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The arterial pattern at the base of arhinencephalic and holoprosencephalic brains

J. J. VAN OVERBEEKE[1], B. HILLEN[2] AND CHR. VERMEIJ-KEERS[2]

[1] *Department of Neurosurgery, Academic Medical Centre, Amsterdam,* [2] *Department of Functional Anatomy, University of Utrecht, Utrecht, and* [3] *Departments of Anatomy and Plastic and Reconstructive Surgery, Erasmus University, Rotterdam, The Netherlands*

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ABSTRACT

The mechanisms by which the anatomical variations of the circle of Willis develop is considered to be related to haemodynamic factors, i.e. the differential growth of the various parts of the brain will continuously change the haemodynamic demands and consequently the flow patterns in the cerebral arteries. It is therefore to be expected that, if a selected part of the brain does not develop, the change in the haemodynamic demand will affect the development of some cerebral arteries. Consequently the arteries at the base of 2 arhinencephalic and 8 holoprosencephalic brains were studied in conjunction with the brain malformations. The defects of holoprosencephaly are believed to arise from a failure of the prosencephalon to separate fully into the telencephalon and diencephalon and become manifest at the time that the prosencephalon normally starts to separate into the hemispheres, i.e. 28–34 d p.c. Arhinencephalic brains are fully diverticulated. There is only a partial or complete agenesis of the olfactory tracts and bulbs. The defect causing arhinencephaly starts at 43 d p.c.

In the arhinencephalic brains no particular vascular abnormalities were found. However, at the base of the holoprosencephalic brains no complete circle of Willis was present; the anterior part was lacking and was replaced by anterior branches which emerged unilaterally or bilaterally from the internal carotid artery. The choroidal arteries were of very large calibre and ran to the highly vascularised wall of the dorsal cyst which is usually present in holoprosencephalic brains. In contrast to the anterior part, the posterior arterial pattern was almost identical to the posterior part of the circle of Willis of normal brains.

The basic vascular patterns found in the holoprosencephalic brains displayed the features of Padget's developmental stages 2 and 3 of the cerebral vasculature, i.e the pattern that has normally developed within 28–40 d p.c. The further modification of this pattern could largely be understood from the functional demand imposed on the circulation by the enlarged anterior choroidal arteries. Because the development of the anterior part of the circle of Willis precedes the developmental derangement causing arhinencephaly, a complete circle was found in these brains.

Key words: Holoprosencephaly; arhinencephaly; cerebral arteries; circle of Willis.

INTRODUCTION

The development of the cerebral vasculature is related to the continuous adjustment of the blood vessels to changes in the morphology and volume of the developing brain and craniofacial structures (Streeter, 1918; Abbie, 1934; Padget, 1948; Piganiol et al. 1960; Moffat, 1962). In studies on the development of the variations of the circle of Willis in normal human brains (van Overbeeke, 1991; van Overbeeke et al. 1991) it was found that the size and shape of the segments composing the circle of Willis were closely associated with the differential growth of the various parts of the brain. In this respect it may also be expected that the development of blood vessels related to a part of the brain that develops in an abnormal way may result in a different vascular pattern compared with the normal development of the same

Correspondence to Dr J. J. van Overbeeke, Department of Neurosurgery, Academic Medical Centre, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.

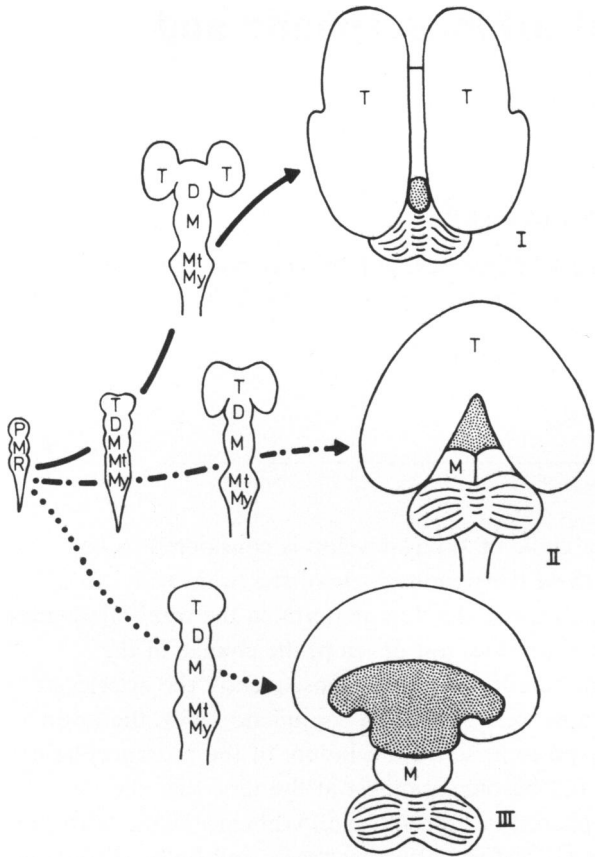


Fig. 1. Diagram showing the development of the normal telencephalon (I), the incomplete holoprosencephalic brain (II) and the complete holoprosencephalic brain (III). The dotted area indicates the tela choroidea which extends to form the dorsal sac in the holoprosencephalic brains. P, prosencephalon; M, mesencephalon; R, rhombencephalon; Mt, metencephalon; My, Myelencephalon; T, telencephalon; D, diencephalon. (After Siebert et al. 1990.)

part of the brain. Accordingly, the basal arteries of 8 holoprosencephalic and 2 arhinencephalic brains were examined.

The defects of holoprosencephaly are believed to arise from a failure of the prosencephalon to separate fully into the telencephalon and diencephalon. In the most severe form, the complete form (Siebert et al. 1990), this failure of the brain to form diverticula results in a single midline ventricle surrounded by an unbroken holosphere of cortex (Fig. 1). At the other extreme, the incomplete form (Siebert et al. 1990), only a single fused gyrus rectus may be found. In either case there is some degree of incomplete diverticulation. Consequently, in the most severe cases, there is no telencephalon medium (impar) from which the anterior midline structures develop and the lateral ventricles are not separated. The latter phenomenon results in a single ventricle which may communicate with a dorsally located cyst which is designated as the dorsal sac. The dorsal sac is considered to be an evaginated tela choroidea (Mettler, 1947; Lichtenstein & Maloney, 1954; Loeser et al. 1968; DeMeyer, 1977).

Arhinencephalic brains are fully diverticulated. There is only a partial or complete agenesis of the olfactory tracts and bulbs (DeMeyer 1977; Kobori et al. 1987). Apart from the brain anomalies, the face may show abnormalities such as cyclopia, hypotelorism and various facial clefts (DeMeyer & Zeeman, 1963; DeMeyer, 1971; Lemire et al. 1981; Cohen, 1982; Vermeij-Keers et al. 1983).

The onset of the abnormal development of the prosencephalon and craniofacial structures leading to holoprosencephaly is considered to occur when the prosencephalon has to separate into hemispheres, in particular between 26–34 d p.c. (Mettler, 1947; O'Rahilly & Gardner, 1971; Robain & Gorce, 1972; Jellinger & Gross, 1973; Probst, 1979; Fitz, 1983; Müller & O'Rahilly, 1989) (Table 1). However, according to Vermeij-Keers et al. (1987) and Vermeij-Keers (1990), this anomaly may manifest itself even at earlier developmental stages, i.e. the preneural plate stages, as a lack of outgrowth of the neuroectoderm and a deficient activity of the neural crest. The defect resulting in arhinencephaly is believed to occur after the formation of the hemispheres and telencephalon impar but before the formation of the external olfactory pathways. This is at about 43 d p.c.

