The Fetal Variant of the Circle of Willis and Its Influence on the Cerebral Collateral Circulation

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Key Words

Circle of Willis, fetal • Cerebral collateral circulation

Abstract

In a fetal-type posterior circle of Willis (FTP) there is an embryonic derivation of the posterior cerebral artery (PCA) from the internal carotid artery (ICA). Besides the fact that a larger area is thus dependent on the ICA, leptomeningeal vessels cannot develop between the anterior and posterior circulation. The tentorium namely prevents cerebellar vessels from connecting to the PCA territory. Therefore patients with an FTP could be more prone to develop vascular insufficiency. An overview of the literature is given. We propose to define a partial FTP, in which a small P1 segment between the basilar artery and the postcommunicating part of the PCA is present, and a full FTP, in which the P1 segment is absent. Whether a full FTP is a risk factor for stroke should be subject of further investigation.

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Collateral circulation in the brain is important for maintaining a sufficient level of cerebral blood flow in case of obstructive disease in the main afferent arteries. This arterial network consists of extracranial and intra-

cranial routes. The intracranial collateral vessels comprise the so-called primary collaterals, consisting of the arterial segments of the circle of Willis, which are used in case of acute need, and the secondary collaterals such as the ophthalmic artery and the leptomeningeal vessels, which develop after an ischemic stimulus when the primary collaterals are insufficient [1]. The leptomeningeal vessels are present or develop between the anterior (ACA), middle (MCA) and posterior cerebral arteries (PCA). They can represent an important connection between the internal carotid artery (ICA) and the vertebrobasilar system.

Leptomeningeal collaterals can develop in the majority of circle of Willis configurations. However, one variant of the circle of Willis, the fetal variant (FTP), makes leptomeningeal collaterals between the ICA and the vertebrobasilar system impossible to develop since both the MCA and the PCA are connected to the internal carotid system and not to the vertebrobasilar system. An important consequence of the fetal variant of the circle of Willis could be an increased stroke risk in patients with obstructive arterial disease, as has been described in postmortem studies.

Collaterals are regularly discussed as to their possible importance in relation to stroke risk, but little attention has been given to the FTP in the literature. In this review we discuss the different collateral pathways, the definition

Fig. 1. MR examination of 2 cases; left: maximum-intensity projection of the circle of Willis; right: regional perfusion imaging of the anterior circulation (**a**) and the posterior circulation (**b**).

and prevalence of FTPs and what is known about the association between collaterals and a subsequent stroke risk.

Cases

We propose 2 cases to illustrate the difference in cerebral perfusion on MR investigations between patients with a normal circle of Willis and patients with an FTP. Figure 1a represents the maximum-intensity projection of the circle vessels and the regional perfusion images [2] of a male patient aged 67 years with a symptomatic right ICA stenosis of 80%. The maximum-intensity projection shows that both posterior communicating arteries (PCoAs) are absent. This has been confirmed on CT angiography images. Although no communication is present between the internal carotid system and the vertebro-basilar system at the level of the circle of Willis, the re-

gional perfusion image scans show that with selective labeling of the posterior circulation, signal is present in the right MCA, as well as the PCA flow territories. Leptomeningeal vessels took care of the collateral flow.

Figure 1b shows the MR images of a 55-year-old male patient with a symptomatic left ICA stenosis of 80%. He has a bilateral FTP configuration of the circle of Willis. The regional perfusion images show that with labeling of the posterior circulation, there is no signal in any cerebral flow territory. Thus, there is no leptomeningeal flow from posterior to anterior to compensate for the stenosis of the left ICA.

The Circle of Willis

The circle of Willis has a major role in redistributing the blood in case of diminished supply through the ICA and the basilar artery. This vessel structure enables inter-

hemispheric flow through the anterior communicating artery and in two directions through the 2 PCoAs [1].

There is a considerable variation in the presence of the arterial segments of the circle of Willis. On the anterior side the anterior communicating artery or one of the A1 (proximal) segments of the ACA can be missing or hypoplastic. On the posterior side, the PCoA can be absent uni- or bilaterally. In healthy individuals, a complete configuration of the circle of Willis is present in 42–52% [3, 4]. In patients with ICA stenosis or occlusion, this percentage is higher [5].

Ophthalmic Artery

Retrograde flow through the ophthalmic artery, between the external carotid artery and the ipsilateral ICA is another source of collateral flow. Slow progression of stenosis to occlusion of the ICA is needed for this collateral flow to develop. Collateral flow through the ophthalmic artery is a sign of reduced cerebral perfusion pressure [6].

