

1 **Association Between The Posterior Part Of The Circle Of**
2 **Willis And Vertebral Artery Hypoplasia**

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12 The authors' contribution

13 * - data collection, study design, interpretation of data, statistical analysis, drafting of the
14 manuscript. ** - study design, data collection and interpretation. All the authors have read
15 and approved the final manuscript.

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19

20 **Abstract**

21 *Background.* It is not clear whether the configuration of the posterior part of the circle of
22 Willis (CW) depends on the proximal part of the vertebrobasilar system. Our aim is to
23 evaluate the posterior part of CW in association with different size of vertebral arteries (VA)
24 in subjects free from stroke and TIA.

25 *Materials and methods.* The present study was based on a sample of 923 subjects free from
26 stroke and TIA who were examined from 2013 through 2018. All the participants underwent
27 MRA examination. The duplex ultrasonographic examination of the extracranial arteries
28 (vertebral and carotid) was performed. VA was defined as hypoplastic (VAH) when VA
29 diameter in the entire course was less than 2.5 mm. We classified the posterior
30 communicating arteries (PCoA) as presence PCoA, absence/hypoplastic PCoA and fetal CW
31 (FCW). The comparison of the posterior part of CW was made in subjects with normal VA
32 and VAH of a different degree (communicating with basilar artery (VAH-BA) and not
33 communicating with the basilar artery and terminating in PICA, neck or aplasia (VAH-
34 PICA)).

35 *Results.* FCW was found in 15.9% of subjects, bilaterally – in 2.3 %. The coexisting VAH
36 was more common in subjects with FCW rather than in those with adult CW (respectively,
37 28.6% and 13.4%, $p<0.001$). Aplasia of A1 of the anterior cerebral artery, i.e. blood flow
38 redistribution in the anterior part of anterior circulation in the majority of cases (in 6 of 7
39 cases) was found ipsilaterally to FCW. FCW was recorded in 50% of the subjects with VA -
40 PICA in comparison with 13.5% of those with normal VA and 22.8% with VAH - BA,
41 $p<0.005$. On the contrary, absence/hypoplasia of both PCoA was mostly found in the group
42 with normal VA in comparison with VAH-BA and VAH-PICA (accordingly, 50.7%, 38.6%
43 and 12.5%, $p<0.01$).

44 *Conclusion.* Individuals with VAH have a different pattern of the posterior part of CW in
45 comparison with those with normal VA. With the increasing degree of VAH, the proportion
46 of FCW increases, while the proportion of absence/hypoplastic of both PCoA decreases.

47 **Key words.** Circle of Willis . Fetal variant. Hypoplasia. Vertebrobasilar system. Vertebral
48 artery.

49

50 **Introduction**

51

52 The Circle of Willis (CW) is a major intracranial collateral circulation that has an important
53 role in ischemic events. The most common configuration of the posterior part of CW is
54 described as 'adult configuration'. In these cases, the posterior cerebral artery (PCA) is a
55 terminal branch of the vertebrobasilar system. The diameter of the precommunicating part
56 (P1) of PCA is larger than the diameter of the posterior communicating artery (PCoA)
57 connecting the vertebrobasilar and carotid systems. The presence of PCoA enables to
58 redistribute the blood flow in both directions through PCoA in cases of diminished blood
59 supply in the internal carotid artery (ICA) or vice versa in the vertebrobasilar system. In the
60 minority of cases the configuration of the posterior part of CW is the so called fetal-type of
61 the posterior circle of Willis (FCW). FCW is a morphological variant of the cerebrovascular
62 anatomy in which PCA arises directly from the terminal ICA, with or without an intact P1
63 segment connecting PCA to the basilar artery. In this variant, the larger brain area is
64 dependent on ICA and could be more prone to develop large ischemic strokes in cases of
65 carotid artery stenosis or occlusion. As described by many authors [1], in these cases the
66 collateral circulation between the anterior and posterior circulation through secondary
67 collaterals, i.e. leptomeningeal vessels cannot develop since both, the middle cerebral artery
68 and PCA are connected to the same internal carotid system.

