex associated with defect of underlying cranium (Fig. C). Both eyes were close together (hypotelorism). Supraorbital ridges were shallow and the palpebral fissures were slanting. Eye brows were absent. Auricles showed abnormal helices, and ears were low-set. There was no nasal bone or nostril. Bilateral cleft lip (false median cleft of the upper lip) and wide, complete cleft palate (Fig. A&E) and tongue tie were observed. Hands and feet showed flexion deformity. An extradigit (polydactyly) of the left foot was present (Fig. D). The bottoms of both feet had convex contours and there were prominent posterior extension of both heels (rockerbottom feet).

Internal examination showed a large globular heart, weighing 20.5 gm and showing an overriding aorta (dextroposition), high ventricular septal defect, infundibular pulmonary stenosis,

right ventricular hypertrophy, hypoplastic left ventricle, and patent ductus arteriosus. Both lungs were incompletely lobulated. Diaphragm was unremarkable. Grossly detected and microscopically proven pancreatic tissue was seen near the hilus of otherwise unremarkable spleen (11.8 gm in weight). Both acinar and insular elements were seen inside the spleen. Total mass of pancreatic tissue was approximately 0.6×0.5 cm, and located deep into the splenic parenchyme near the hilus. Surrounding splenic tissue did not show any evidence of compression (Fig. D). The main pancreas weighed 4.0 gm and was of normal shape and location. The liver, kidneys and adrenals were unremarkable. The uterus was of infantile type, 4cm in length, and rudimentary bicornuate with separation of the right tube and ovary from the uterus was noted (Fig. K). The right tube was small and contained a small nodule measuring 0.4cm in diameter. This nodule consisted of Müllerian duct elements.

The brain was small and weighed 154 gm. The base of skull was shortened and narrowed in its frontal portion. There was no olfactory bulbs or tracts seen. Lamina cribrosa and crista galli were also absent. Shallow anterior and middle cranial fossae contained a small, extremely congested brain. No falx cerebri or evidence of fissuration was seen in the anterior portion of the brain, and instead, all large gyri were oriented vertically from base to top frontally (Fig. F). However, definite fissure was recognized in the posterior part of the cerebral hemisphere (Fig. G). The cerebral hemispheres were fused into one single mass and were covered with congested and tortuous blood vessels running over the brain mass. There was an extremely attenuated cerebellar tentorium which was caudally displaced. Through this deficient tentorium, the roof of the common ventricle could be seen. The frontal surface of the fused hemispheres

was comprised of gyri of approximately normal size, and was running in a disorderly manner. One could identify paired anterior and middle cerebral arteries that were dilated and very tortuous, running vertically along the surface of abnormal gyri (Fig. F). Sectioning of the brain showed a large unpaired ventricle, with minute midline structures, bound by a thin, smooth layer of white matter covered with ependyma (Fig. H). Basal ganglia were fused in the midline. The thalamus was partly fused also, particularly in its basal portion. The third ventricle was barely seen as slit. Brain stem and cerebellum were relatively preserved. At the region of pituitary, amorphous mass of 0.7 cm was seen, which showed microscopically irregular mixture of glial cells and ganglion cells. No pituitary gland was identified. The occipital lobes were partly differentiated, and there was no horseshoe shaped hippocampi or dorsal cyst. Both eyes showed coloboma of iris. However, no abnormality was seen in the retina microscopically.

DISCUSSION

Almost all the congenital anomalies seen in this patient have been repeatedly described in reported cases of 13 trisomy syndrome (Patau, 1960; Miller, 1963; Warkany, 1971). All the essential features of 13 trisomy syndrome were found in this infant.

All the findings (anomalies) seen in our case might be classified into three categories; one, those anomalies that were already described along with 13 trisomy syndrome; two, those anomalies that were not usually described in 13 trisomy syndrome; and three, those that were expected but not found in this case.