In brains which develop in a normal way the anterior communicating artery is considered to be complete by 45 d p.c. (Padget, 1948; Piganiol et al. 1960). Thus before the formation of this artery there is a deficient development of the cerebral hemispheres in the holoprosencephalic and arhinencephalic brains. In these brains it is therefore to be expected that a wider range of variations of the anterior part of the circle of Willis may exist than in brains that have developed in a normal way. However, because in the arhinencephalic brains the derangement takes place in later developmental stages, a less abnormal pattern is to be expected. The present study examines this hypothesis by detailed descriptions of the arterial pattern at the base of 8 holoprosencephalic and 2 arhinencephalic brains. The role of the functional demand of the developing brain as described by Abbie (1934) is used to explain the abnormal development of the arteries.

MATERIAL AND METHODS

Two arhinencephalic and 8 holoprosencephalic brains were investigated. The age of the individuals ranged from 19 wk p.c. to full term pregnancy, and 1 brain

Table 1. *Schematic representation of the Carnegie stages, the corresponding crown–rump (C–R) length, the postconceptional (p.c.) age and development of the telencephalon**

Carnegie stage	C–R length (mm)	Days (p.c.)	Development of the telencephalon	Onset of brain anomalies	Padget stage	Vascular pattern
XI	2.5–4	24	Transformation of neural plate into neural tube	—	—	—
XII	3–5	26	Evagination of optic vesicles	—	1	—
XIII	4–6	28	—	Complete HPE	2	C
XIV	5–7	32	Evagination of prosencephalic vesicle	Complete and incomplete HPE	—	C
XV	6–9	34	Onset of formation of hemispheres; large telencephalic ventricle	Incomplete HPE	—	C/B
XVI	8–11	37	Differentiation of cortical regions	Incomplete HPE	3	B
XVII	11–14	40	Formation of telencephalon impar	Incomplete HPE	4	B/A
XVIII	13–17	43	Olfactory bulbs appear and start to evaginate	Arhinencephaly	—	A
XIX	16–18	45	Onset of formation of anterior midline commissures		5	A

* The onset of the holoprosencephalic (HPE) and arhinencephalic brain anomalies is given in column 5. The final column the vascular patterns found in the specimens under study.

was of a 10-y-old child. Two brains were obtained at routine autopsy; 8 specimens showed the craniofacial anomalies commonly associated with holoprosencephaly or arhinencephaly. Therefore, following the statement that the face predicts the brain (DeMeyer & Zeeman, 1963), these specimens were selected for brain dissection. The facial features of these specimens (Cases 1, 2, 4–9) have been described by Vermeij-Keers et al. (1983, 1987) and Vermeij-Keers (1990).

In order to study the relationship between the brain abnormalities and the vascular pattern, only selected features of these brains were studied. The emphasis was focused on the identification of the external features such as the interhemispheric fissure, the cerebral lobes, in particular the temporal lobes, and the presence of a dorsal sac. On internal examination special attention was given to the identification of the telencephalic anterior midline structures such as the anterior commissure, corpus callosum, septum pellucidum and fornix. In addition, the hippocampal structures were of special interest because in some holoprosencephalic brains the temporal lobes could not be identified on external examination. Here the recognition of the pes hippocampi enabled us to identify the temporal horn on internal examination.

CASE REPORTS

The vascular pattern is emphasised and the arteries that are important in the scope of this study are described in detail whereas the craniofacial, external and internal cerebral findings are only briefly mentioned. The main features of the cases are summarised in Table 2.

Case 1 Female fetus, 32 wk p.c.

Craniofacial findings. Hypotelorism. Arhinia with septate proboscis, microcephaly, astomia, agnathia. *External cerebral features.* Arhinencephalic brain. Absence of only the right olfactory bulb and tract. Rudimentary remnant of the left olfactory bulb and tract. Hypoplasia of the gyrus cinguli. *Internal cerebral findings.* Communicating hydrocephalus. *Vascular pattern* (Fig. 2). The right internal carotid artery mainly supplied the territories of both anterior cerebral arteries and the right middle cerebral artery; the left supplied the territory of the left middle cerebral artery and contributed to the posterior cerebral circulation by means of a large posterior communicating artery. The right posterior communicating artery and left anterior cerebral artery were of small calibre. The variations found in the posterior basal arteries were within the range of variations found in normal fetal brains (Milenkovic et al. 1985; van Overbeeke et al. 1991).

Case 2 Female fetus, 19 wk p.c.

Craniofacial findings. Bilateral facial cleft. Moderate hypotelorism. Malformed proboscis-like nose. *Ex-*

Table 2. *Summary of the 10 cases**

Case	1	2	3	4	5	6	7	8	9	10
Olfactory tract (L/R)	−/+	−/−	−/−	−/−	−/−	−/−	−/−	−/−	−/−	−/−
Anterior midline structures	+	+	−	−	−	−	−	−	−	−
Type	I	I	II	II	II	II	II	III	III	III
Temporal horn (L/R)	+/+	+/+	+/+	+/+	+/+	−/−	−/−	−/−	−/−	+/−
Dorsal sac	−	−	−	+	+	+	+	+	+	+
Anterior choroidal artery (L/R)	+/+	+/+	+/+	++/++	++/+	++/+	++/+	++/−	+/++	−/++
Middle cerebral artery (L/R)	+/+	+/+	+/+	+/+	+/+	−/−	−/−	−/−	−/−	+/−
Vascular pattern	A	A	B	B	C	C	C	C	C	C

* I, Arhinencephaly; II, incomplete holoprosencephaly; III, complete holoprosencephaly; −, absent; +, present; ++, large.

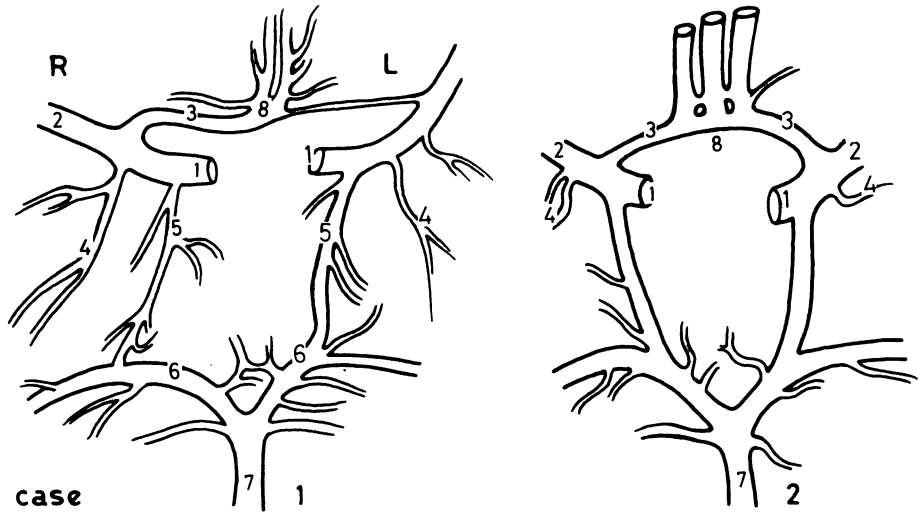


Fig. 2. Type A vascular pattern. Schematic representation of the basal cerebral arteries of the arhinencephalic brains (Cases 1 and 2). 1, Internal carotid artery; 2, middle cerebral artery; 3, anterior cerebral artery; 4, anterior choroidal artery; 5, posterior communicating artery; 6, posterior cerebral artery; 7, basilar artery, 8, anterior cerebral artery.

ternal cerebral features. Arhinencephalic brain. Both olfactory bulbs and tracts absent. *Internal cerebral findings.* No internal cerebral abnormalities were detected. *Vascular pattern* (Fig. 2). A normal circle of Willis was present. The anterior communicating artery was fenestrated. An arteria mediana corporis callosi was found.

