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Fatal subarachnoid hemorrhage from an aneurysm of a persistent primitive hypoglossal artery: Case series and literature overview

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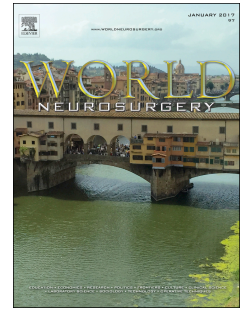
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**hypoglossal artery: Case series and literature overview**

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**Running title:** Fatal subarachnoid hemorrhage from an aneurysm of a persistent primitive hypoglossal artery

**Background:** Persistent carotid-basilar connections have a prevalence of 0.14%. Recognizing such persistent fetal anastomoses between the carotid and the vertebrobasilar circulation is of great importance since they are reportedly associated with an increased prevalence of intracranial aneurysms.

We report the case of a 15-year-old female who presented with a WFNS grade 5 subarachnoid hemorrhage from an aneurysm at the junction of a persistent primitive hypoglossal artery and the posterior inferior cerebellar artery origin. Supratentorially, unfortunately, there was no parenchymal blush or cortical venous return. Eventually, a multidisciplinary decision was made to withdraw care.

Fifty-seven cases were reported in the literature to date of persistent hypoglossal arteries, 16 of which presented with an associated aneurysm, 5 with an arterio-venous malformation and 6 with a subarachnoid haemorrhage. Our case is the youngest patient reported so far. Hypoplasia or aplasia of the vertebral artery were often encountered (36 and 13 cases respectively), as well as carotid artery stenosis (15 cases).

**Conclusions:** Although uncommon, it is important to recognize persistent carotid-basilar connections, since they have a considerable hemodynamic impact on the posterior cerebral circulation via the carotid system. A critical reduction in the carotid blood flow will, therefore, have ischemic consequences in the posterior cerebral territories. In addition, such connections might be associated with anomalies of the vessel wall and be predisposed to aneurysm formation. The endovascular neuro-interventionalist, as well as the vascular and skull base neurosurgeon need to be aware of their anatomy and variations.

Persistent carotid-basilar connections have a prevalence of 0.14%<sup>1</sup>. Four such persistent fetal anastomoses between the carotid and the vertebrobasilar circulation have been recognized, i.e. the primitive trigeminal, otic, hypoglossal, and proatlantal intersegmental arteries. A persistent primitive hypoglossal artery (PPHA) is extremely rare, second in frequency to the persistent primitive trigeminal artery, with an incidence of 0.02% – 0.26%<sup>2-40</sup>. Recognition of a primitive hypoglossal artery is, nonetheless, of great importance clinically since they are reportedly associated with an increased prevalence of intracranial aneurysms<sup>41</sup>. Furthermore, since they can form the sole arterial supply to the posterior circulation, injury during surgery or endovascular treatment may cause posterior circulation ischemia and serious morbidity and mortality<sup>42</sup>.

## Material and methods

We report the case of a 15-year old female who presented to the Erasmus MC Stroke Center with a subarachnoid hemorrhage from an aneurysm at the right PPHA-PICA junction.

The local prevalence was calculated by searching all cases within the Erasmus MC Radiology Department PACS suite on previous cases of PPHA from 2006 to 2016. We discovered three more cases that were described briefly.

A systematic literature review was performed using the key words “persistent primitive hypoglossal artery”, “hypoglossal artery aneurysm”, “hypoglossal artery case report” and various combinations on Ovid MEDLINE, EMBASE, and Google Scholar. Grey literature was assessed on Web of Science and Google Scholar. Two investigators (IV, VV) independently conducted the search and a third investigator solved any existing conflicts (RD). We included all case studies or case series of hypoglossal arteries reported in the literature, with or without associated aneurysms.

A previously healthy 15-year-old female was admitted to the emergency room of the Erasmus MC University Medical Center, Sophia Children's Hospital with sudden loss of consciousness. She was swimming with her sister and upon emerging from the water she reported feeling ill, grabbed her head and collapsed. Basic life support was immediately started, with bystanders resorting to an automatic external defibrillator. Upon arrival of the medical mobile team, she was unconscious, with a Glasgow Coma Score of 3, with respiratory insufficiency and exhibiting ventricular fibrillation. She was intubated and after cardioversion she returned to sinus rhythm.

