Holoprosencephaly in neurosurgical practice

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The clinical, angiographic, and pneumoencephalographic features of seven cases with holoprosencephaly are reported. Three of the alobar type in this series revealed the facial dysmorphia characteristic of the anomaly. In the other four cases (one alobar, one semilobar, and two lobar), such facial anomaly was absent, and the diagnosis was achieved only after contrast studies.

An azygous anterior cerebral artery running over the cerebral surface due to a defective interhemispheric fissure is pathognomonic for alobar and semilobar holoprosencephaly. Dysgenesis of the deep venous system was found in alobar, semilobar, and lobar holoprosencephaly, a finding helpful in diagnosis, especially of the lobar type. Air study and computerized tomography scan revealed incomplete separation of the ventricular system. The basic nature of holoprosencephalization and its differentiation from non-holoprosencephalic malformation are discussed. Six of the seven patients reported had hydrocephalus.

KEY WORDS □9 hydrocephalus □9 anterior cerebral artery □9 cerebral ventricle □9 corpus callosum □9 azygous artery □9 cerebral vessels □9 cerebral malformation

The term "holoprosencephaly" was proposed by DeMyer and Zeman to indicate a group of cerebral malformations characterized by "the tendency for the prosencephalon to remain as a whole, as a simple vesicle incompletely transformed into a complex di- and telencephalon with lobes and hemispheres." The prosencephalon is one of the three primitive vesicles of the human brain. Subsequent development of the prosencephalon is made by diverticulation and cleavage. The olfactory, optic, and telencephalic vesicles diverticulate from the prosencephalon with simultaneous cleavage sagittally into the cerebral hemispheres as well as transversely into the telencephalon and the diencephalon. In holoprosencephaly, such diverticulation or cleavage is disturbed or arrested, and the patients retain various patterns of embryonic prosencephalon ranging from the undivided cerebrum with the monoventricle to a minor disturbance such as dysplasia of the olfactory bulbs or fusion of only the cingulate gyrus. Such disorders of varying degree were divided by DeMyer and Zeman into an alobar type (such as a monoventricular forebrain lacking interhemispheric fissure), a semilobar type (such as rudimentary cerebral lobes and a partially formed interhemispheric fissure in the posterior region), and a lobar type (in which the cerebral lobes and an interhemispheric fissure are fairly well formed, but a midline continuity of the frontal neocortex or a broader intraventricular communication still remains).
FIG. 1. Case 1. *Upper:* Plain skull film reveals a small frontal bone and marked hypotelorism. *Center:* Phlebogram of the right brachial angiogram. *Black arrows* show the draining vein runs laterally and is drained into the right lateral sinus (*white arrows*). *Lower Left:* Dorsal view of the brain. The dorsal sac extends anteriorly over the cerebrum (*arrows*). Most of the dorsal sac wall is torn off, but its remnant is shown by an *open arrow.* *Lower Right:* Coronal section of the brain. There is no interhemispheric fissure. The lateral ventricle is not divided, and forms a monoventricle.
Previously, most of holoprosencephaly was called "arhinencephaly;" however, DeMyer and Zeman and Yakovlev made it clear that, although the olfactory vesicles almost always fail to evaginate in holoprosencephaly, the resultant defect of the olfactory bulbs represent only a minor feature of the severe malformation of the prosencephalon. Moreover, some holoprosencephalic brains are reported to retain the olfactory bulbs. The term "arhinencephaly" has recently been replaced by "holoprosencephaly," which reflects better the basic feature of the entity. The term "arhinencephaly" should be reserved for its specific meaning, absence of the olfactory bulbs and tracts.

This communication reports the clinical and roentgenological features of seven patients with this entity, and reviews the previously reported cases for better understanding of this important group of cerebral malformations.

**Case Reports**

**Group I**

There were three patients in the first group, with facial dysmorphias characteristic of holoprosencephaly.

**Case 1.** A 1-day-old girl was transferred to Kobe University Hospital because of difficulty in feeding. Her mother experienced moderate vaginal bleeding at 3 months of pregnancy, and had to be hospitalized for 1 week. The baby was born at full term by an uneventful delivery.