Case 3 Child aged 10 y

Craniofacial findings. Microcephaly. Hypotelorism. *External cerebral features.* Incomplete holoprosencephalic brain. Both external olfactory bulbs and tracts absent. Normal optic nerves. Unseparated frontal part of the brain. Symmetric development of the other cerebral lobes, i.e. the temporal lobes. *Internal cerebral findings* (Fig. 3). Monoventricle. Symmetric temporal and posterior horns. Fused basal ganglia and thalamic nuclei. Absence of the anterior midline structures and corpus callosum. *Vascular pattern* (Fig. 4). On both sides a large extension of the internal carotid arteries arched anteriorly over the inferior and superior frontal part of the brain and divided into multiple small

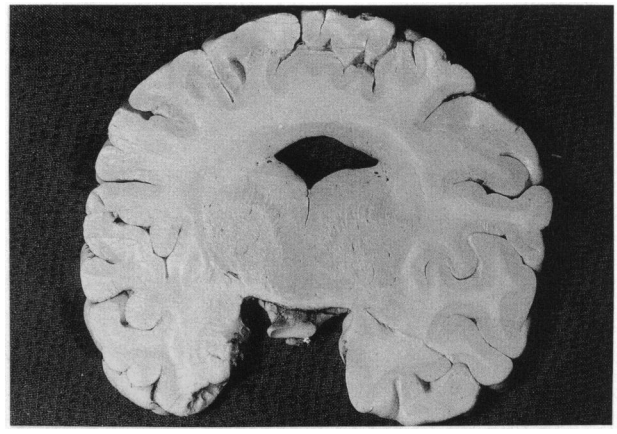


Fig. 3. Case 3. Coronal section of an incomplete holoprosencephalic brain. The interhemispheric fissure is absent and the basal and thalamic nuclei are partially fused.

Fig. 4. Type B vascular pattern. Schematic representation of the cerebral basal arteries of Cases 3 and 4. 1, Internal carotid artery; 2, middle cerebral artery; 3, anterior continuations of the internal carotid arteries; 4, anterior choroidal artery; 5, posterior communicating artery; 6, posterior cerebral artery; 7, basilar artery, 8, arteries running to the dorsal sac; 9, analogue of the anterior cerebral artery; 10, analogue of the anterior communicating artery.

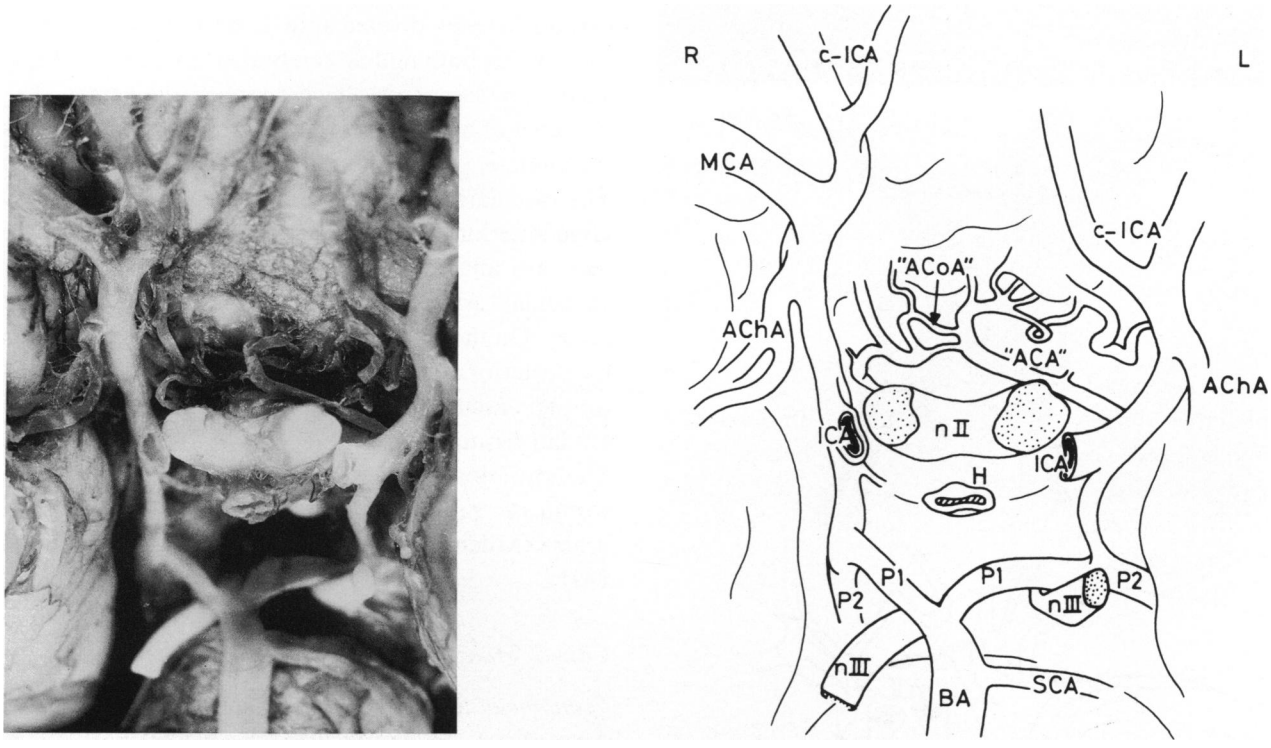
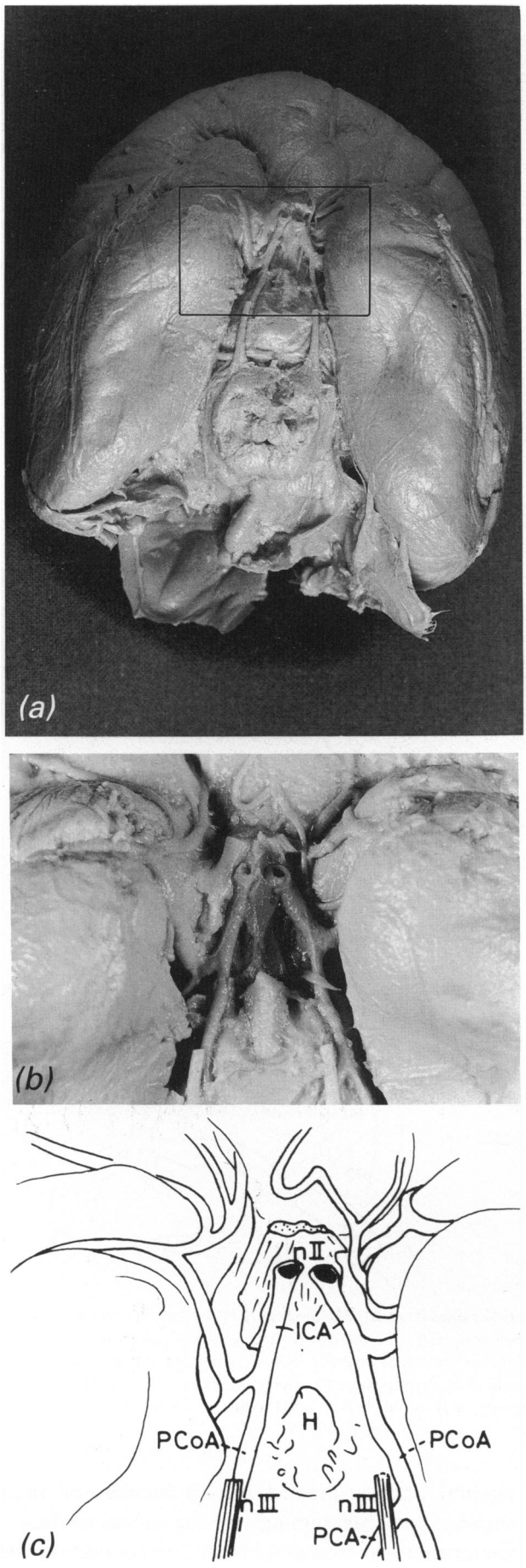