Leptomeningeal Vessels

Leptomeningeal vessels are anastomoses up to 1 mm in diameter, in which the blood direction is dependent on the hemodynamic and metabolic circumstances of the two connected territories [7]. The vessels can be formed throughout the distal regions of the complete brain, between the anterior and posterior, middle and posterior, and anterior and posterior cerebral arteries. Large inter-individual variability of leptomeningeal vessels exists. Similar to the ophthalmic artery collateral, these vessels need time to develop. Although there is a benefit to be expected from these collaterals, the presence of leptomeningeal vessels is associated with a poor hemodynamic status, in which collateral flow through the circle of Willis was not sufficient [6, 8]. No consensus exists about the ability of leptomeningeal vessels to improve cerebral hemodynamics [7].

Usually the ACA and MCA are part of the ICA system, and the PCA is part of the vertebrobasilar system. When the circle of Willis provides insufficient collateral flow, leptomeningeal vessels can connect the two systems. In situations where a PCoA is absent and an ICA is partially or completely obstructed, these connections can be important.

Leptomeningeal Collaterals and the Fetal-Type PCA

In a fetal-type PCA there is an embryonic derivation of the PCA from the ICA. The vascularization of the PCA flow territory is thus completely dependent on the ICA. In this situation an obstruction of the ICA can not be compensated by the development of leptomeningeal vessels between the PCA and the MCA because they are derived from the same vessel and the tentorium prevents cerebellar vessels from connecting to the PCA territory (fig. 2). We think that therefore patients with fetal-type PCA could be more prone to develop vascular insufficiency. This prompted us to review the literature concerning fetal-type PCA.

Development of FTPs

At the 4- to 5.7-mm stage of the embryo (28–30 days), the ICA, which develops as a cranial extension of the paired dorsal aorta, is formed [9]. Paired longitudinal neural arteries appear along the hindbrain and coalesce to form the basilar artery at the 5- to 8-mm stage. The caudal divisions of the ICA anastomose with the neural arteries and become PCoAs. At the 40-mm stage (8 weeks) the PCAs are an extension of the PCoA. The vertebrobasilar system develops and thus participates in the supply of the PCA through the segment between the basilar artery and the postcommunicating part of the PCA, the P1 segment. In that phase, the component vessels of the circle of Willis all have the same caliber. In the remaining fetal period, the circle develops into one of three variants: an adult configuration, a transitional configuration or a fetal (embryonic) configuration [10]. In the adult configuration, the P1 segment has a larger diameter than the PCoA. In the transitional configuration, the PCoA and P1 have an equal diameter. Both the basilar artery and the ICA thus contribute equally to the PCA. The fetal or embryonic configuration is the variant in which the P1 is smaller than the PCoA and the ICAs are the main blood suppliers to the occipital lobes. It has been shown that these variations in morphology arise during fetal brain development [11]. In this period, the frequency of adult and fetal configurations increases, while the number of transitional configurations decreases.

Definition

The term fetal-type PCA is also used when there is still a communication with the basilar artery through a hypoplastic P1 segment of the PCA. Others refer to it only

Fig. 2. Schematic lateral view of a 'normal' circle of Willis, in which the vertebrobasilar system supplies the PCA (**a**) and a fetal type cerebral artery, supplied by the carotid system (**b**). In the latter, the cerebellar tentorium inhibits a leptomeningeal connection between both supplying systems. LM = Leptomeningeal vessels.

Fig. 3. Schematic illustration of the variants of the posterior part of the circle of Willis. LM = Leptomeningeal vessels; A = ACA; M = MCA; P = PCA; CS = superior cerebellar artery; BA = basilar artery; P1 = segment between the basilar artery and the postcommunicating part of the PCA.

Fig. 4. Variations of FTPs described by Kameyama and Okinaka [12] in 1963 (copied with permission of *Neurology*). **a** The A1 segment of the ACA is larger on the side of the FTP than on the contralateral side. **b** The A1 segment is smaller on the side of an FTP. **c** ACAs are normal. **d** 'Primitive type embryonic derivation'. **e** Normal adult-type circle of Willis.

when the P1 segment is not visible or when the PCA does not fill after contrast injection of a vertebral artery.

