Brain pathology following fetal vascular occlusion: An experimental study

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The Laboratory of Perinatal Physiology received a remarkable monkey brain specimen in 1964 from a group at the Oregon Regional Primate Research Center who had been investigating the effects of chronic anemia on the in utero development of the monkey fetus.* These investigators had ligated the common carotid artery and the jugular vein bilaterally in the neck of a monkey fetus at 84 days of gestational age during the cannulation of these vessels for the recording of fetal blood pressures and the withdrawal of fetal blood samples. Over many hours blood was withdrawn from this fetus until its hematocrit had dropped from 42 per cent to a low of 18 per cent. The fetus was returned to the uterus and sustained there until its spontaneous vaginal delivery at an estimated gestational age of 163 days—a term infant. Despite its fully developed appearance, the infant was stillborn. However, it gave no evidence of tissue maceration or postmortem change. Clearly, the infant had continued its development in utero and had survived until the time of delivery.

On postmortem examination, the fetal head was fully developed and of normal conformation. On opening the calvarium, a large quantity of clear fluid spilled out. The cerebral hemispheres, themselves, appeared as thin membranous sacs which collapsed allowing escape of the cerebrospinal fluid. Nevertheless, when filled with fluid, the over-all size and outline of the brain was within normal limits. The appearance of the brain of this animal following its removal may be seen from Fig. 1. On examination, the hemisphere walls in the areas of supply of the anterior and middle cerebral arteries were reduced to paper-thin transparent membranes. In the supply areas of the posterior cerebral arteries, which include the occipital and inferior portions of the temporal lobes, there was a greater preservation of the cerebral tissue with, however, a considerable reduction in its thickness. The best preserved portions of the hemispheres were the tips of the temporal lobes bilaterally. In the areas of better cortex preservation, the fissurational patterning was still considerably effaced with the cortical surface appearing smoothened with, however, a certain appearance of corrugation along its extent.

*This group included Drs. Karlis Adamsons and L. Stanley James of Columbia University, New York, Jerald F. Lucey of the University of Vermont School of Medicine, and Molly Towell of the University of British Columbia School of Medicine.
Fig. 1. Hydranencephaly following bilateral carotid artery and jugular vein ligation in the neck of a rhesus monkey fetus of 84 to 86 days of gestational age. The regions of supply of the anterior and middle cerebral arteries are reduced to thin transparent membranes. Better preserved are the supply areas of the posterior cerebral arteries. The basilar artery exhibits mild enlargement and some tortuosity. The reduction of major portions of both hemispheres to thin-walled sacs is particularly well illustrated in the lower, cross-sectional view.

The thalamus and basal ganglia were reduced in size and distorted in development due to destructive changes. The brainstem and cerebellum, on the other hand, appeared unremarkable except for a diminished prominence of the basilar pons and of the pyramids.

The pattern of destruction and the gross appearance of this brain is closely similar to that of hydranencephaly as it occurs in man. Because of the special interest and importance of this relatively uncommon pattern of brain pathology in the human being, further studies were carried out in the Laboratory of Perinatal Physiology, in San Juan, Puerto Rico, investigating the implications of the ligation of the major vessels in the neck during fetal development. The following description outlines some of the early and tentative conclusions drawn from this study.

In the NINDB investigation to date 28 monkey fetuses have been surgically removed from the uterus, subjected to bilateral ligation of the carotid artery and jugular vein in the neck, and returned to the uterus for completion of gestation. Fig. 2 illustrates the nature of this procedure. As detailed in Table I, one of several consequences resulted from these procedures: (1) The infants' brains, with continued development to term, may exhibit no abnormalities on gross or microscopic examination. (2) Abnormalities in fissurational patterning may be noted with or without over-all gross changes in conformation of the cerebrum. (3) Tissue destructive changes may occur with infarction of widespread areas of the cerebrum. (4) Finally, in a proportion of cases, fetal death may occur in relation to the procedures.

Although these results are preliminary and numbers of cases are few, the following general conclusions are suggested by the data: Bilateral carotid artery and jugular vein ligation early in gestation (prior to 90 days) tends to result in cerebral dysgenesis, severe cerebral destruction, or fetal death. During a later period in pregnancy (90 to 110 gestational days of 168), ligation results in the larger number of infants exhibiting either cerebral destructive changes or fetal death. Observation of the over-all results suggests that the earlier the procedure is carried out during pregnancy, the greater is the probability of a cerebral dysgenetic outcome. Contrariwise, the later in pregnancy the procedure is carried out, the more likely there will be no demonstrable clinical or neuropathological effect. Both cerebral dysgenetic and cerebral destructive lesions are uncommon
Fig. 2. The left carotid artery undergoing ligation in a 74 day monkey fetus. The rhesus monkey fetus may be completely removed from the uterus while its attachment to the placenta through the umbilical cord is carefully maintained. A variety of surgical procedures and experimental manipulations may be carried out on such exteriorized fetuses. With careful sterile techniques and with maintenance of the fetus in a warm and moist condition, many interventions may be successfully accomplished with return of the fetus to the uterus and continuation of pregnancy to term.