Upon arrival at the emergency room she was intubated and mechanically ventilated with a Glasgow Coma Score of 3, and had bilaterally reactive pupils. CT and CT angiography of the head revealed a massive subarachnoid hemorrhage (modified Fisher grade 4), with blood on the tentorium and in both Sylvian fissures, plus triventricular hydrocephalus [Fig 1]. CT angiography showed an aplastic right vertebral artery and a primitive persistent hypoglossal artery (PPHA) on the right side, with a small aneurysm, most probably at the take-off of the posterior inferior cerebellar artery (PICA) [Fig 2]. Unfortunately, the supratentorial cortical vessels exhibited poor filling. The patient was therefore rushed into surgery and bilateral external ventricular drains were placed. The intracranial pressure was over 50 cm H<sub>2</sub>O. Immediately after the procedure she was taken to the angiography suite for endovascular treatment of the aneurysm.

Four-vessel angiography revealed an absent vertebral artery on the right side and an atrophic vertebral artery on the left side. The right hypoglossal artery exhibited a small aneurysm at the PICA origin [Fig 3]. The basilar artery and cerebellar parenchyma had sufficient flow through the persistent hypoglossal artery [Fig 4], but supratentorially there was no parenchymal blush or cortical venous return. Despite the ventricular drainage, she developed a fixed, maximally dilated left pupil. A multidisciplinary decision was then made to withdraw care, as the prognosis was deemed unsalvageable due to the widespread supratentorial hypoperfusion had been ongoing for about 3 hours. Eight hours after the initial bleed she was

## **Additional cases and literature review**

### *Additional cases*

In the Erasmus MC University Medical Center department of Radiology database we were able to extract three more cases of PPHA since 1980. These were all incidental findings. The first patient was a 78-year-old woman who underwent an MRI because of recurrent abducens nerve palsy. There was no explanation to be found, but a persistent hypoglossal artery without aneurysms on the right side was noted. The second patient, a 41-year-old woman, was evaluated for carotid artery occlusion, hypertension and renal artery stenosis. Digital subtraction angiography could only be performed through the left vertebral artery since the rest of the vessels were too stenotic. The brachiocephalic trunk and common carotid arteries on the right and left sides were fully occluded. The anterior circulation turned out to be completely supplied by the persistent pro-atlantal and hypoglossal arteries. There was also retrograde filling of the right vertebral artery demonstrating a subclavian steal syndrome. There were no aneurysms. The diagnosis of Takayasu arteritis was made. The third patient was a 60-year-old woman who presented with headache and a 5 x 5 cm right temporal lobe arachnoid cyst. Because of the tortuous trajectory of the basilar artery seen on the MRI, CT angiography was performed. This revealed no vertebral arteries, only a right-sided persistent hypoglossal artery functioning as a basilar artery as well. There were no aneurysms present.

### *Literature review*

The search criteria revealed 57 articles describing cases of PPHA [Table 1]<sup>1,3,7,21,33,38,42-92</sup>. The age ranged between 14-days-old to 78-years-old with a mean age of 51.8 years. In two cases, the sex of the patient was not specified and in one case the age was not specified. In 52 patients (89.7%), the origin of the PPHA was at the internal carotid artery (ICA). The external carotid artery (ECA) was noted as the origin in

5 cases and the common carotid artery (CCA) in one case. The end point of the PPHA was the vertebral artery (VA) in 5 cases, PICA in one case and the basilar artery (BA) in the rest.

Out of the 57 cases, 16 patients (27.6%) were found to have aneurysms; 7 (12.1%) were associated with an aneurysm on the PPHA and 9 with aneurysms elsewhere. The associated aneurysms were present at the following locations: 4 on the PICA - one on the left and three on the right, all ipsilateral to the PPHA; 1 on the left anterior inferior cerebellar artery (AICA); 1 on the anterior communicating artery (ACA); and 2 on the BA. One patient exhibited multiple intracranial aneurysms (left ICA aneurysm, a right middle cerebral artery (MCA) aneurysm and a basilar tip aneurysm). Six patients presented with subarachnoid hemorrhage, the rest were incidental findings.

Stenosis was fairly common in patients with PPHA. Fifteen (25.8%) cases presented with severe stenosis of the internal carotid arteries. There was also stenosis identified on the CCA, one severe and one moderate. The PPHA presented itself with moderate stenosis in 2 cases. There were also two cases of stenosis on the MCA and two cases of stenosis on the basilar artery.

Hypoplasia was a common finding: in 78% of the reported cases, the VAs were hypoplastic or aplastic and in 79% of cases. The posterior cerebral arteries (PCA) appeared hypoplastic or aplastic<sup>2</sup>. Vertebral artery hypoplasia was present in 36 cases (62%), and aplastic VAs were seen in 13 (22.4%) cases; the posterior cerebral artery was hypoplastic in 5 cases, and 11 were completely absent. One case presented with a hypoplastic posterior communicating artery and one with an absent internal carotid artery.