Fig. 5. Case 3. Basal view of the large continuations of both internal carotid arteries (type B). The analogues of the anterior cerebral arteries are very small and supply a limited area of the brain anterior to the optic chiasm. ICA, Internal carotid artery; c-ICA, anterior continuation of the internal carotid artery; MCA, middle cerebral artery; AChA, anterior choroidal artery; 'ACoA', analogue of the anterior communicating artery; 'ACA', analogue of the anterior cerebral artery; H, stalk of the hypophysis; P1, precommunicating part of the posterior cerebral artery; P2, postcommunicating part of the posterior cerebral artery; n II, optic chiasm; n III, oculomotor nerve.

branches (Fig. 5). Both anterior cerebral arteries were connected by means of a tortuous and tiny anterior communicating artery. The distal part of both anterior cerebral arteries divided into a number of small terminal branches running over the inferior surface of the unseparated frontal lobes. A 2nd connection was



found between the left internal carotid artery and the left distal part of the anterior cerebral artery. The branches of the anterior cerebral arteries and internal carotid arteries did not cross the midline. In both sylvian fissures a middle cerebral artery was present. The posterior part of the circle of Willis did not show notable abnormalities.

Case 4 Male fetus, 32 wk p.c.

Craniofacial findings. Two eyes in a single orbit. Arhinia with proboscis. Agnathia with astomia and synotia. Microcephaly. *External cerebral features.* Incomplete holoprosencephalic brain. Olfactory tracts absent. Fused optic nerves. Unseparated frontal part of the brain with symmetric temporal poles and bilateral sylvian fissures. Dorsal sac. *Internal cerebral findings.* Large monoventricle with bilateral temporal horns. Fusion of the thalamic nuclei and basal ganglia. Absence of the anterior midline structures and corpus callosum. *Vascular pattern* (Fig. 4). On both sides a large communicating posterior artery emerged from the internal carotid artery. More distally both internal carotid arteries divided into 2 large trunks (Fig. 6) from which both middle cerebral arteries and multiple smaller vessels arose which supplied the cortex. The branches of both internal carotid arteries did not cross the midline, i.e. the anterior cerebral artery is missing. The vascularisation of the dorsal sac came from very large anterior choroidal arteries on both sides. There was an anastomosis between the right anterior choroidal artery and the right posterior cerebral artery. On the left side a special branch emerged from the posterior communicating artery which contributed to the vascularisation of the dorsal sac. In both sylvian fissures a middle cerebral artery was found. The variations in the posterior basal arteries were within the range of variation found in normal fetal brains (Milenkovic et al. 1985; van Overbeeke et al. 1991).

Case 5 Male fetus, 34 wk p.c.

Cranofacial finding. Hypotelorism and microcephaly. Agenesis of the premaxillae, the medial part of the

Fig. 6. Case 4. (*a*) Basal view of an incomplete holoprosencephalic brain. The cerebellum and distal part of the brainstem have been removed to show the remnants of the dorsal sac. The area enclosed by the rectangle is enlarged in (*b*) and illustrated diagrammatically in (*c*). Two internal carotid arteries are visible posterior to the optic nerves. Distally from the origin of the posterior communicating artery the internal carotid artery bends frontally and gives origin to multiple branches. ICA, Internal carotid artery; PCoA, posterior communicating artery; PCA, posterior cerebral artery; H, hypophysis; n II, optic nerve; n III, oculomotor nerve.