On admission, her respiration was irregular and her cry was weak. The head was trigonocephalic and small with the flat anterior fontanel. The head transilluminated in the posterior third portion. The eyes were close-set, and bulged slightly. The nose and nasal bridge were flat. There were clefts of the upper lip and the palate. The extremities were somewhat spastic, but the patient moved them freely. Moro's and sucking reflexes could not be elicited. The rest of the physical examination was not remarkable.

An x-ray film of the skull showed a small frontal bone, a small anterior cranial fossa, and hypotelorism (Fig. 1 upper). Right brachial and left carotid angiograms were obtained at 1 month of age. There was only one anterior cerebral artery (azygous ACA). It did not curve normally along the corpus callosum, but ran along the frontal bone with excessive loops. The branches of the middle cerebral artery (MCA) seemed to come out directly from the bifurcation. There was only one thalamic image in the midline. From this fused thalamus, several small draining veins ran out posteriorly and were united into one large draining vein, which coursed to the right and drained into the elevated lateral sinus. The internal cerebral veins, the vein of Galen, the straight sinus, and the inferior sagittal sinus were not shown (Fig. 1 center). The appearance of the vertebrobasilar system was unremarkable.

For the first 2 months, the patient was kept in a constant-temperature environment since her temperature fluctuated and tended to be too low. She had to be fed by gavage. She had frequent convulsions affecting all extremities in spite of extensive anticonvulsant treatment. She failed to make any developmental progress and gained little weight during a hospital stay of 7 months. She died at the age of 7 months. Autopsy examination disclosed a typical holotelencephalon (Fig. 1 lower right). The olfactory bulbs and tract were absent. There was a large space (dorsal sac) between the cerebellum and the holotelencephalon. The dorsal sac communicated freely with the anteriorly situated monoventricle, and extended anteriorly over the partially divided cerebrum (Fig. 1 lower left).

**Case 2 and Case 3.** Both patients, a 1-month-old girl (Case 2) and a newborn boy (Case 3) had the facial anomaly as shown in Fig. 3 upper. In Case 2, the head was large with bulging fontanels at birth. In Case 3, the head was not large initially, but began to enlarge with full and tense anterior fontanel at 2 months of age. Other neurological and physical findings were similar to those in Case 1. The angiogram also revealed similar changes. An azygous ACA took an undulating course along the inner table of the frontal bone (Fig. 2 upper). The distal branches of the artery curved around the round avascular area. The horizontal portion of the MCA was very short. The branches spread in a fan-like manner in anteroposterior projection, and were distributed exclusively in the anterior half of the brain, leaving an avascular area in the posterior portion of the head. The inferior sagittal, and straight sinuses, and the internal
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FIG. 2. Case 2. Upper: Left carotid angiogram, anteroposterior (left) and lateral (right) views. The azygous anterior cerebral artery (arrows) runs along the frontal bone with excessive undulations. A round avascular area can be seen in the midline. Lower: Air ventriculography, anteroposterior view. A large round space in the midline communicates well with the monoventricle. This abnormal midline space is an anterior extension of the dorsal sac.

cerebral veins seemed to be absent. The thalamus and the internal cerebrum were drained by the peculiar veins as shown in Fig. 3 lower. In Case 2, pneumoencephalogram was tried, but failed since the air was caught in the cisterna magna and did not go up. Pneumoventriculography disclosed the monoventricle and a large space over the brain corresponding with the midline avascular area in the angiogram (Fig. 2 lower). In addition to it, a huge space was found behind the elevated lateral sinus and seemed to connect with the round space over the cerebrum. All these spaces communicated freely without any hindrance. Both patients were shunted for hydrocephalus, but they made no developmental progress, and died suddenly at the age of 7 months.