CTA and MRA data retrieved from 25,000 scans performed in the Erasmus MC between 2006 and 2016 revealed 4 patients diagnosed with PPHA. Of these, only one presented an aneurysm. Prevalence is low, at 16/100,000 (4/25,000).



Although uncommon, it is important to recognize persistent carotid basilar connections. One important reason is that it creates dependence between posterior cerebral circulation and the carotid system. A critical reduction in the carotid blood flow will have ischemic consequences in the posterior cerebral territories. Another reason is that they might be associated with anomalies of the vessel wall, which give rise to hemodynamic stress predisposing to the appearance of aneurysms, with possible hemorrhagic consequences. This potential SAH may have grave consequences, as illustrated by the present case report.

In the prechoroidal stage (gestational age of approximately 4 weeks), the blood supply to what will be the future brain is provided by the anterior circulation by means of the internal carotid artery which gives rise to a cranial ramus to support the forebrain (the forerunner of the anterior cerebral artery) and a caudal ramus which is a continuation of the carotid distal to the cranial ramus and supports the midbrain and hind-brain (forerunner of the future posterior communicating artery, first segment of the posterior cerebral and part of the basilar). The caudal ramus input is not enough to support the growing necessities of the part of brain supplied by it. To accommodate tissue needs, new vascular supply is established via segmental vessels: trigeminal, hypoglossal and proatlantal type I and type II. The hypoglossal artery arises from the distal cervical ICA, usually between the C1 and C3 vertebral bodies; early in its course it joins the 12<sup>th</sup> cranial nerve and enters the posterior cranial fossa via the (enlarged) hypoglossal canal and it terminates at the level of basilar artery. In certain cases, it may also originate from the external carotid (ECA)<sup>59</sup> or the common carotid artery (CCA)<sup>73</sup>. The four arteries regress and disappear synchronously with the development of the posterior communicating and basilar arteries at the sixth week of fetal development. First, the otic artery regresses, followed by the hypoglossal artery, the trigeminal artery, and finally the proatlantal arteries.

Four criteria for identifying a PPHA have been described<sup>38,85</sup>: 1) It arises from the cervical part of the internal carotid artery at C1-C2 vertebral level; 2) It enters the posterior fossa along with the accessory nerve through the hypoglossal canal; 3) The basilar trunk appears filled only beyond its anastomosis with the PPHA; and 4) vertebral arteries and posterior communicating arteries may be hypoplastic or absent.

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The occurrence of a persistent primitive hypoglossal artery is rare with an incidence of 0.02% – 0.26%<sup>27</sup> and is encountered even less in the pediatric population. Generally, it is an incidental finding. In our literature review, out of 57 we could only find four pediatric cases with reported PPHA (6.9%). None of these was reported with an associated aneurysm. In total, 16 cases (27.6%) with an association between PPHA and an aneurysm was found. Six of them had presented with SAH but no mortality or morbidity was described. We present the first unfortunate case of a 15-year old young woman with an SAH from an aneurysm at the origin of the PICA on a PPHA. This would correspond to a mortality of 14.3% (1/7). There seems to be a poignant positive reporting bias in the literature regarding aneurysms associated with the PPHA, as most of the studies present cases with successful identification and treatment of said aneurysms.

A PPHA is commonly associated with hypoplastic or aplastic VA, PCA, and/or AICA, thus making it an important supplier to the posterior cerebral territories. Accidental findings of hypoplasia or aplasia of these vessels should also lead us to consider the involvement of a carotid basilar anastomosis in general. In skull base surgery, the failure to identify this vessel and sacrificing it intentionally or by mistake will most certainly induce ischemia in the posterior territories. Furthermore, identification of a primitive persistent posterior circulation artery is important for planning of neuroradiologic intervention to prevent possible risks.

## Conclusion

We present the case of a 15-year old girl presenting with subarachnoid haemorrhage from an aneurysm of the PPHA. While rare, these persistent carotid-basilar anastomoses pose unique challenges in the treatment of aneurysms and AVMs associated with them. Both from an endovascular as well as from an open surgery perspective, knowledge of the anatomy and its variations, as well as their potential associations with aneurysm formation is crucial.