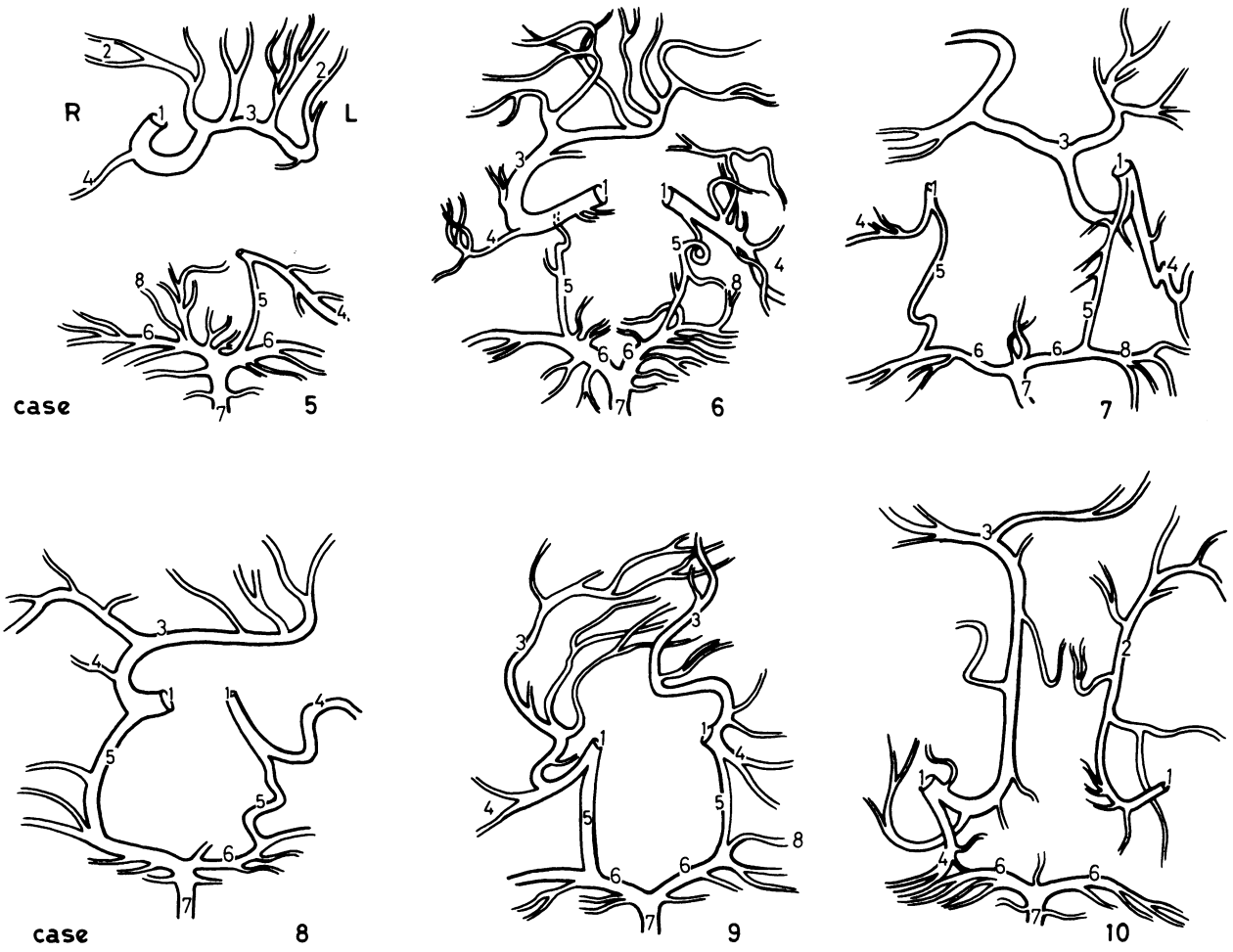


Fig. 7. Type C vascular pattern. Schematic representation of the basal cerebral arteries in Cases 5–10. 1, Internal carotid artery; 2, middle cerebral artery; 3, anterior continuation of the internal carotid arteries; 4, anterior choroidal artery; 5, posterior communicating artery; 6, posterior cerebral artery; 7, basilar artery; 8, arteries running to the dorsal sac.

upper lip and nasal septum. Cleft palate. *External cerebral features.* Incomplete holoprosencephalic brain. Olfactory bulbs and tracts absent. Optic nerves close together in the midline. Unseparated frontal part of the brain. Slight indication of the temporal lobes and sylvian fissures. Wide separation between the parietal and occipital lobes because of a dorsal sac. Macrogyria. *Internal cerebral findings.* Monoventricle, symmetric temporal horns and sylvian fissures. Thalamic and basal ganglia fused. Anterior midline structures and corpus callosum absent. *Vascular pattern* (Fig. 7). On the right side a large internal carotid artery was present. This ran anteriorly. From its continuation 4 large curving branches emerged which divided into multiple smaller branches and curved bilaterally over the inferior and superior surface of the cortex (Fig. 8). The right posterior communicating artery was absent. On both sides the middle cerebral artery arose from the most lateral branches and ran in the sylvian fissures. The left middle cerebral artery thus originated from the right internal carotid artery. In addition, the anterior choroidal artery ran from the right internal carotid artery to the dorsal sac. The left internal carotid artery was small and divided into the posterior communicating artery and a large anterior choroidal artery which ran straight to the dorsal sac. The variations in the posterior basal arteries were within the range of variation found in normal fetal brains (Milenkovic et al. 1985; van Overbeeke et al. 1991). Some small vessels arose from the right posterior cerebral artery and ran to the wall of the dorsal sac.

Case 6 Male fetus, 40 wk p.c.

Craniofacial findings. Two incompletely fused eyes in a single orbit. Arhinia with a proboscis. *External cerebral features* (Fig. 9). Incomplete holoprosencephalic brain. Olfactory tracts absent. Fusion of the optic nerves. Large unseparated frontal part of the

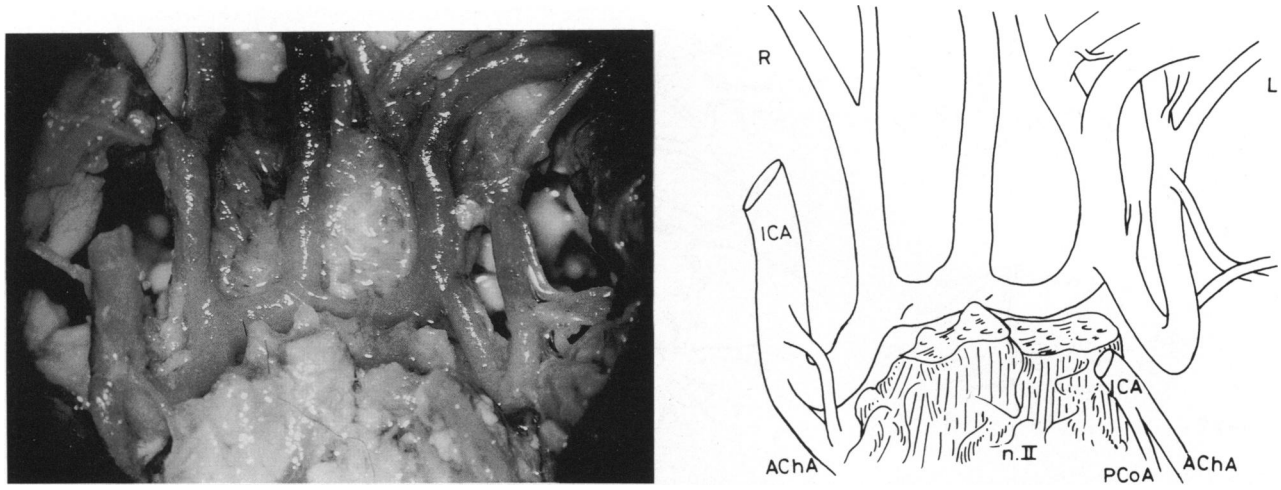


Fig. 8. Case 5. Basal view of the right internal carotid artery and its branches (type C). This artery supplies bilaterally the main part of the cortex of the holosphere. The left anterior choroidal artery runs as a continuation of the left internal carotid artery to the dorsal sac. Both optic nerves are fused. ICA, Internal carotid artery; AChA, anterior choroidal artery; PCoA, posterior communicating artery; n II, optic nerve.

brain. Dorsal sac. Broad gyral pattern. *Internal cerebral findings*. Monoventricle. Temporal horns, anterior midline structures and corpus callosum all absent. Unseparated thalamic nuclei and basal ganglia. *Vascular pattern* (Figs 7, 9*a*). The 2 internal carotid arteries were of equal diameter. The right one curved anterolaterally and divided into multiple tortuous branches which coursed bilaterally over the inferior and superior surface of the cortex. On the left the internal carotid artery extended as a large anterior choroidal artery to the dorsal sac. A small anterior choroidal artery arose from the right internal carotid artery. The left posterior communicating artery was long and tortuous. The variations in the posterior basal arteries were within the range found in normal fetal brains (Milenkovic et al. 1985; van Overbeeke et al. 1991). Some branches from the left posterior cerebral artery ran to the dorsal sac.

Case 7 Female fetus, 32 wk p.c.

Craniofacial findings. Fused midline orbit with a single eye. Arhinia with proboscis. *External cerebral features* (Fig. 10). Incomplete holoprosencephalic brain. External olfactory tracts absent. Fused optic nerves. Small posterior interhemispheric fissure. Slight symmetric bilateral indications of the sylvian fissures. Dorsal sac. Macrogyria. *Internal cerebral findings*. Monoventricle. Temporal lobes absent. Fused thalamic nuclei and basal ganglia. Anterior midline commissures and corpus callosum absent. *Vascular pattern* (Fig. 7). On the left, a large internal carotid artery divided into 2 branches. One ran anteromedially and divided into 2 branches which gave rise to large vessels which ran bilaterally over the inferior and superior surface of the cortex. From the same internal carotid artery a large anterior choroidal artery with many branches ran to the dorsal sac. On both sides a communicating posterior artery was present. The right one emerged from a small internal carotid artery together with a small anterior choroidal artery, the latter ran to the dorsal sac. The variations in the posterior basal arteries were within the range found in normal fetal brains (Milenkovic et al. 1985; van Overbeeke et al. 1991). From the left posterior cerebral artery branches ran to the dorsal sac.