In assessing the influence of having an FTP, information on the presence or absence of a small connection between the carotid system and the vertebrobasilar system, a P1 segment, is important, as it is possibly recruitable in case of increasing need. We propose the following definitions. In a full FTP, uni- or bilateral, the P1 segment is not visualized on CT or MRI or does not fill after injection of contrast in a vertebral artery. A partial FTP, uni- or bilateral, is when the P1 segment is smaller than the PCoA. In an intermediate posterior circle configuration, the P1 segment is as large as the PCoA. The adult configuration, finally, is the situation in which the P1 segment is larger than the PCoA, the PCoA sometimes even being absent. Figure 3 illustrates these possible variants of the posterior part of the circle of Willis.

Kameyama and Okinaka [12] described four types of what they called the 'embryonic PCA', combining the morphology of the posterior part and the anterior part of the circle of Willis (fig. 4). In type A, the A1 segment of

the ACA is larger on the side of the FTP than on the contralateral side. In type B, the A1 is smaller on the side of an FTP. In type C, the ACAs are normal. The bilateral FTPs were called the 'primitive-type embryonic derivation'. Although their definitions are not used in the literature, it could be important to assess the combination of anterior and posterior part of the circle of Willis, since it makes a difference if e.g. an ICA has to feed an MCA, both ACAs and a PCA, compared with an MCA and a PCA only.

Prevalence

We have reviewed the literature available in Pubmed on the circle of Willis (search term: circle of Willis). All publications were screened for estimates of FTP prevalences. In table 1 we have summarized these prevalences, sorted by definition of the FTPs. The definition most often used is a partial FTP, mentioned as 'partial' in the table. Only few publications have looked explicitly for full FTPs.

Table 1. Prevalence of FTPs described in the literature

Reference	n	Population	Method of determination	Definition of FTP	FTP %	Unilateral FTP, %	Bilateral FTP, %
Lazorthes et al. [13], 1979	200	not mentioned	autopsy	partial	12	11	1
Milenković et al. [14], 1985	60	fetal brains, 20–40 weeks of age	autopsy	partial	21	–	–
Alpers et al. [4], 1959	350	‘normal brains’	autopsy	partial	15	11	4
Kameyama and Okinaka [12], 1963	90	‘normal brains’	autopsy	partial	27	18	9
Krabbe-Hartkamp et al. [3], 1998	150	healthy subjects	MRA	partial	32	25	7
Saeki and Rhoton [15], 1977	50	randomly selected adult brains	autopsy	partial	22	20	2
Riggs and Rupp [16], 1963	994	adults with neural dysfunction	autopsy	partial	22	16	6
Hoksbergen et al. [17], 2000	76	atherosclerotic patients without cerebrovascular disease	TCCD	partial	7	–	–
Hartkamp et al. [5], 1999	75	patients with $\geq 70\%$ ICA stenosis or occlusion	MRA	partial	26	13	3
Miralles et al. [18], 1995	38	ICA occlusion	MRA	partial	5	–	–
Alpers and Berry [19], 1963	194	cerebral softening	autopsy	partial	29	–	–
Kameyama and Okinaka [12], 1963	167	cerebral infarction	autopsy	partial	36	29	7
Jongen et al. [20], 2004	50	young healthy subjects	MRA	full	30	26	4
Jongen et al. [21], 2002	194	patients without severe atherosclerotic disease	angiography	full	20	–	–
Schomer et al. [22], 1994	29	ICA occlusion	MRA	full	3	–	–
Jongen et al. [20], 2004	47	patients with an occipital lobe infarct	MRA	full	6	4	2
Bisaria [23], 1984	126	not mentioned	autopsy	unknown	32	–	–
Battacharji et al. [24], 1967	88	healthy control subjects	autopsy	unknown	18	17	1
Macchi et al. [25], 1996	100	healthy subjects	MRA	unknown	13	–	–
Battacharji et al. [24], 1967	49	patients with cerebral infarction	autopsy	unknown	29	27	2

– =Data not available; TCCD = transcranial color-coded duplex ultrasonography.

Others do not define FTPs at all. Where available, we mentioned the uni- and bilateral prevalence of FTPs. Prevalences highly fluctuate in the literature. For the partial FTPs, 11–29% of the study participants had a unilateral FTP, and 1–9% a bilateral FTP. When the definition of a full FTP was used, 4–26% had a unilateral FTP and 2–4% a bilateral FTP.