69 Insufficient attention has been given to the FCW coexistence with other vascular congenital
70 variants and its influence on both cerebral circulation and neurological symptomatic. It was
71 described [2] that the coexistence of FCW, basilar artery (BA) hypoplasia and vertebral artery
72 hypoplasia (VAH) was more common in patients with cerebral ischemia, i.e. this arterial
73 variant may increase TIA/stroke risk. According to [3], individuals with FCW have an 18%
74 reduction in BA diameter. It is not clear if the configuration of the posterior part of CW
75 depends on the proximal part of the vertebrobasilar system, more exactly, on the vertebral
76 artery (VA) diameter and in cases of a small diameter vertebrobasilar system, which
77 configuration of posterior collateral circulation is more beneficial.

78 Our aim is to evaluate the posterior part of CW in association with different sizes of VA
79 (normal diameter, VAH of different degree (communicating with the basilar artery (VAH-
80 BA) and not communicating with the basilar artery and terminating in PICA, neck or aplasia
81 (VAH-PICA)) in subjects free from stroke and TIA.

82

83 **Material and methods**

84 The present study was based on a sample of 923 subjects without cerebrovascular disease
85 (TIA or stroke) history before and at the time of the study enrollment. All of them were
86 examined by magnetic resonance imaging (MRI) and magnetic resonance angiography
87 (MRA) in the Republican Vilnius University Hospital from 2013 through 2018.

88 The inclusion criteria were as follows: (1) no history of transient ischemic attack, ischemic or
89 hemorrhagic stroke; (2) no disabling neurological deficits on examination; (3) extracranial or
90 intracranial vessels without significant stenosis (>50%) or occlusion; (4) the study excluded
91 the patients who did not undergo MRI or MRA investigation, their intracranial vessels were
92 not visualised or they refused to participate in the study.

93 *Imaging studies.*

94 All the participants underwent MRA examination using 1.5 Tesla MRI (GE Optima MR450w
95 1.5T MRI System) for the brain and CW evaluation.

96 The following sequences were obtained: 3D T1 weighted, T2 FLAIR, T2 weighted, diffusion
97 weighted imaging (DWI, b-0, b-1000), SWAN (Susceptibility weighted Angiography), 3D
98 Time of Flight MR angiography (3D-TOF-MRA). CW anatomy of each individual was
99 evaluated using both 3DTOF MRA MIP reconstructions and source images.

100 The duplex ultrasonographic examination of extracranial arteries (vertebral and carotid) was
101 performed by using the 7.5 MHz linear array transducer of Aloka Prosound F 75 ultrasound
102 system. The diameter of VA in our previous study was measured similarly [4].

103 *Image analysis.*

104 MRA were reviewed by two independent neuroradiologists. If they had disagreements
105 regarding the configuration of the circle of Willis, they discussed it until a consensus was
106 reached.

107 The classification of CW and VA was carried out as follows:

- 108 1. When interpreting MRA, the presence or absence of PCCoA and P1 segment of PCA
109 was assessed. P1 segment and the posterior communicating artery (PCoA) were
110 scored as normal (diameter ≥ 0.8 mm), hypoplastic (diameter < 0.8 mm in MRA),
111 absent or non-visualised. The threshold of 0.8 mm in MRA was chosen in order to be
112 consistent with other studies reported in literature [5].
- 113 2. The posterior part of the circle of Willis was defined as complete in cases of presence
114 of both PCoA and P1 segment of PCA with diameter ≥ 0.8 mm. All other variants
115 were defined as the incomplete posterior part of CW.

- 116 3. We defined the circle of Willis as fetal if PCA arises from the internal carotid artery,
117 independent on the presence or absence of the atretic P1 segment. All other
118 individuals were named as having” adult” configuration of CW. The subjects with
119 adult and rarely found transitional CW configuration were included in this group. In
120 cases of adult configuration, P1 segment of PCA had a diameter larger than PCoA
121 while in transitional configuration, P1 segment and PCoA have close diameters.
- 122 4. The posterior part of CW was documented as presence of PCoA, absence/hypoplastic
123 PCoA and FCW. The subjects with hypoplastic PCoA were included in the same
124 group as those with absence of PComA since both groups have minimal or no
125 possibilities to compensate the reduced posterior circulation from carotid arteries
126 through PCoA in comparison with the individuals with presence of normal PCoA.
- 127 5. The absence of A1 segment of the anterior cerebral artery (ACA) was documented.
128 In these cases both A2 segments are supplied by the existing A1 from the contralateral
129 ACA.
- 130 6. VAH was established according to MRA (V4 segment) and duplex scanning (V1-V3
131 segment). We defined VA as hypoplastic when VA diameter in the entire course was
132 less than 2.5 mm. We also studied the group named “VAH-PICA” with VA aplasia or
133 hypoplastic VA not communicating with BA and terminating in PICA or the neck ,
134 i.e. subjects with the possibility of the greatest reduced blood flow through VA.