Case 8 Female fetus, 28 wk p.c.

Craniofacial findings. Microcephaly. Agnathia and synotia. Nasal anlage between the eyes and ears. *External cerebral features*. Complete holoprosencephalic brain. No interhemispheric fissure. Olfactory tracts absent. Dorsal sac. No gyral pattern. *Internal cerebral findings*. Monoventricle. Fused thalamic nuclei and basal ganglia. Anterior midline structures and corpus callosum absent. *Vascular pattern* (Fig. 7). The right internal carotid artery curved anteriorly and divided into 2 main trunks from which multiple branches arose to supply the main portion of the cortex on both sides. A small anterior choroidal artery arose on this side from the internal carotid artery. Vessels emerging from the right posterior communicating artery and from the junction of the posterior communicating artery and posterior cerebral artery ran to the dorsal sac. On the left, a small internal carotid artery gave origin to the posterior communicating artery and the anterior choroidal artery

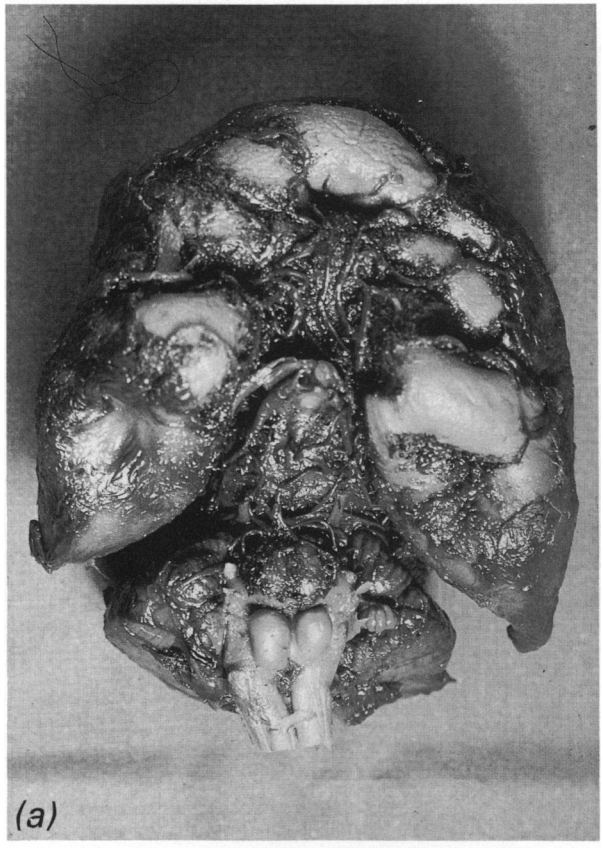


Fig. 9. (*a*) Basal view of an incomplete holoprosencephalic brain (Case 6). Both optic nerves lie close together in a single sheath. Apart from rather large olives the brainstem and cerebellum have developed normally. (*b*) Detail showing many tortuous vessels running over the inferior cortical surface. These vessels originate from the right internal carotid artery.

which ran to the dorsal sac. The variations in the posterior basal arteries were within the range found in normal fetal brains (Milenkovic et al. 1985; van Overbeeke et al. 1991).

Case 9 Male fetus, 35 wk p.c.

Craniofacial findings. Single eye in a single orbit. Arhinia without proboscis. Agnathia with astomia.

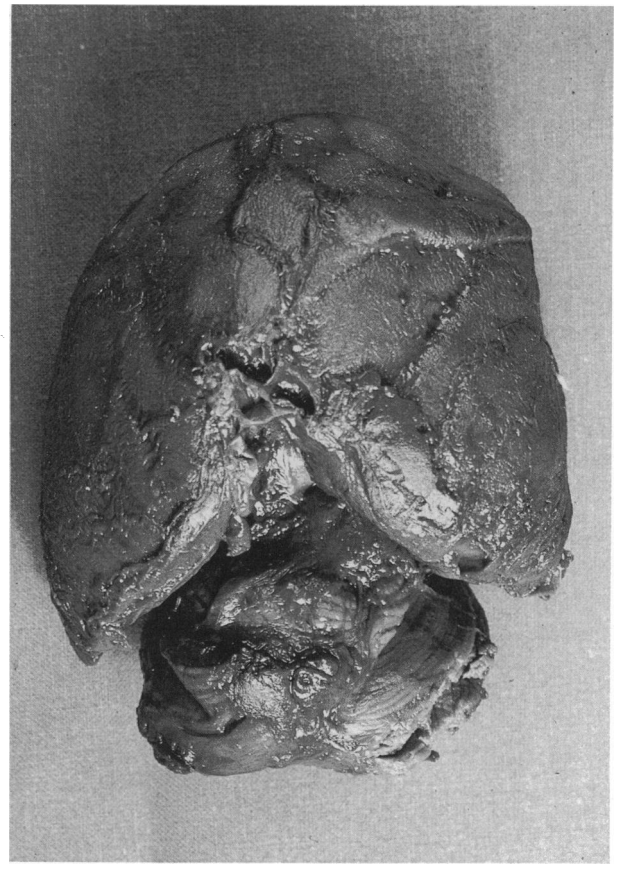


Fig. 10. Dorsal view of an incomplete holoprosencephalic brain (Case 7). There is a small posterior interhemispheric fissure in which some remnants of the dorsal sac are visible. The space between the posterior rims of the brain and superior surface of the cerebellum are filled by the dorsal sac. The cerebellum has developed normally.

External cerebral features. Complete holoprosencephalic brain. Olfactory tracts absent. Fused optic nerves. No interhemispheric fissure. Dorsal sac. No gyral pattern. *Internal cerebral findings.* Monoventricle. Fused basal ganglia and thalamic nuclei. Anterior midline structures and corpus callosum absent. *Vascular pattern* (Fig. 7). Two internal carotid arteries of equal diameter were present. The right one divided into the anterior choroidal artery, which ran to the dorsal sac, and a large branch that supplied the main part of the cortex on both sides by means of many smaller branches. The left internal carotid artery split into the anterior choroidal artery which ran to the dorsal sac, the posterior communicating artery and a branch that also participated in the vascularisation of a minor part of the left side of the unseparated cortex. Branches coming from the junction of the left communicating artery and posterior cerebral artery also ran to the dorsal sac. The variations in the posterior basal arteries were within the range found in normal fetal brains (Milenkovic et al. 1985; van Overbeeke et al. 1991).