Table I. Brain pathological outcome of bilateral carotid artery and jugular vein ligation in 28 monkey fetuses ranked according to gestational age at manipulation

<table>
<thead>
<tr>
<th>Gestational age (days)</th>
<th>No. of cases</th>
<th>% no change</th>
<th>% cerebral dysgenesis</th>
<th>% cerebral destruction</th>
<th>% death</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>7</td>
<td>0</td>
<td>29 (2)*</td>
<td>14 (1)</td>
<td>57 (4)</td>
</tr>
<tr>
<td>70-90</td>
<td>9</td>
<td>0</td>
<td>11 (1)</td>
<td>56 (5)</td>
<td>33 (3)</td>
</tr>
<tr>
<td>90-110</td>
<td>8</td>
<td>12 (1)</td>
<td>0</td>
<td>38 (3)</td>
<td>50 (4)</td>
</tr>
<tr>
<td>110-130</td>
<td>3</td>
<td>66 (2)</td>
<td>0</td>
<td>0</td>
<td>33 (1)</td>
</tr>
<tr>
<td>130</td>
<td>1</td>
<td>100 (1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Numerals in parentheses represent absolute numbers of cases in each category.

in infants subjected to vascular ligation during the latter portion of pregnancy. The category of fetal death must be viewed as somewhat ambiguous since death is likely produced by causes other than the ligation of the vessels itself, particularly when the technical difficulties of the surgical procedure itself are considered.

Cerebral dysgenesis

Two degrees of cerebral dysgenesis or brain malformation are seen in the present study. Interestingly, the magnitude of cerebral dysgenesis appears to be a function of the gestational age of the fetus at the time of vascular ligation. Fig. 3 portrays a more severely dysgenetic brain along
Fig. 3. Marked cerebral dysgenesis resulting from bilateral carotid artery and jugular vein ligation at a gestational age of 65 days. Below, for comparison, is the brain of a normal animal of the same age photographed at the same magnification.

with the brain of a normal animal of the same age for comparison. The experimental animal sustained ligation of the major vessels in the neck at a gestational age of 65 days. On examination on later delivery at term, the brain of this animal exhibits a considerable shortening in anteroposterior dimension and a concomitant increase in height. The temporal and occipital lobes are both particularly short and stubby while the former presents an increase in its angulation from the horizontal. The over-all patterning of the convolutions is generally preserved, but the convolutions themselves tend to be shortened in length and increased in width. The secondary and tertiary gyral folds exist in greater profusion. Despite the considerable distortion in over-all conformation, this brain weighs within the normal range. On gross or microscopic examination, this brain fails to reveal any evidence of focal destructive lesions within the hemispheres or anywhere throughout its extent. A second brain of this same type was seen in the present experiment.

A lesser degree of cerebral dysgenesis appears following ligation at a somewhat later gestational age as shown in Fig. 4. Monkey No. 902 with bilateral common carotid artery and jugular vein ligation at 83 days exhibits a configuration of the gyri, suggesting an abnormality in development. The alterations in gyrational pattern in this brain appear primarily in the prefrontal lobes where the sulcus principalis joins posteriorly with the inferior ramus of the arcuate sulcus. The superior ramus of

Fig. 4. Right and left lateral views of monkey No. 902 illustrating an unusual patterning of the convolutions in the anterior portions of the frontal lobes bilaterally.
the arcuate sulcus is absent on both sides. Lesser alterations in gyral pattern occur in other lobes as well in this brain. The deviations from the usual sulcal pattern exhibited by this brain appear to be greater than that which might be expected for the brain to be considered normal. Despite the probable abnormalities in gyral patterning, the hemispheres of this brain preserve a normal conformation. This monkey also displays multiple zones of focal destruction in the thalamus and in the hemispheric white matter bilaterally.

The brain of another monkey not included in Table I also exhibits abnormalities in convolutional patterning as seen in Fig. 5. This animal had been subjected to bilateral carotid artery and jugular vein ligation at 103 days of gestational age but had sustained, in addition, an episode of acute anoxic insult produced by manually compressing and occluding the umbilical cord for 30 minutes. This brain exhibits a considerable distortion of the patterning of the central fissures bilaterally, particularly in the parasaggital regions. In addition to fissurational disarrangement, the brain of this animal exhibits foci of destructive change in the cortex of the depths of sulci in widely scattered regions, but again most pronounced in the paracentral area. The thalamus shows significant distortions in the patterning of its nuclear masses, but without focal lesions. The over-all conformations of the hemispheres are normal.