135 We present a pattern of the posterior part of CW found in our individuals. We have
136 estimated what concomitant vascular variants of the vertebrobasilar system are more
137 common in FCW in comparison with the adult CW. Also, we have estimated if FCW
138 influence blood flow redistribution in the anterior part of anterior circulation, i.e. if both
139 A2 segments are supplied by the existing A1 from the contralateral or ipsilateral sides of
140 ACA.

141 We assessed if the posterior part of CW differs in subjects with normal VA, VAH
142 communicating with BA and VAH not communicating with BA or VA aplasia.

143

144 *Statistics*

145 The *Chi* square independence (χ^2) test was applied in carrying out the comparison between
146 the categorical variables, while Fisher's exact test was used in the case of a small sample size.
147 Continuous variables meeting the assumptions of normality were analysed using t-tests for
148 independent groups. The chosen significance level was $\alpha=0.05$.

149 **Ethics.** This study was approved by the Ethics Committee for the Vilnius region (No.
150 158200-15-767-281).

151

152 **Results**

153

154 *Posterior part of CW.* The characteristics of the posterior part of CW are presented in Table
155 1. FCW was found in 15.9 % of subjects free of stroke and TIA. Side-related differences in
156 the posterior part of CW observed in both types of CW did not reach a statistically significant
157 difference. In 47.9% of individuals both PCoA were absent or hypoplastic. 2.3 % of the
158 subjects had both-sided FCW.

159 Table 1. The characteristics of the posterior part of the circle of Willis (n=923)

Type of posterior part of CW	N	Proportion (%)
Adult type	776	84.1
• Absence of both PCoA	442	47.9

• Absence of one PCoA	191	20.7
○ Absence of left PCoA	112	12.1
○ Absence of right PCoA	79	8.6
• Both PCoA	143	15.5
Fetal type	147	15.9
Side of fetal circle of Willis		
• Left-sided	58	6.3
• Right-sided	68	7.4
• Both-sided	21	2.3
Contralateral PCoA		
• Absence/hypoplasia	81	8.8
• Normal	45	4.9
• Fetal circle of Willis (both-sided)	21	2.3

160

161 *Demographic characteristics and coexisting arterial variants in adult CW and FCW (Table*
 162 *2). The proportion of men and women did not differ in both configurations of CW. The*
 163 *coexisting VAH was more common in subjects with FCW than in subjects with adult CW*
 164 *(correspondingly, 28.6% and 13.4%, $p < 0.001$). Aplasia of A1 was rare in both groups,*
 165 *although aplasia of A1 was more common in the group with FCW compared to those with*
 166 *adult CW. Moreover, in the majority of the subjects with FCW (in 6 of 7 cases), A1 aplasia*
 167 *was found ipsilaterally to FCW, the carotid artery supplies blood to PCA and MCA, while*
 168 *ACA is receiving blood from the contralateral carotid artery.*

169 Table 2. The comparison of coexisting characteristics in FCW and adult CW

	Fetal circle of Willis N=147	Adult circle of Willis N=776	p-value
<i>Demographics:</i>			
Men	79 (53.7%)	448 (57.7%)	NS*
Age	46.4±1.4	48.1±0.4	NS
<i>Vertebrobasilar system</i>			
VAH	42 (28.6%)	104 (13.4%)	<0.001
VAH terminating in PICA/aplasia	16 (10.9%)	16 (2.1%)	<0.001
BA hypoplasia /aplasia	2 (1.4%)	5 (0.64%)	NS
Fenestretion of BA	1 (0.7%)	3 (0.4%)	NS
<i>Anterior part: Aplasia of A1 (ACA artery) segment and both A2 segments are supplied from one side by the existing A1</i>	7 (4.8%) Ipsilateral side: 6 (4.1%) Contralateral side: 1 (0.7 %)	13 (1.7%)	0.018

170

171 *NS-p>0.05

172 *Association between VAH and the pattern of the posterior part of CW.* The association
 173 between VAH and the variants of the posterior part of CW is presented in Table 3. The
 174 pattern of the posterior part of CW in subjects with VAH differs from those with normal VA.