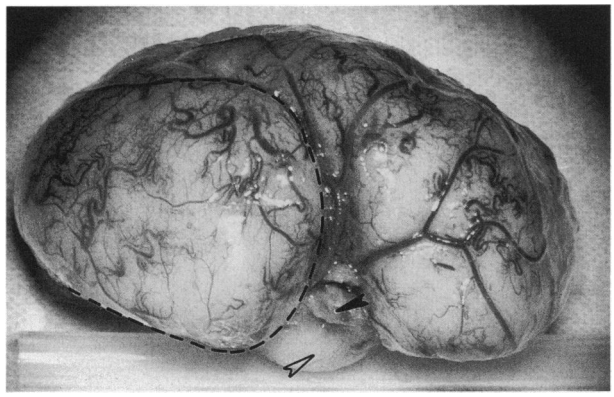


Fig. 11. Frontal view of a complete holoprosencephalic brain (Case 10). The large frontal fissure is the sylvian fissure which separates the right temporal lobe from the rest of the brain. The artery visible in this fissure is the right middle cerebral artery which is a direct continuation of the right internal carotid artery. The right temporal lobe is outlined by a black interrupted line. Black arrow, fused optic nerves; open arrow, diencephalon.

Case 10 Male fetus, 27 wk p.c.

Craniofacial findings. Proboscis. Anophthalmia. *External cerebral features.* Complete holoprosencephalic brain. One localised frontal fissure which divided the frontal part of the brain into 2 asymmetric parts (Fig. 11). Olfactory pathways absent. Fused optic nerves. Brainstem and cerebellum of reduced size. Dorsal sac. No gyral pattern. *Internal cerebral findings.* Monoventricle. On the left an indication of the temporal lobe corresponding with the fissure found on the frontal side of the brain (left sylvian fissure). Thalamic and basal ganglia fused. Anterior midline structures and corpus callosum absent. *Vascular pattern* (Fig. 7). The right internal carotid artery divided into 2 large arteries. One curved anteriorly and divided into 2 frontal arteries supplying the largest part of the unseparated cortical surface, the other ran as the right anterior choroidal artery to the dorsal sac. The left internal carotid artery was small and coursed frontally as the middle cerebral artery in the left sylvian fissure. Both posterior communicating arteries absent. The variations in the posterior basal arteries were within the range found in normal fetal brains (Milenkovic et al. 1985; van Overbeeke et al. 1991).

RESULTS

Three clearly distinguishable types of vascular pattern of the anterior part of the circle of Willis were found in the brains under study (Table 2).

Type A (*Fig. 2*). There is a closed anterior part of the circle of Willis. This type was found in both arhinencephalic brains, i.e. a normal pattern.

Type B (*Figs 4–6*). Both internal carotid arteries contribute to the vascularisation of the cortical surface. The continuations of both internal carotid arteries curve anteriorly and laterally over the cortex. From these vessels smaller branches arise and extend over the inferior, anterior and superior cortical surface. The vascular territory of both internal carotid arteries does not extend beyond the midline; the anterior communicating artery is absent. The vascular pattern is largely symmetric. This type was found in 2 incomplete holoprosencephalic brains with anterior choroidal arteries of equal size.

Type C (*Figs 7–9*). One of the internal carotid arteries supplies the largest part of the brain. This artery divides into many small arteries which subdivide again into smaller vessels which fan out in wandering courses over the cortical surface. The vascular territory of this dominant internal carotid artery crosses the midline. The contralateral internal carotid artery participates only in a minor way to the vascularisation of the cortex of these brains. This type was found in 3 incomplete and 3 complete holoprosencephalic brains. These brains showed anterior choroidal arteries of an unequal size.

Other relevant details are summarised in Table 2.

DISCUSSION

It is both a semantic and an anatomical problem to name the vessels found in abnormal brains so that they correspond to those of normal brains. In the description of the vessels found in the holoprosencephalic brains we made use of the normal nomenclature based on the localisation and destination of the vessels. Considering its topographic relationship to the optic tract and the connection of the choroid plexus with the dorsal sac the posterolateral extensions of the internal carotid artery to the dorsal sac were considered as the anterior choroidal arteries. A middle cerebral artery could be identified only in the brains (Cases 1–5 and 10) which had evidence of temporal lobes. The timing of the onset of the developmental disturbances that cause arhinencephaly, holoprosencephaly and associated abnormalities is an important clue for the explanation of the vascular patterns. A comparison with the normal development of the brain and cerebral arteries as described by Padget (1948) is necessary (Table 1). In the arhinencephalic brains only the olfactory bulbs and tracts were missing. The onset of the disturbances causing arhinencephaly occur after Carnegie stage 17. By that time, stage 4 of Padget has been completed and the anterior cerebral artery and subsequently a closed anterior part of the circle of Willis were found.

Differing opinions exist about the time that the

developmental derangement causing holoprosencephaly becomes manifest. According to Vermeij-Keers et al. (1987) and Vermeij-Keers (1990) the derangement is already evident at the preneural plate stages. Robain and Gorce (1972), Probst (1979), Jellinger & Gross (1973) and Fitz (1983) described the onset of the derangement in Carnegie stage 13 (28 d p.c.), Müller & O'Rahilly (1989) in Carnegie stage 13/14 (28–32 d p.c.) and Leech & Shuman (1986) in Carnegie stage 15 (33 d p.c.). These stages encompass the time that according to Padget (1948) the internal carotid artery forms 2 divisions (Fig. 12). Its cranial division splits into the future primitive anterior choroidal, primitive middle cerebral and primitive olfactory arteries and its posterior division becomes the future posterior communicating artery (Padget stages 1 and 2; Carnegie stages 13 and 14; C–RL 4–7 mm, 28–32 d p.c.). During further development (Padget stage 3; Carnegie stages 15 and 16; C–RI 8–11 mm, 37 d p.c.) the anterior choroidal artery becomes the largest branch. The middle cerebral artery has a relatively short stem which divides into several branches running over the lateral side of the brain. A branch of the olfactory artery, which becomes the future anterior cerebral artery, runs to the midline. At the end of stage 3 this branch expands considerably, together with the proximal part of the olfactory artery. The distal part does not show such a large expansion and may even disappear during further development. Plexiform anastomoses are formed in the midline between both primitive anterior cerebral arteries at the end of the 4th stage of Padget (Carnegie stage 17; C–RI 11–14 mm; 41 d p.c.).

From this time schedule (Table 1) it can be concluded that the disturbances resulting from non-division of the prosencephalon, i.e. holoprosencephaly, arise during the 1st 3 stages of Padget (1948). The results of this study strongly suggested that the failure to diverticulate into symmetric hemispheres is reflected in the vascular pattern. The anterior cerebral and anterior communicating arteries have not developed. The primitive arrangement of the vascular pattern as found in Padget's stages 2 and 3 has therefore remained and is extended to supply the partial or complete holosphere of the holoprosencephalic brain. The vascular pattern of type B reflects at most the primitive situation of Padget's stage 3 (Padget, 1948) corresponding the Carnegie stages 15–16 (8–11 mm C–RL, 37–40 d p.c.) (Fig. 12). In this type a bilaterally similar vascular pattern is found which consists of a well developed anterior choroidal artery, a middle cerebral artery and branches which originate from the primitive olfactory artery.

Derangement in neural crest activity are expressed in craniofacial malformations (Müller & O'Rahilly, 1989; Siebert et al. 1990; Vermeij-Keers, 1990). This means that the severity of the brain and facial anomalies can be related to the onset and the site of the defect in the neural crest activity. In this regard there can be a wide spectrum of holoprosencephalic and craniofacial abnormalities including asymmetric development of the brain. In the more severe holoprosencephalic brains a more asymmetric vascularisation was found (type C). A unilateral primitive cranial division of the internal carotid artery could be recognised (Fig. 12). In Case 10 the large fissure near the midline (Fig. 11) which looked like a frontal fissure, after internal examination appeared to be the sylvian fissure. The artery running in this fissure was designated as the middle cerebral and consequently the arterial pattern as type C.