Comment. In these infants, the central nervous system revealed the changes typical of holoprosencephaly: undivided cerebral hemispheres, monolateral ventricle, absent olfactory bulbs, and the dorsal sac present behind the fused cerebrum. In addition to these changes, they had the facial dysmorphias characteristic of the entity. The angiograms of these patients were characterized by the azygous ACA coursing along the frontal bone and the peculiar malformation of the deep venous system. Alobar holoprosencephaly was our diagnosis for these patients. In Case 1, some trace of posterior lobe development was noticed, but we did not think the development was significant enough to classify the case as a semilobar type.
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**Fig. 3. Case 3.** *Upper:* Note the cleft lip, marked hypertelorism, and trigonocephalic head. *Lower:* Anteroposterior (left), and lateral (right) views of venous phase of the right brachial angiogram. Superior and inferior sagittal sinuses absent. The draining veins (arrows) from the cerebrum and the basal ganglions run laterally to the elevated lateral sinus.

**Group II**

There were two patients in the second group with extracranial extension of the dorsal sac.

**Case 4.** This 2-day-old boy was admitted because of frequent convulsions and a huge tumor extending from the mid-parietal region. His facial appearance was otherwise normal. He had had to be resuscitated at birth and his respiration was still irregular on admission. Right brachial angiogram revealed an azygous ACA which deviated to the right. The MCA group did not form the Sylvian triangle. The posterior inferior cerebellar artery could not be identified (Fig. 4 *upper left*). In the phlebogram, the sagittal sinus was off midline and curved around the midline mass. The thalamic draining vein coursed posteriorly and laterally to the elevated lateral sinus (Fig. 4 *upper center*). Pneumoencephalogram failed, and air was in-
FIG. 4. Case 4. Upper Left: Arterial phase of the right brachial angiogram. The anterior cerebral artery (arrows) runs just under the frontal bone. The middle cerebral artery complex does not form a Sylvian triangle. Upper Center: Phlebogram of the right brachial angiogram. The superior sagittal sinus is off midline, and curls around the midline cyst. Note the abnormal course of the draining vein from the thalamus (arrows). Upper Right: The cyst in the scalp was punctured and air was introduced. There is a broad communication between the scalp cyst and the monoventricle (the undivided lateral ventricle) in the cerebrum. Lower: Coronal section of the brain. The lateral ventricle is not divided, and the cyst (arrow) is extended upward from it. The thalamus is partially fused.

Introduced by puncture of the midline mass. It demonstrated free communication between the extracranial midline space and the lateral monoventricle (Fig. 4 upper right). The aqueduct was not visualized. Daily ventricular tap was necessary to relieve ventricular pressure, but the family eventually refused any further treatment and the baby died in convulsion 1 month later.

At autopsy the following findings were made: The interhemispheric fissure was found posteriorly, but the frontal lobes lay across the midline. Olfactory bulbs and tracts were absent. The thalamus was partially fused. The lateral ventricles formed a single cavity, from which a midline sac extended through the skull. The wall of the sac consisted of dense fibrous tissue. The aqueduct was closed. The cerebellum was hypoplastic, and the lower half of the vermis was absent. The fourth ventricle was huge and bulged out (Fig. 4 lower right).

Case 5. This 1-day-old boy was born also with a large bulging tumor in the mid-parietal region (Fig. 5). The tumor transilluminated well and became hard when the boy cried. Head circumference was 32 cm. The tumor became increasingly hard over the next few days. He became irritable, developed sun-set eyes, and vomited occasionally. The result of right brachial angiography is schematically presented in Fig. 5 right. An azygous ACA could be seen but its course was separated from the frontal bone. The inferior sagittal and the straight sinuses were not visualized, and the basal ganglions were drained by the abnormal veins. Computerized tomography
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Fig. 5. Case 5. Left: Photograph of the patient. Note the cystic mass extending from the mid-parietal region. Right: Schematic presentation of the angiographic findings. Upper: Arterial phase. Arrows point to the azygous anterior cerebral artery. Its course implies that an interhemispheric fissure is present in the frontal region. Lower: Venous phase. Arrows show the draining veins from the basal ganglia.

(CT) scan revealed incomplete separation of the ventricle and a large space in the mid-posterior region (Fig. 6 upper). After a ventriculoperitoneal shunt was placed, the extracranial mass was excised. The cyst communicated with the lateral ventricles. Microscopic examination of the cyst wall revealed collagenous fibers, numerous small vessels, and thinned nervous tissue (Fig. 6 lower). After the operations, the infant improved. At the age of 1½ months, his head control is almost normal, but he still does not follow moving objects with his eyes, and his reactions to his surroundings seem slow.