175 FCW was more frequent in individuals with VAH than in those with normal VA
176 (accordingly, 28.8 % vs. 13.5%, $p<0.001$), while the absence/hypoplasia of both PCoA was
177 more common in subjects with normal VA in comparison to those with VAH (accordingly,
178 50.7% and 32.9% , $p<0.001$).

179

180 Table 3. The comparison of the posterior part of CW in patients with VAH and normal VA.

	Normal (n=777)	VAH (n=146)	P-value
Adult type:			
Absence of both PCoA	394 (50.7%)	48 (32.9%)	<0.001
Absence of one PCoA	164 (21.1%)	27 (18.5%)	NS*
Presence of both PCoA	114 (14.7%)	29 (19.9%)	NS
Fetal circle of Willis			
Unilateral	105 (13.5%)	42 (28.8%)	0.001
Bilateral	96 (12.4%)	30 (20.5%)	0.008
	9 (1.2%)	12 (8.2%)	<0.001

181

182 *NS- $p>0.05$

183

184 *Difference of the posterior part of CW in subjects with VAH not communicating with the*
185 *basilar artery and those with VAH communicating with the basilar artery.* The above
186 mentioned regularity was even more striking in the least developed hypoplastic VA that do
187 not communicate with the basilar artery (Table 4). Half of the patients with VAH - PICA had
188 FCW compared to 13.5% of those with normal VA diameter and to 22.8% of individuals with
189 VAH that communicates with the basilar artery, $p<0.005$. Moreover, the proportion of

190 bilateral FCW was largest in the subjects with VAH-PICA. On the contrary, the absence of
 191 both PCoA was most frequent in the group with normal VA and rare in VAH-PICA group
 192 (accordingly, 50.7% and 12.5%, $p < 0.001$).

193 Table 4. Comparison of the posterior part of CW in patients with a different degree of VAH.

194

	Normal (n=777)	VAH-BA (n=114)	VAH-PICA (n= 32)	p-value
Adult type:				
Absence of both PCoA	394 (50.7%)	44 (38.6%)	4 (12.5%)	0.001
Absence of one PCoA	164 (21.1%)	22 (19.3%)	5 (15.6%)	NS
Presence of both PCoA	114 (14.7%)	22 (19.3%)	7 (21.9%)	NS
Fetal circle of Willis	105 (13.5%)	26 (22.8%)	16 (50%)	0.001
Unilateral	96 (12.4%)	20 (17.5%)	10 (31.3%)	0.004
Bilateral	9 (1.2%)	6 (5.3%)	6 (18.8%)	0.001

195

196 *The sides of VAH and FCW.* VAH and FCW were more frequently observed on the same
 197 side: VAH was observed ipsilaterally to FCW in 76% of cases, VAH - PICA - ipsilaterally to
 198 FCW in 82.4% of cases.

199

200 Discussion

201

202 FCW was found in 15.9% of individuals, bilaterally - in 2.3% of cases. According to other
203 authors, the proportion of FCW ranges from 11 to 32% [1], [6], [7], [8], [9]. VAH was
204 observed in 12.5 % of subjects. According to the data presented by other authors, depending
205 on the VAH definition, the method of examination and the category of population, this
206 proportion ranges from 1.9% to 25% [10]. Therefore, the population under our investigation
207 was a typical population.

208 FCW was more frequently observed in subjects with VAH, i.e. with an insufficiently
209 developed proximal part of the vertebrobasilar system, compared to those with normal VA
210 diameter. Among individuals with a very small VA terminating in PICA/neck/aplasia,
211 compared to those subjects whose VA is wider and forms the basilar artery, the proportion
212 of FCW was larger. Moreover, FCW was more common in ipsilateral to VAH side rather
213 than contralateral.