The first category consists of holotelencephaly (arhinencephaly), bilateral cleft lip and palate without philtrum, coloboma of iris, abnormal

shape and low-setting of ears, microcephaly, congenital heart disease, abnormal lobation of the lungs, bicornuate uterus with abnormal fallopian tube, polydactylia, congenital skin defect of scalp, flexion of fingers and hands, and rocker-bottom feet.

The second category would be intrasplenic pancreatic tissue and tetralogy of Fallot with typical infundibular stenosis. These two anomalies are exceptional in 13 trisomy syndrome. Townes et al. (1962) described a similar cardiac anomaly.

The third category would consist of absence of genitourinary tract anomalies and hemangioma. These two anomalies are fairly commonly seen in 13 trisomy syndrome (Atkins, 1961; Mottet & Jensen, 1965). We have to state here that simian crease was not examined attentively. Therefore we are not in the position to state the presence or absence of it. The umbilical cord was, for some reason, extremely dried up. One could not examine the cross sections.

Embryologically, the development of the face is related to the frontonasal process superiorly and maxillary processes inferiorly. The frontonasal process is the anlage of the forehead and nose. A deficient development of this structure results in a spectrum of midline facial anomalies ranging from a broad flat nose with sloping forehead to cyclopia (DeMyer et al., 1964). Active proliferation of this mesodermal tissue begins in 5 weeks embryo (6.5 to 7.5 cm). Bilateral cleft lips and cleft palate occur when the hypoplastic median nasal aspect of the frontonasal process fails to fuse with bilaterally hypoplastic maxillary processes. These midfacial anomalies are also intimately related to induction of cleavage of developing prosencephalon and results a spectrum of brain anomalies ranging from alobar holotelencephaly to lobar holotelencephaly and to normal brains (DeMyer & Zeman, 1963; Miller et al., 1963).

A brain with only partial forebrain cleavage having a monoventricular sphere and lacking olfactory bulbs and tracts is often called arhinencephaly. These days, however, particularly after Yakovlev (1959) description the term, holotelencephaly is more commonly used in the literature. Anteriorly in the holosphere the failure of cleavage is total in all cases. However, posteriorly, there is a great difference in extent of malformations in regards to postero-lateral out-pocketing of simple ventricular cavity, bilateral representation of hippocampi, bilateral representation of isocortex and interlobar fissure.

DeMyer et Zeman (1963) described three types of holotelencephaly, namely lobar, semilobar and alobar according to above mentioned gradient. However, anterior half of the brain is exactly same as in alobar holotelencephaly that has no anterior gradient at all. We described such a case in a newborn infant previously (Chi et al., 1979). In lobar holotelencephaly the brain has well formed lobes and a distinct interhemispheric fissure. And olfactory bulbs and tracts may or may not be present. In semilobar holotelencephaly as seen in this case, evidence of cleavage is clearly demonstrable posteriorly. As seen in serial coronal sections of our case paired occipital horns of the lateral ventricle could be seen together with interhemispheric fissure.

After review of the related literatures we expressed an opinion (Chi et al., 1979) that there seem to be at least 2 types of holotelencephaly in regard to the association with extracephalic anomalies. Those cases of holotelencephaly associated with microcephaly and multiple other congenital anomalies often show chromosome anomalies particularly 13 trisomy, whereas isolated holotelencephaly cases are more often associated with normal karyotype. According to this contention the case under discussion is probably associated with 13 trisomy syndrome although

karyotyping was failed.

Among cardiovascular anomalies ventricular septal defect, patent ductus arteriosus, and atrial septal defect are the leading malformations(Warkany, 1966). However, tetralogy of Fallot is extremely rare. Among 32 cases Warkany(1966) reviewed only one case had tetralogy of Fallot which was combined with dextrocardia. The essence of tetralogy of Fallot is infundibular stenosis(Van Praagh et al., 1970). And this was characteristically demonstrated in this case(Fig. J). Tetralogy of Fallot is also seen in Trisomy 21 although rare. Hypoplastic left ventricle and overriding aorta can be seen in Trisomy 18 syndrome.