Comment. The holoprosencephalic changes in both patients are obvious with incomplete separation of the lateral ventricles. Dysgenesis of the deep venous system was also observed in both cases. However, the facial appearance was normal except for the midparietal bulging which was made by extracranial extension of the dorsal sac. Case 4 was diagnosed as having a semilobar type of holoprosencephaly, since the frontal lobe was fused but the posterior lobe and posterior horn of the lateral ventricle were developed. The course of the azygous ACA in Case 5 implied that an interhemispheric fissure had developed in the frontal lobe. Case 5 was diagnosed as a lobar type.

Group III

Two patients were in the third group, without apparent facial dysmorphia.

Case 6. It was noticed by the obstetrician that this baby already had an extremely large...
Case 5. This 8-month-old newborn was admitted because of frequent vomiting and steady increase in head size. The patient was delivered at full term by Caesarean section. The head circumference was 50 cm and the head transilluminated except for its anterior portion. The baby’s face was normal except for rather wide interorbital distance. Immediately after birth, a ventricular tap was performed, and about 100 cc of xanthochromic fluid was removed. After the ventricular tap, the baby cried weakly. Birth weight was 4180 gm but his body was rather small, implying that much of the excessive weight was due to the abnormal amount of ventricular fluid. After a ventriculoperitoneal shunt was placed, he improved, but his head was deformed by severe decrease in its anteroposterior diameter. An angiogram at the age of 4 months revealed an abnormal azygous ACA (Fig. 7 upper); a diagnosis of holoprosencephaly was made from the angiograms, and later the diagnosis of alobar holoprosencephaly was established by CT scan, which revealed a monoventricle (Fig. 7 lower).

At 1 year old the patient’s head control is still poor. He does not follow moving objects with his eyes. He lies immobile, and does not pay any attention to his surroundings.

Case 7. This 2-week-old baby girl was admitted because of frequent vomiting and steady increase in head size. Her head circumference was 38 cm at birth, and increased to 44.5 cm in 2 weeks. Examination revealed a large head with prominent bulging in the occiput, bulging anterior fontanel, and widely split cranial sutures. The head transilluminated easily in the posterior third portion. Her facial appearance was normal except for a rather wide, flat nose. A ventriculoperitoneal shunt was placed as an emergency procedure. Later, at the age of 4 months, she was readmitted for further examination.

Left carotid and left brachial angiograms were performed. Both ACA’s were present; they were widely separated in their A2 portions but followed a normal course along the frontal bone. In the posterior circulation, the cerebellum was small and a large avascular area was present inferoposterior to the elevated lateral sinus. The inferior sagittal and straight sinuses were absent. Two separated thalamic images were observed. The draining vein from the thalamus coursed laterally and drained into the elevated lateral sinus (Fig. 8 upper). Pneumoencephalography failed since air was trapped in the cisterna magna. Ventriculography by a cisternal puncture disclosed a large interhemispheric space that extended to the inner table of the skull (Fig. 8 lower). The air bubbles moved freely from side to side, and from the lateral ventricles to the midline space. There was an abnormal space, containing fluid, inferoposterior to the elevated lateral sinus (Fig. 8 lower right). It communicated freely with the interhemispheric midline space. When the child was 1½ years of age, a CT scan showed the presence of an interhemispheric fissure, broad intraventricular communication, and an abnormal midline space extending upward and backward (Fig. 9). The abnormal posterior space behind the elevated lateral sinus shown...
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Fig. 7. Case 6. Upper: Left carotid arteriogram, anteroposterior view (left), and lateral view (right). Note the azygous anterior cerebral artery (arrows) which courses abnormally along the frontal bone. Lower: Computerized tomography scans. The lateral ventricles are undivided and an interhemispheric fissure is not seen.

by ventriculography should probably be the posteroinferior extension of the midline space.