Because of the wide variety in FTP percentages, we have examined the determinants of this variation. We used linear regression analysis and weighted the model according to the number of participants in the studies. Year of publication, study population (asymptomatic/healthy or symptomatic arterial disease), method of determination (autopsy, MRA, transcranial color-coded duplex ultrasonography, angiography) and FTP definition (partial or full) were considered as possible determinants. In more recent years of publication, lower prevalences were found ($\beta = -0.34$; 95% confidence interval: $-0.68, -0.01$; i.e. for every calendar year, the prevalence decreased by 0.34%). Also, related to this finding, lower prevalences were found in newer methods of determination compared with autopsy studies ($\beta = -12$; 95% confi-

dence interval: $-21, -3$; i.e. the prevalence was 12% lower in more recent methods). The study population and the FTP definition did not influence the prevalences.

Association between Collaterals and Stroke

The most rapidly recruited collaterals are the communicating arteries of the circle of Willis. In FTPs, the ICA covers a larger area to provide with blood than in the ‘normal’, non-FTP configuration of the circle of Willis. It is probable that patients with ICA obstruction and a full FTP more often encounter ischemic problems than patients with a ‘normal’ circle, in which the PCoA is preserved and leptomeningeal vessels can develop between the carotid and the vertebrobasilar system. Patients who also have a missing contralateral A1 segment, thus having to feed the area of the ACAs, an MCA and a PCA with 1 ICA could be even more at risk.

The number of collaterals has been associated with lower stroke incidence in 2-year follow-up studies in patients with ICA obstruction [26, 27]. One of these studies

was performed in the NASCET study, where angiographic collateral filling was assessed in patients with severe ICA disease [26]. It was shown prospectively, in 434 patients without collaterals and 247 patients with collaterals, that the presence of these collaterals decreased the 2-year risk of stroke considerably. In medically treated patients, stroke risk decreased from 28 to 11%, and for surgically treated patients from 8 to 6%. FTPs were not assessed in this study. A case-control study, assessing the collateral flow through the circle of Willis with transcranial color-coded duplex ultrasonography in patients with acute ischemic stroke ($n = 109$) and in patients with peripheral arterial disease ($n = 113$), also showed that the presence of a nonfunctional anterior collateral pathway was associated with ischemic stroke (odds ratio = 7.3; 95% confidence interval 1.2–76.5) [28]. FTPs were not considered as a separate category in this study. Two other cross-sectional studies, visualizing the circle of Willis with MRA in patients with ICA occlusion, showed that the presence of PCoAs was associated with the absence of border zone infarcts [22, 29]. In one of these studies, 1 patient with an FTP was found in a total of 29 patients, which was classified as having an absent PCoA [22]. Considering the fact that patients with an FTP have no communication between anterior and posterior, as in patients without a PCoA, it could be argued that a conclusion can be drawn from these publications that the presence of an FTP, as well as the absence of PCoAs, is related to a higher prevalence of border zone infarcts. However, a direct assessment of this risk in patients with FTPs would be preferable.

In an autopsy study of 49 brains with infarcts and 88 without, more FTPs were found in brains with infarcts than in brains without (27 vs. 17%) [24]. In another autopsy study, describing 167 brains with infarcts and 90 without, also more FTPs were found in the brains with infarcts [12]. The latter study emphasizes that the morphology of the anterior part of the circle of Willis is also important in the risk assessment. The authors described the highest infarct incidence in brains where 1 ICA mostly or exclusively supplied 2 ACAs, an MCA and a PCA.

Recently a study has shown that FTPs and occipital lobe infarcts were related [20]. In 47 patients with occipital lobe infarcts and 50 control subjects, MRA showed that the controls more often had an FTP than the patients with infarcts (15 controls vs. 3 patients). This study implies that FTPs could be protective against occipital lobe infarcts. However, the study had a small sample size.

Few studies have focused on the risk assessment of patients with FTPs. In our opinion, more research is needed

to indicate if the assessment of the presence of this variant has any clinical value.

No mention has been made in the literature of the presence of leptomeningeal arteries between the anterior and posterior circulation in combination with the assessment of the presence of FTPs.

Conclusion

In this review, we gave an overview of the literature concerning FTPs. Since a uniform definition was lacking, we proposed to define a partial FTP, in which a small P1 segment is present, and a full FTP, in which the P1 segment is absent. In full FTPs the possibility for collateral circulation to develop between the anterior and posterior part of the cerebral circulation by way of leptomeningeal vessels is impossible, making collateral flow completely dependent on the anterior circulation of the contralateral side. Whether this is a risk factor for stroke should be subject of further investigation.

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