**Declarations of interest:** none

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**Table 1** – Characteristics of the cases described in the literature and associated pathologies. ICA= Internal Carotid Artery, ECA= External Carotid Artery, CCA= Common Carotid Artery, AVM= arterio-venous malformation, SAH= subarachnoid haemorrhage, BA= Basilar Artery, VA= Vertebral Artery, PICA= Posterior Inferior Cerebellar Artery, PCA = Posterior Cerebral Artery, MCA= Middle Cerebral Artery, AICA= Anterior Inferior Cerebellar Artery

**Figure 1** = Non-contrast enhanced CT which shows massive subarachnoid hemorrhage (modified Fisher grade 4), with blood on the tentorium and in both Sylvian fissures, plus triventricular hydrocephalus

**Figure 2** = CT angiography showing the origin of the persistent primitive hypoglossal artery and its trajectory through the hypoglossal canal

**Figure 3** = Three-dimensional reconstruction of the four vessel angiography, showing the aneurysm at the junction of the persistent primitive hypoglossal artery and the posterior inferior cerebellar artery.

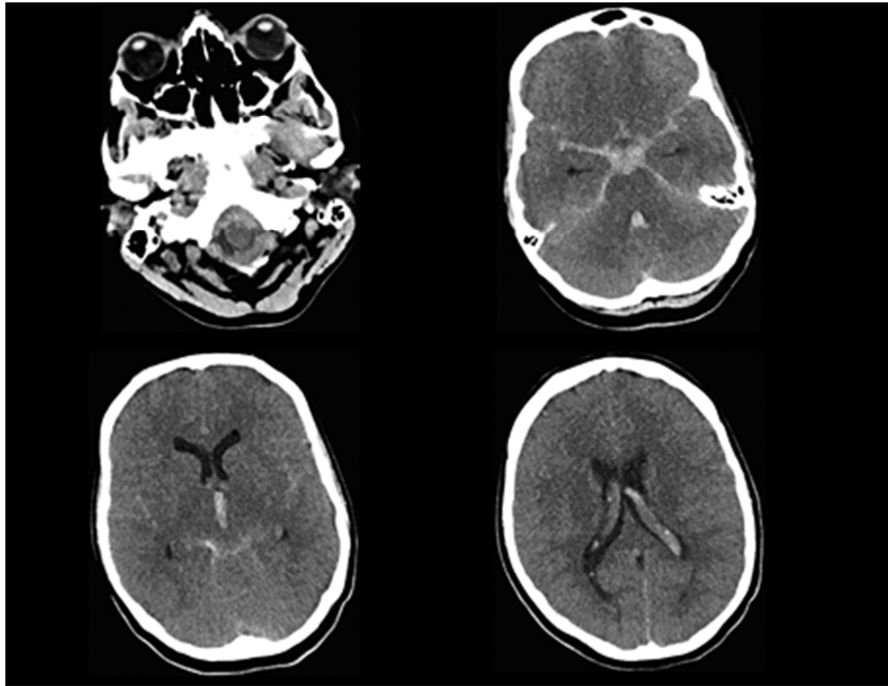
**Figure 4** = Lateral native right common carotid injection, demonstrating the persistent primitive hypoglossal artery (left) and the lack of supratentorial parenchymal cortical blush (right).

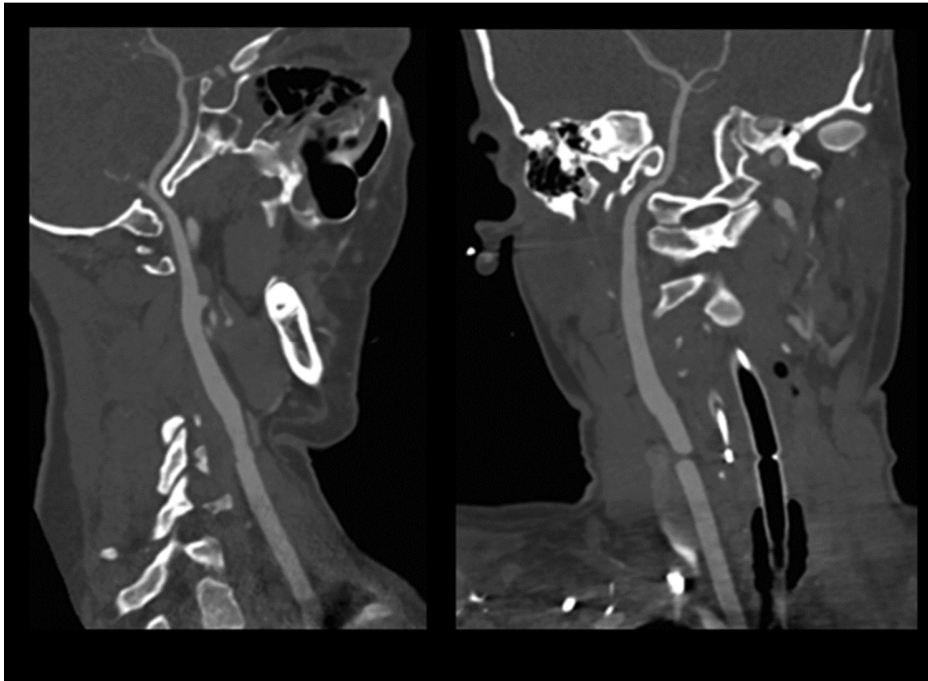
			TOTAL	NO ANEURYSM	ANEURYSM
			57	41	16
SEX	Female (F)		33	21	12
	Male (M)		24	18	4
AGE	F	Mean± SD	52.9 ± 18.2	55.8 ± 20.3	47.8 ± 12.7
	M	Mean± SD	50.4 ± 24.1	47.3± 25.4	64.5± 8.5
ORIGIN*	ICA		51	36	15
	ECA		5	4	1
	CCA		1	1	0
END	BA		51	37	14
	VA		5	3	2
	PICA		1	1	0
Associated AVM			5	4	1
Associated SAH			6	N/A	6
STENOSIS	ICA		15	14	1
	CCA		2	2	0
	MCA		2	2	0
	BA		2	2	0
HYPOPLASIA	VA		36	25	11
	PCA		5	5	0
	AICA		1		1
APLASIA	VA		13	10	3
	PCA		11	6	5
	PCOM		1	0	1
	ICA		1	1	0