Since the shunt was placed, she has done well except for occasional convulsions. At 2 years old, her development is greatly retarded. She smiles at her mother, but she cannot sit up by herself. She does not say words, nor does she seem to understand any.

Comment. The patient in Case 6 did not have the facial characteristics of holoprosencephaly, but his cerebral malformation was of the severest degree, alobar type. In Case 7, differentiation of frontal, temporal, and posterior horns can be discerned, although it is very incomplete. Interhemispheric fissure is present. The large midline space is probably the remnant of the dorsal sac. The dorsal sac extends posteriorly, mimicking the feature of Dandy-Walker cyst. The case was the lobar type of holoprosencephaly.

Discussion

Ventricular Configuration and Definition of Holoprosencephaly

In alobar holoprosencephaly, the brain contains a large, fluid-filled space, called a "dorsal sac"1,2,3,4,5 (Fig. 10). The dorsal sac lies in the space from the free posterior margin of the pallium to the prepineal region.1,2,3,4,5 The origin of this dorsal sac is controversial; it has been attributed to the expanded velum transversum,4 the paraphyseal arch,5 the diencephalic tela choroidea,6 and a combination of di- and telencephalic roof,7 in which case the cavity within the dorsal sac should be analogous to the diencephalic ven-
FIG. 8. Case 7. Anteroposterior (left) and lateral (right) views. *Upper:* Phlebogram of the right carotid angiogram. The inferior sagittal sinus, the internal cerebral veins, the vein of Galen, and the straight sinus are not visualized. The basal ganglia are drained by an abnormal vein (arrows) that runs to the side and drains directly into the elevated lateral sinus. *Lower:* Ventriculography. The lateral ventricles are partially separated. There is a huge space (DS) extending to the inner table of the skull. This midline space freely communicates with the lateral ventricles, and should be the counterpart of the dorsal sac in alobar holoprosencephaly. There is another large space in the occipital region (PS). This space also communicated well with the lateral ventricles.

FIG. 9. Case 7. Computerized tomography scans reveal an interhemispheric fissure (arrow), broader interventricular communication, and a large midline space extending upward and backward. The findings imply that the large space in the occipital region (PS) shown in Fig. 8 lower right should be the posterior extension of the midline space (dorsal sac).
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tricle or to a combination of both tel- and diencephalic ventricle. In less severe types (semilobar and lobar holoprosencephaly), the cerebrum is better formed posterolateral to the dorsal sac, and the remaining dorsal sac appears as an "interhemispheric cyst" as seen in our Cases 4, 5, and 7 (Figs. 11 and 12). In these cases, interventricular communication remains much broader due to incomplete "diverticulation" of the telencephalic vesicle. The remnant of the dorsal sac may protrude extracranially as in our Cases 4 and 5. The protruded extracranial cyst is actually part of the ventricular system, and should not be mistaken for an ordinary meningocele. The dorsal sac may extend posteriorly, sometimes over the cerebellum, thus resulting in abnormal transillumination of the posterior skull. Previously, "holoprosencephalization" of lesser severity, as represented by our Cases 4, 5, and 7, has not been well understood, and most cases have been reported as agenesis of the corpus callosum, agenesis of the corpus callosum with interhemispheric cyst, primary interhemispheric cyst of Probst, diencephalic cyst of Brocklehurst, hydroencephalodysplasia, primary interhemispheric cyst or just cerebral malformation. All these cases had a midline cyst and ventricular configuration similar to our semilobar and lobar holoprosencephaly, and meet DeMyer and Zeman's definition of holoprosencephaly. Such "primary interhemispheric cyst" or "diencephalic cyst" should be regarded as the remnant of the dorsal sac of alobar holoprosencephaly. Actually Swett and Nixon reported that Brocklehurst's patient with "diencephalic cyst" was found at autopsy to have a lobar holoprosencephaly defect of the olfactory bulbs and nerves. Holoprosencephaly may be included

Fig. 11. Diagram showing the configuration of the supratentorial ventricular system in four of our patients.
in “hydroencephalodysplasia,” but such a vague diagnostic term should be avoided when a more specific diagnosis, holoprosencephaly, can be made.