SUMMARY

An autopsy of a still-born infant to a 26 year old Korean woman showed all characteristic pathological features described in 13 trisomy syndrome. Semilobar holotelencephaly, bilateral cleft lip and cleft palate, microcephaly, polydactyly, congenital heart disease, coloboma of iris, and bicornuate uterus were present. In addition intrasplenic pancreatic heterotopia and a typical tetralogy of Fallot were seen in this case.

Although chromosome study failed because of inadequate specimen from a dead born infant, the findings seen in this case are fairly consistent with 13 trisomy syndrome.

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》國文抄錄《

다발성 기형을 동반한 Holotelencephaly

(13 Trisomy라 생각되는 1 부검증례)

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지 제 근 · 이 윤 성

26세의 초산부가 41주만에 사산아를 분만하였는데 이

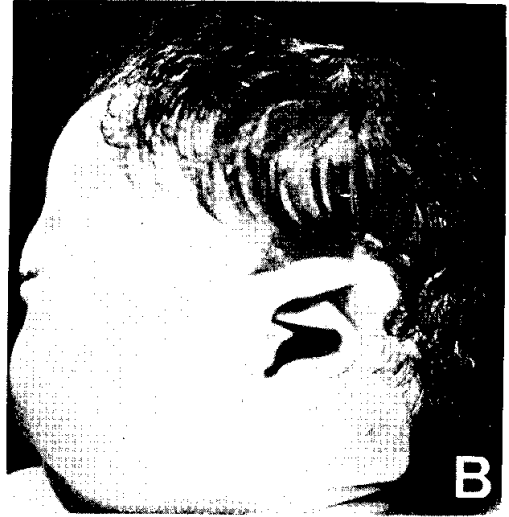
사산아부검에서 이미 기재된 13 trisomy의 모든 소견에 부합되는 특징적 선천성 기형이 관찰되어 본 예를 보고하였다.

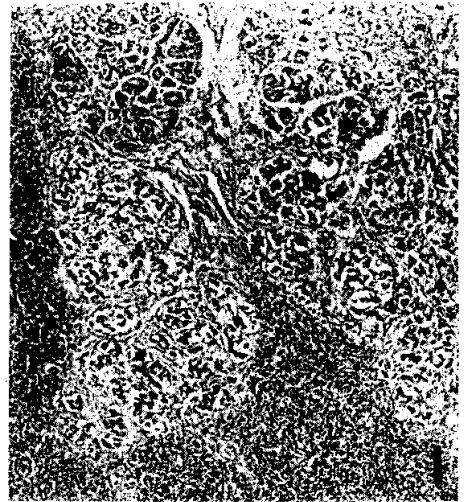
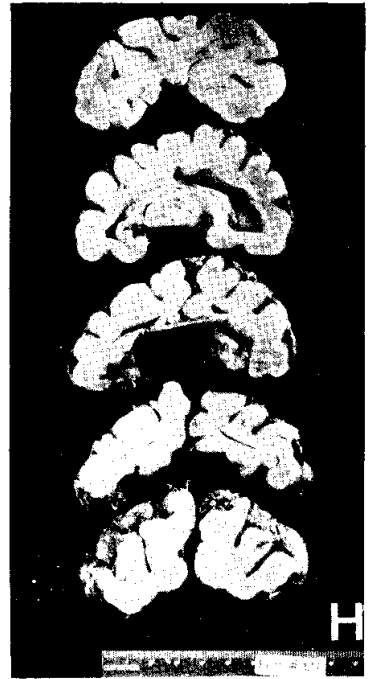
본 예가 가졌던 기형들은 semilobar holotelencephaly, 양측성 구순 및 구개파열, 소두증, 다지증, 선천성 심기형, 홍채결손(coloboma), 이각자궁 및 난관기형 등이었다. 그외에 비장내에 함입된 췌조직과 tetralogy of Fallot가 수반되어 있었다.