214 According to [3], BA diameter is inversely associated with FCW. Otherwise, FCW was more
215 common in individuals with an insufficiently developed distal part of the vertebrobasilar
216 system which can lead to inadequate posterior circulation, rather than in those with the
217 normal basilar artery. The influence of an insufficiently developed proximal part of the
218 vertebrobasilar system, including VAH or aplasia on the posterior circulation insufficiency
219 and as a consequence the demand to compensate the possible inadequate blood supply to the
220 brain is under discussion. Although, many authors estimate VAH as an independent predictor
221 of stroke or TIA [10]. The hypothesis that VAH can lead to the posterior circulation
222 insufficiency is also supported by our results that with the decreasing VA diameter, the risk
223 of stroke/TIA increases [4]. Moreover, VAH can lead to a relative regional hypoperfusion in
224 the PICA territory [11]. As described in a study [1], during the embryological development
225 the anterior circulation supplies the occipital region, the brain stem and the cerebellum via

226 multiple anastomoses because the posterior circulation is not yet well developed. After the
227 development of VA and sufficient posterior circulation, these anastomoses regress. FCW as a
228 result of failed regression that may be associated with insufficient blood supply via the
229 insufficiently developed vertebrobasilar system, including hypoplastic. In these cases the
230 carotid artery may particularly recall the role of the vertebrobasilar system by supplying
231 blood to the posterior fossa as in the embryological development. The greater proportion of
232 FCW in subjects with more severe VAH whose blood flow through VA is reduced to a
233 greater degree supports the hypothesis that with the decreasing blood supply from VA to the
234 brain, the possible inadequate perfusion in posterior circulation is more frequently
235 compensated through FCW from anterior circulation, ICA. In case of small diameter VA,
236 compared to normal diameter VA, FCW may provide better blood supply to the brain and
237 prevent from cerebral ischemia.

238 In summary, the pattern of the posterior part of CW in stroke/TIA-free subjects with VAH
239 and normal VA was different. The proportion of absence/hypoplasia of both PCoA, i.e. the
240 absence /hypoplasia of primary collaterals was larger in subjects with normal proximal
241 circulation, i.e. normal VA diameter compared to those with insufficiently developed
242 proximal part of the vertebrobasilar system, VAH. And vice versa, the proportion of FCW
243 was larger in those with VAH compared to those with normal VA diameter. The proportion
244 of subjects with a complete posterior part was larger in those with VAH although the
245 difference did not reach a statistically significant difference. These results support the
246 hypothesis that in cases of small vertebral arteries the collateral circulation through PCoA or
247 FCW may be important for prevention of stroke/TIA in the posterior circulation.
248 Future investigations are needed in order to assess whether in cases of VAH the configuration
249 of the posterior part of CW can prevent or increase the stroke/TIA risk. The study [1]
250 revealed that the coexistence of the basilar artery hypoplasia, VAH and the fetal CW were

251 more common in stroke patients. However, in the above mentioned study, the role of FCW is
252 not clear. Is FCW an independent stroke predictor, or is FCW not able to compensate the
253 reduced blood flow in cases of coexistence of small proximal and distal parts of the
254 vertebrobasilar system? Future investigations are needed on the associations between a small
255 vertebrobasilar system, CW configuration and neurological symptoms such as vertigo.
256 Patients with stroke/TIA were excluded from our study, however, suggestions can be made
257 for further studies to compare how CW differs in vertigo patients and healthy subjects.
258 In cases of FCW, the territory supplied with blood by the carotid artery increases up to three
259 arteries (ACA, middle cerebral artery (MCA) and PCA). A1 aplasia in most cases is found
260 ipsilateral to FCW and may be associated with the need to redistribute the blood flow in the
261 anterior circulation and to reduce the territory of blood supply from the carotid artery from
262 three arteries territory (ACA, MCA, PCA) to two arteries territory (MCA, PCA, while both
263 ACA are supplying from the contralateral carotid artery.

264

265 **Conclusions**

266 Individuals with VAH have a different pattern of the posterior part of CW in comparison
267 with those with normal VA diameter. With the increasing degree of VAH, the proportion of
268 FCW increases while the proportion of absence/hypoplasia of both PCoA decreases.

269

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