The corpus callosum is defective in almost all holoprosencephalic brains. But we agree with DeMyer and Zeman that agenesis of corpus callosum itself is not necessarily a feature of holoprosencephalization, and that absence of the corpus callosum alone does not warrant the diagnosis of holoprosencephaly, unless it accompanies other features reflecting incomplete cleavage or diverticulation of the prosencephalon. Holoprosencephaly is a disorder induced in embryonic stages (earlier than 60 days after gestation), and their essential features become apparent as early as Streeter's Horizon XVI (approximately 40 days after gestation), whereas the corpus callosum is formed from about 70 to 120 days of gestational age, and its absence is attributed to the disturbance of the lamina reunion in the anterior wall of the third ventricle. Before formation of the corpus callosum begins, diverticulation and cleavage of the prosencephalon has been mostly accomplished with anteroinferior infolding of the diencephalic roof and appearance of the falx cerebri. Therefore, in simple agenesis of the corpus callosum, the diencephalic roof is folded deep in the interhemispheric fissure and the cerebral falx is well developed, although the diencephalic roof may be mildly elevated as the result of a defective corpus callosum (Fig. 12). In some occasions, however, the once in-folded diencephalic roof may be pushed up again through the defective corpus callosum due to hydrocephalus, and may form a huge interhemispheric cyst. Such cases are reported by Loeser and Alvord (Cases 1 and 3), and Probst (Cases 3, 5, 6, 8, and 23).
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called the condition “secondary interhemispheric cyst.” In cases of secondary elevation of the diencephalic roof, there is a well formed cerebral falx, which indents the bulging diencephalic roof (Fig. 12). This condition should not be confused with lobar holoprosencephaly, where the diencephalic roof has never been folded in and the cerebral falx is defective.

A still milder form of holoprosencephaly has been reported in the literature. There is no remnant of the dorsal sac as an interhemispheric cyst, and the cerebral configuration is grossly normal except for dysplasia of the olfactory tracts or fusion of only the cingulate gyrus, with or without aplasia of the corpus callosum. Such a trivial malformation is also included in DeMyer’s “lobar holoprosencephaly.” In the present communication, these minor disturbances are called “abortive holoprosencephaly,” and the term “lobar holoprosencephaly” has been limited to those cases in which the dorsal sac is retained as a large interhemispheric cyst.

DeMyer and Zeman claimed that when aplasia or hypoplasia of the corpus callosum is associated with midline continuity of frontal neocortex (“abortive holoprosencephaly” in our definition), the pneumoencephalogram will reveal a broader communication between the ventricles, and a flatter ventricular roof instead of bicornuate or butterfly appearance characteristic of simple agenesis of the corpus callosum. However, further experience is necessary before accepting DeMyer and Zeman’s criteria for abortive holoprosencephaly, since the reported cases are scarce and most of them were diagnosed at autopsy.

Vascular Changes

The most conspicuous finding of the angiogram is the azygous ACA, which courses just beneath the inner table of the skull with excessive undulation. This finding implies fusion of the frontal neocortex and absence of the interhemispheric fissure. Anterior cerebral arteries emerge from the midline vascular network on the prosencephalon. With the failure of midline cleavage of the telencephalon, the ACA’s also tend to fail to separate, and the single ACA runs over the cerebrum without being folded deep in the interhemispheric fissure. Azygous ACA’s are reported in other conditions, but they never take such an abnormal course. The presence of this peculiar azygous ACA is pathognomonic of alobar or semilobar holoprosencephaly.

The horizontal portion of the MCA (M1) is absent or very short, and the branches seem to come out directly from the bifurcation in alobar and semilobar holoprosencephaly. Failure to form the Sylvian triangle by the MCA group suggests maldevelopment of the temporal lobe. If there is only one thalamic image in anteroposterior view, it implies that the thalamus is fused or incompletely separated.

In venograms, the superior sagittal sinus is often dysgenetic and composed of a network of the large veins. When it is developed, it may lie off the midline, or go around the protruded dorsal sac. The changes of the deep venous system are most important. The basal ganglia and the internal cerebrum are drained by the abnormal veins that course laterally and are drained into the lateral sinus. The internal cerebral veins, the great vein of Galen, the straight sinus, and the inferior sagittal sinus seem to be deficient. This unusual venous drainage resembles the embryonic pattern.