In Case 9 a slight indication of pattern B was still recognisable (Fig. 7) so that this is a borderline case. Because the branches originating from the right internal carotid artery crossed the midline, this pattern, by definition, was designated as type C.

In the present study, although small in number, it was striking that in none of the cases was the internal carotid artery the main source to the posterior part of the brain. In 1 brain even both posterior communicating arteries were missing (Case 10) and in another artery this was absent unilaterally (Case 5). The severely disturbed haemodynamic situation as defined in the vascular patterns of types B and C and probably this displacement of the posterior part of the brain by the dorsal sac may be responsible for the development of the posterior part of the brain by the dorsal sac may be responsible for the development of the posterior communicating artery becoming less pronounced in these brains.

The vascularisation of the wall of the dorsal sac by the unilaterally or bilaterally expanded anterior choroidal artery supports the notion that this wall forms a part of the tela choroidea. Furthermore, the enlargement of the anterior choroidal arteries reflects the primitive vascular pattern as described by Padget (1948). In Padget's stage 3 (Carnegie stages 15 and 16; C–RL 8–11 mm, 37–40 d p.c.) a relatively large anterior choroidal artery is a characteristic feature. In Cases 4–7 and 9 branches from the posterior communicating and posterior cerebral arteries to the dorsal sac were found, indicating a stronger participation of the posterior cerebral artery in the vascularisation of the tela choroidea. In 1 case (Case 4) (Fig. 4) a large anastomosis between the choroidal artery and the posterior part of the circle of Willis was

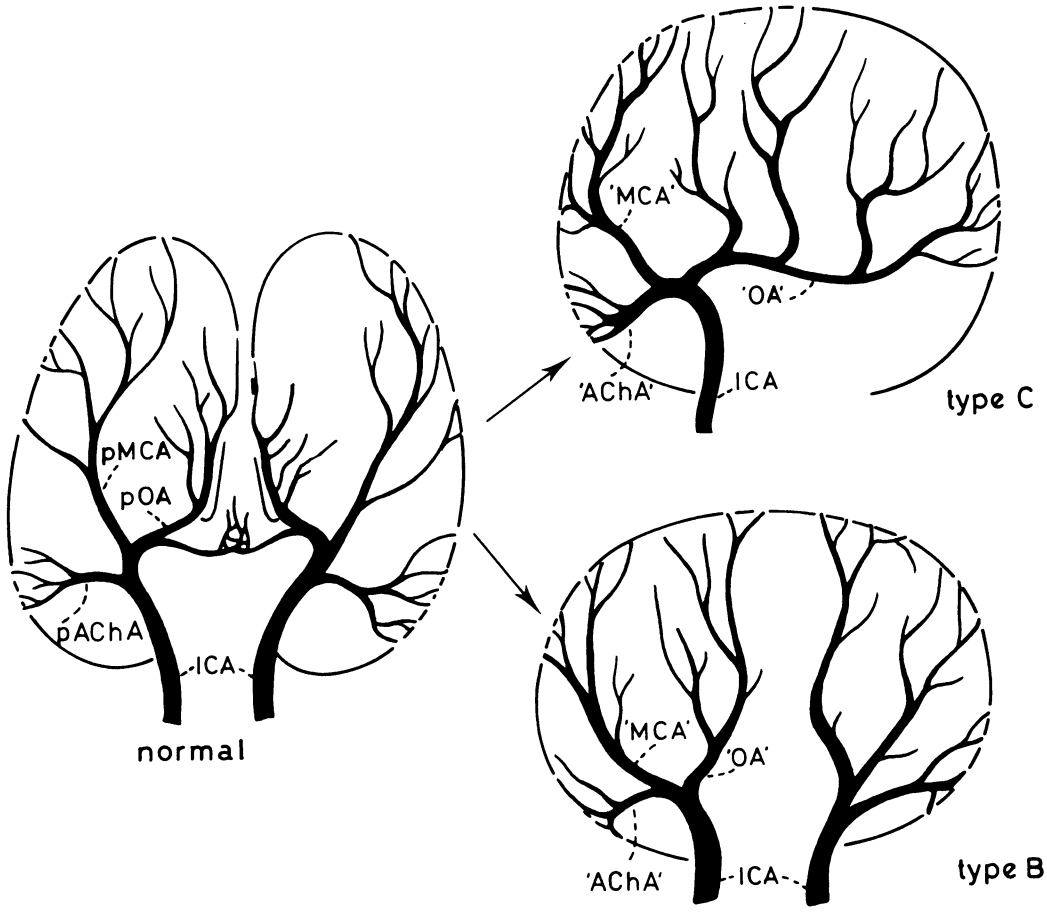


Fig. 12. Schematic illustration of the transition between the vascular pattern in brains with normal development to those found in holoprosencephaly. Normal development represents the situation at the end of stage 3 of Padget (8–11 mm C–R1, 37 d p.c., Carnegie stage 16). The prosencephalon has divided into 2 symmetric hemispheres. From this arterial configuration type C or type B develop in holoprosencephalic brains. Type C is considered to develop in the most severe cases of holoprosencephaly with an asymmetric development of the holosphere. Type B develops in cases with a symmetric development of the holosphere. ICA, Internal carotid artery; pAChA, primitive anterior choroidal artery pMCA, primitive middle cerebral artery; pOA, primitive olfactory artery. Analogues of these vessels are given in quotation marks for types B and C brains.

found. These anastomoses have been described by Kier (1974) and occur mainly in an 'early embryonic period'.

A single (azygous) anterior cerebral artery, whether in combination with 2 middle cerebral arteries or not, has been described as the most striking and frequent angiographic finding in holoprosencephaly (Yakovlev, 1959; Zingesser et al. 1966; Maki & Kumagai, 1974; Hamano et al. 1976; Osaka & Matsumoto, 1978). However, angiographic examinations are not entirely conclusive in this respect. Factors such as flow dynamics and pressure gradients during contrast injection are involved and may influence the cross-over circulation. One of the wandering arteries over the frontal lobe, as so frequently found in this study, therefore cannot be distinguished from an azygous artery on angiography. An enlarged anterior choroidal artery, which was also a prominent feature in this study, has also been described by Wisen et al. (1965) and Maki & Kumagai (1974) in complete as well as incomplete holoprosencephalic brains. None of the authors described abnormalities of the posterior part of the circle of Willis.

Concerning the vasculature of type B and the vessels emerging from the posterior cerebral and posterior communicating arteries to the wall of the dorsal sac there is a phylogenetic conformity. The pattern of the large cranial continuations of both internal carotid arteries supplying both sides of the hemisphere is found in the brains of fish and some amphibians. Also in the lower evolutionary scale the choroid plexus is vascularised by vessels coming from the posterior communicating and the distal part of the posterior cerebral arteries (Abbie, 1934; Kier, 1974). These data emphasise the primitive state of the vascularisation of the holoprosencephalic brains. Moreover, it is shown that the vascular pattern of the holoprosencephalic brains as presented in this study

fits well into the embryological concept of the dominance of neural over vascular development. This may support the concept of the role of functional demand.

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