These latter two cases suggest that more subtle distortions or alterations in the over-all configuration of the fissures and sulci may occur without associated gross distortions in the shape of the cerebrum. Curiously, in these two cases, but not in the more severe cases earlier described, focal lesions are also found in the subcortical regions or in the white matter.

Cerebral destructive changes

The proportion of animals surviving vascular ligation which exhibit dysgenetic effects is in the minority or nonexistent in all groups except those manipulated earlier than 70 days. When vascular ligation is carried out between 70 to 110 days, the greatest number of animals exhibit destructive changes within the brain. Tissue de-
Fig. 6. Two examples of tissue necrosis with scarring in the regions of supply of the anterior and middle cerebral arteries following major vessel ligation in the neck.

Fig. 7. Unequal distribution of infarction in the two hemispheres of monkey No. 1161 related to difference in regions of supply of the posterior cerebral arteries.

Variations in extent and distribution of necrosis and scarring are more usually found to reflect variations in the regions of supply of the cerebral arteries involved. For example, monkey No. 1161, illustrated in Fig. 7, exhibits inequality in the distribution of infarction of the two hemispheres occurring after bilateral carotid artery and jugular vein ligation is distributed in the region of supply of the anterior and middle cerebral arteries. This pattern of damage is illustrated in Fig. 6. Monkey No. 1184 underwent the operation at a gestational age of 78 days and monkey No. 1187 at 105 days. Monkey No. 1184 exhibits tissue necrosis with collapse and scarring encompassing the entire supply area of the anterior and middle cerebral artery. The remaining cortex exhibits gross distortion in its conformation along with a considerable thinning. Monkey No. 1187, by contrast, reveals tissue destruction with scar formation in a region smaller than that anticipated from the area of supply of the anterior and middle cerebral arteries. Blood vessel dissection fails to clarify the reasons for the marked differences in extent of tissue destruction in these 2 animals. The smaller territory of tissue destruction in monkey No. 1187 may be due to more adequate anastomotic links between the territories of the posterior cerebral arteries and the terminal vessels of the anterior and middle cerebral arteries in later gestational stages.
following vascular ligation at 103 days of gestational age. The left hemisphere of this animal appears totally infarcted. However, the inferior temporal convolution and the tip of the temporal lobe on this side are well preserved but not visible in this illustration. The right hemisphere, on the other hand, exhibits infarction in the usual supply area of the anterior and middle cerebral artery. As always occurs in such circumstances, there is an expansion with considerable distortion in the conformation of the remaining viable tissue which is much flattened, thinned, and displaced forward into the anterior portions of the cranial cavity. Despite outward appearances, only a small proportion of the total mass of the right hemisphere in this animal remains preserved. The differences in distribution of infarction in the two hemispheres in this case relate to differences in the regions of supply of the two posterior cerebral arteries as was clearly demonstrated on dissection of these vessels.

The animals which sustain gross areas of tissue infarction with tissue collapse and scarring also exhibit considerable distortions in shape of the skull involving primarily the calvarium. There occurs a considerable reduction in height of the cranial vault.
while its anteroposterior measurement is less affected. Fig. 8 illustrates these changes in skull appearance. Significant changes which occur in the scheduling of tooth development and in their shapes will be described later (Krause and Myers).

The above pattern of brain tissue destruction associated with regional collapse and scarring represents only one type of destructive change. A second type also may be seen as reference to Fig. 1 makes clear. Consideration of this and of several other cases within the present series suggests that tissue destructive processes, particularly when they occur earlier in fetal development, may result in liquefaction necrosis. When liquefaction necrosis occurs, there may be complete removal and replacement of the zone of destruction such that there remains only a fluid-filled cavity bounded by a thin-walled membrane. The brain illustrated in Fig. 9, for example, represents a likely stage in the sequence of tissue changes which may lead to the reduction of an area of tissue destruction to a fluid-filled cavity. Monkey No. 1077 sustained bilateral ligation of the carotid arteries and jugular veins in the neck on the seventy-second day of gestation. Eight days later this baby was delivered by cesarean section to determine the short-term effects on the brain tissue of the acute vascular occlusion. As may be seen, the area of supply of the anterior and middle cerebral artery in this animal after the short-term survival exhibited liquefaction necrosis bilaterally with a total dissolution of the area of prior tissue substance. Only flocculent necrotic tissue debris was seen floating in the fluid-filled zone of tissue death. Note the intact preservation of tissue in the area of supply of the posterior cerebral artery bilaterally. The brain depicted in Fig. 10 illustrates the end stages in the removal of necrotic tissue with conversion of the area of destruction after longer survival to a thin transparent membrane. Portions of the thalamus and of hippocampus may be clearly seen through the preserved transparent membranes. Intact but distorted are the brain areas supplied by the posterior cerebral arteries. In many ways, the brain pathological pattern exhibited by monkey No. 1109 represents a *forme fruste* of hydranencephaly.