According to Padget, the diencephalon in the embryonic period is not drained by the internal cerebral veins, but by the embryonic dorsal and ventral diencephalic veins. The diencephalic veins course laterally and drain into the tentorial sinus. The tentorial sinus runs posteriorly to join with the lateral sinus. The primitive internal cerebral veins are the continuation of the prominent superior choroid veins that drain the voluminous choroid plexus. In the embryo and early fetus, the primitive Galenic system is situated extracerebrally and lies in dorsal contact with the epithelial diencephalic roof. The Galenic system does not fulfill its final role of draining parts of the internal brain until the veins are later enclosed within the brain in response to the relatively great increase in the substance of the cerebral hemisphere. In alobar to lobar holoprosencephaly, the diencephalic roof is never folded deep in the interhemispheric fissure, and the Galenic venous system would probably not be developed. The abnormal deep draining veins from the basal ganglia may be interpreted as remnants of the embryonic diencephalic veins. Such dysgenesis
TABLE 1
Incidence of hydrocephalus in relation to the degree of holoprosencephalic changes and facial anomaly*

<table>
<thead>
<tr>
<th>Facial Anomaly</th>
<th>Degree of Holoprosencephalic Changes</th>
<th>Total</th>
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<tbody>
<tr>
<td></td>
<td>Alobar</td>
<td>Semilobar</td>
</tr>
<tr>
<td>present</td>
<td>38 (7)†</td>
<td>5 (0)‡</td>
</tr>
<tr>
<td>absent</td>
<td>4 (2)</td>
<td></td>
</tr>
<tr>
<td>total</td>
<td>42 (9)</td>
<td>16 (4)</td>
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</table>

*Facial anomaly means cleft lip or palate; milder anomalies are not included. The number of hydrocephalic patients is shown in parentheses.
†References 2, 5, 6 (Cases 15, 17), 11 (Cases 1–3), 13 (Case III 6), 15 (Cases 2, 3), 18, 19, 24 (Case 2), 30, 31, 33, 38 (Cases 1–4), 39, 46 (Cases 1, 2), 63 (Case 1), 70 (Case 163), 75 (Cases 1–9), 78 (Case 1), and present Cases 1–3.
‡References 6 (Case 14), 8, 23, 38 (Cases 5, 6).
§References 6 (Cases 8, 11, 13), 63 (Case 2).
||References 29 (Case 2), 34, 43 (Case 2), and present Case 6.
**References 3 (Case 4), 9 (Case 1), 27 (Case 6), 29 (Cases 3, 4), 35 (Case 1), 40 (Case 4), 43, (Case 1), 52, 75 (Case 10), and present Case 4.
††References 3 (Cases 1–3), 14, 17, 21, 22 (Case 5), 26, 27 (Case 2), 45 (Case 12), 48, 51 (Cases 1, 2), 65 (Cases 1, 2, 4, 6, 7, 10), 73 (Cases 1–5), 76, and present Cases 5, 7.
‡‡References 1, 16, 25, 28, 32, 50, 53, 69 (Cases 2, 3), 71, 77 (Case 1).

of the deep venous system has never been reported, but this feature seems helpful in the diagnosis of lobar holoprosencephaly in which the arterial phase does not reveal the characteristic azygous ACA 69 (see our Cases 5 and 7). The finding is also helpful to distinguish lobar holoprosencephaly from simple agenesis of the corpus callosum, or secondary interhemispheric cyst. In the latter cases, the deep venous system is well developed, although it may be deviated by the anomalous position of the third ventricle. 67,68 However, we should not forget that presence of a well developed deep venous system will not preclude the possibility that the case might be one of abortive holoprosencephaly.