본 예가 사산아여서 염색체 검사를 의뢰하였으나 생체포가 없어 검사를 할 수 없었으나 이상의 여러 소견들을 종합하여 본 예가 13 trisomy 증후군이라 생각되었다.

REFERENCES

- Atkins L, Rosenthal MK: *Multiple Congenital Abnormalities associated with Chromosomal Trisomy. New Engl J Med* 165:3314, 1961
- Chi JG, Kim BT, Lee JY, Suh HS: *Holotelencephaly (An Autopsy Case report). Seoul J Med* 20:139, 1979
- DeMyer W, Zeman W: *Alobar Holoprosencephaly (Arhinencephaly) with Median Cleft Lip and Palate; Clinical, Electroencephalographic, Nosological Considerations: Conf Neurol* 23:1, 1963
- DeMyer W, Zeman W, Palmer CG: *The Face predicts the Brain; Diagnostic Significance of Median Facial Anomalies for Holoprosencephaly(Arhinencephaly). Pediatrics* 34:256, 1964
- Miller JQ, Picard EH, Alkan MK et al: *A Specific Congenital Brain Defect (Arhinencephaly) in 13-15 Trisomy. New Engl J Med* 268:120, 1963
- Mottet NK, Jenssen H: *The Anomalous Embryonic Development associated with Trisomy 13-15, Amer J Clin Path* 43:334, 1965
- Patau K, Smith DW, Therman E, Inhorn SL, Wagner HP: *Multiple Congenital Anomaly caused by Extra Autosome. Lancet* 1:790, 1960
- Smith DW, Patau K, Therman E, Inhorn SL, DeMars RI: *The D₁ Trisomy Syndrome. J Pedias* 62:326, 1963
- Townes PL, Dehart GK, Jr., Hecht F, Mannin JA: *Trisomy 13-15 in a Male Infant. J Pediat* 60:528, 1962





Van Praagh R, Corwin RD, Dahlquist EH Jr., et al:

Tetralogy of Fallot with severe left Ventricular Outflow Tract Obstruction due to Anomalous Attachment of the Mitral Valve to the Ventricular Septum. Amer J Cardiol 26:93, 1970

Warkany J, Passarge E, Smith LS: *Congenital Malformations in Autosomal Trisomy Syndrome. Amer*

J Dis Child 112:502, 1966

Warkany J: *Congenital Malformations, Chicago: Year Book Medical Publisher, Inc. 1971*

Yakovlev PI: *Pathoarchitectomic Studies of Cerebral Malformations: III, Arhinencephalies (Holotelencephalies). J Neuropath Exp Neurol* 18:22, 1959

LEGENDS FOR FIGURES

- A. Face with bilateral cleft lip, flat nose, hypotelorism, and absent eye brows. Note also a small head.
- B. Lateral view of head showing slanting forehead and also abnormally shaped and low-set left ear.
- C. Characteristic skin defect at the top of scalp.
- D. Extradigit is seen in the left foot.
- E. Mouth roof showing wide, complete cleft palate without philtum.
- F. Frontal view of the removed brain showing typical holotelencephaly. Broad, vertically oriented gyri are seen together with tortuous blood vessels.
- G. Posterior view of the cerebral hemisphere, showing partial formation of interhemispheric fissure and other evidence of cleavage.
- H. Coronal sections of the brain showing anterior-posterior gradient of cleavage, indicative of semilobar type holotelencephaly.
- I. Photomicrograph of spleen containing islands of mature pancreatic tissue. H&E×100
- J. Right ventricular outflow tract of the heart, showing infundibular stenosis(tetralogy of Fallot).
- K. Uterus showing rudimentary right horn and separated anomalous tube and ovary in the right.