Thus, when the major vessels in the neck directly supplying the forward reaches of the cerebrum undergo ligation in the neck during development, two general types of tissue destructive processes may become evident. In one circumstance there occurs a liquefaction necrosis of large areas of tissue with disappearance and removal of the necrotic tissue and conversion of the zone into a fluid-filled cavity in continuity with the ventricular system surrounded by a thin transparent membrane. In the other circumstance an area of tissue necrosis or destruction obtains. The area of tissue

![Image](image-url)
necrosis undergoes subsequent collapse and organization with the production of a fixed area of tissue scarring.

Vascular changes

One of the curious and unexpected results of the ligation of the major vessels in the neck, particularly when carried out during the earlier stages of development, is the appearance of marked enlargement and tortuosity of the vertebral and basilar arteries (see Fig. 11). Of course, the vertebral-basilar arterial complex represents the major alternate pathway for the supply of blood to the anterior cerebrum following occlusion of the more directly supplying bilateral carotid arterial systems. It is the presumed increase in volume flow through the vertebral-basilar system supplying its usual area of distribution plus that anteriorly through anastomotic channels that likely results in its enlargement and the development of tortuosity. It is not known whether there occurs a concomitant increase in blood pressure in this system.

The basilar artery in the monkey bifurcates at the rostral end of the pons in the region of the interpeduncular space into

Fig. 11. Appearance of the vertebral-basilar artery complex in monkey No. 1182 at term after bilateral carotid artery and jugular vein ligation on the seventy-ninth gestational day. Note the enlargement of these vessels and their striking tortuosity. This general appearance characterized the majority of animals in this series after prolonged survival.
two main vessels. These, in the vast majority of cases, directly form the two posterior cerebral arteries. This pattern is of more frequent and constant occurrence in the monkey than in man where the posterior cerebral artery origins are quite variable between the vertebral-basilar and the carotid artery systems. This greater uniformity of vascular pattern in the monkey accounts for the surprising symmetry, generally speaking, in the extent of cerebral destruction in the two hemispheres following cervical vascular ligation.

Significance

The lesion types described in the present paper including cerebral dysgenesis, hydranencephaly, and gross cerebral infarction with scarring each have counterparts in the altered brains of damaged human babies. It appears likely from the present study that these patterns, as they obtain in the human being, follow damaging events occurring early in pregnancy of an anoxic-vascular nature.

The appearance of patterns of severe cerebral dysgenesis following vascular ligation is of great importance. Such brains, exhibiting no evidence of focal destructive lesions and preserving a normal weight, closely resemble the brains found in a proportion of children who exhibit severe mental retardation. The brains of these children also may exhibit severe cerebral dysgenesis including an over-all change in cerebral conformation, a shortening of the cerebral lobes, and an increased angulation of the temporal lobe. These brains additionally may exhibit abnormalities in fissurational patterning. They commonly may exhibit no signs of focal lesions. The cause for such cerebral dysgenesis without focal lesions in the human has remained a puzzle to those who have concerned themselves with the pathogenesis of the various patterns of brain change in mental retardation. The absence of focal lesions in such brains has, generally speaking, discouraged the interpretation of an anoxic-vascular basis for their altered development. Studies of family background in most such cases have, on the other hand, failed to suggest a hereditary basis for the cerebral maldevelopment. The present study suggests that this pattern of brain change may result from anoxic-vascular insults even though such brains fail to exhibit the type of focal lesions which are commonly associated with anoxic or vascular insults.

Summary

A series of monkey fetuses were subjected to bilateral ligation of the carotid arteries and jugular veins in the neck at different gestational ages. These animals were then restored to the uterus and brought to term. Examination of the effects on brain morphology indicates that: (1) Hydranencephaly may result from such vascular ligation particularly when carried out during earlier gestational ages. (2) Bilateral cerebral infarction may result in the areas of supply of the anterior and middle cerebral arteries associated with tissue collapse and the formation of extensive tissue scars. (3) Cerebral dysgenesis may be seen involving over-all distortions in brain shape and in convolutional patterning. Such brains may be of normal weight and exhibit no focal lesions. (4) Bilateral carotid artery and jugular vein ligation may produce no effect on the brain particularly when ligation is carried out during later stages of gestation. (5) Fetal death may result as a consequence of the vascular ligation combined with the surgical assault on the fetus. Primary fetal death occurred in approximately 46 per cent of all cases studied in the present series.

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