Facial Appearance of the Patients
Holoprosencephaly is known to be associated with numerous nasolabial malformations such as probiosis, hypo- or hypertelorism, and clefting of the lip or palate. This association of median facial anomalies is explained by the close interrelationship between the rostral neural tube and the prechordal mesoderm in their early embryonic development. 12,46 Pecordial mesoderm gives rise to nose, mouth, and lip. DeMyer, et al.,12 emphasized that the type of brain malformation can be predicted by the facial malformation, with the general rule that as the face approaches to normal, so does the brain. But this face-brain correlation seems to be overemphasized. As these authors themselves stated, the face-brain correlation does not hold true in the category of lesser severity, and facial defects associated with semilobar and lobar holoprosencephaly are poorly documented. Many patients with holoprosencephaly are free of apparent facial anomalies, as in our Cases 4 to 7. In these patients, occasional presence of hypertelorism may suggest the abnormality, but contrast studies are still the only way to establish the diagnosis.

Importance of Holoprosencephaly in Neurosurgical Practice
Hydrocephalus was present in six of seven cases in our series. Two cases were referred to our clinic because of hydrocephalus, but the other five patients were transferred from the pediatric department of our university. No other case of holoprosencephaly was recorded in the pediatric department during the 5 years that this study was in progress. During the same period, we received 62 congenital hydrocephalus cases including 16 meningo-myelocele, 14 cerebral malformations other than holoprosencephaly, and 26 of simple
congenital hydrocephalus (aqueductal stenosis included). Six holoprosencephalic patients comprised about 10% of the total number of congenital hydrocephalus cases in our clinic. Many similar cases are reported from other clinics in Japan.\textsuperscript{19,22,27,46,51,76} Two cases reported as hydroencephalodysplasia by Kaneko, et al.\textsuperscript{27} were probably holoprosencephaly; those cases represented approximately 4% of the incidence of congenital hydrocephalus in their clinic.

The ratio of holoprosencephaly in total congenital hydrocephalus in Japan may be higher than elsewhere, since we saw no similar cases while at Children's Memorial Hospital, Chicago, where we saw about 200 patients with congenital hydrocephalus. Nevertheless, many Caucasian hydrocephalic patients with holoprosencephaly have been reported.\textsuperscript{3,17,20,27,46,73,75} Table 1 summarizes the incidence of hydrocephalus in 100 cases of holoprosencephaly, including our seven cases. The data were not complete in all cases, so the review might be subject to criticism, especially with regard to our type classification of holoprosencephaly. The review showed that hydrocephalus is not prevalent in patients with apparent facial dysmorphias, whereas it is common without the facial stigmata. Hydrocephalus is not prevalent in alobar holoprosencephaly, but it is common in the semilobar, and is almost always present in the lobar type of holoprosencephaly. The extremely high incidence of hydrocephalus in lobar holoprosencephaly may have resulted from the fact that only those with suspected hydrocephalus received contrast studies and were diagnosed as such. However Probst's report\textsuperscript{85} suggests that hydrocephalus is really common in this group. In his extensive study on 50 patients with callosal defect, five patients with "primary interhemispheric cyst" were all hydrocephalic, whereas only five of 45 patients with non-holoprosencephalic callosal defects were hydrocephalic. Hydrocephalus in the abortive type seems rare, but its incidence in this review is not very reliable since the collected cases are few and most of them are in adult patients found at autopsy.

The patients with alobar and semilobar holoprosencephaly are hopelessly demented and usually succumb in infancy or early childhood. For these patients, the conservative approach for hydrocephalus may be justified. The outcome of lobar type does not seem so gloomy. Some patients are reported to exhibit little or no neurological deficit,\textsuperscript{3,17,70} although most patients manifest severe-to-moderate mental retardation.\textsuperscript{3,46,51,58,73} Surgical correction of hydrocephalus should be performed in this group. We prefer to perform the operation by Raimondi's method with minimal sedation,\textsuperscript{67} since these patients sometimes seem to develop an unpredictable reaction to general anesthesia.

Conclusions

Holoprosencephaly, a cerebral anomaly complex retaining embryonic features of prosencephalon of various kinds and severity, is often accompanied by hydrocephalus, requiring surgical intervention. Lobar holoprosencephaly is especially important in neurosurgical practice, since patients usually have hydrocephalus and the prognosis does not seem so desperate.

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