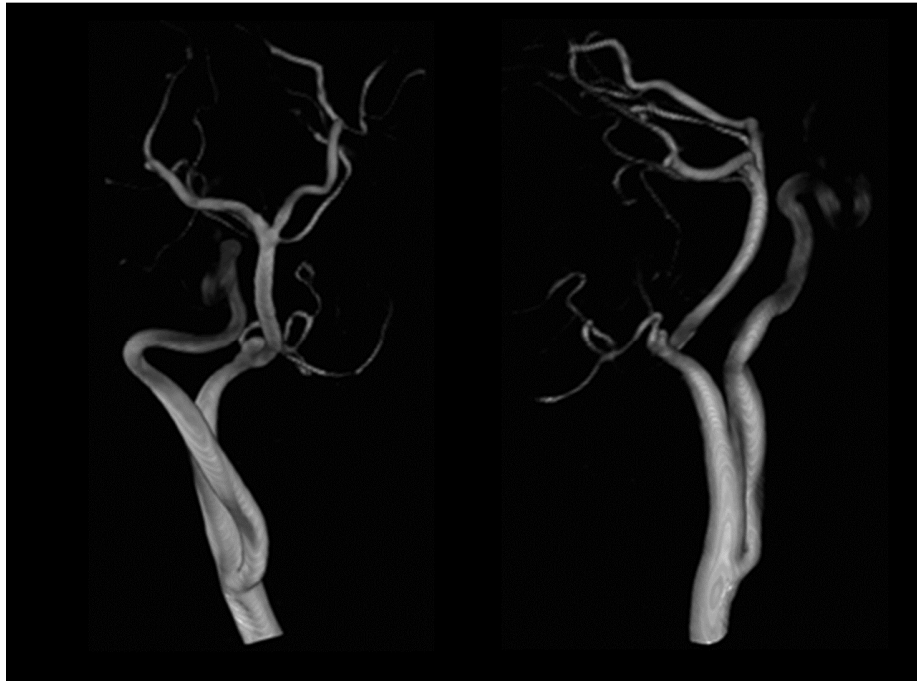
\*17 of the articles did not specify origin and end; 1 article only specified the origin (unspecified origins and ends were considered as normal variants)

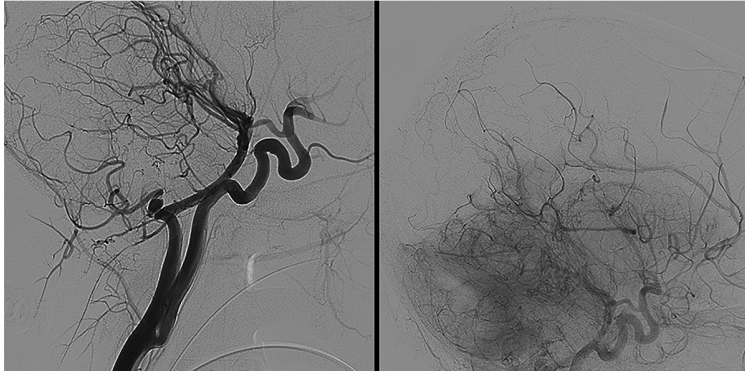
Table 1











**Highlights**

- First paper to report a pediatric case of a persistent primitive hypoglossal artery with subarachnoid haemorrhage
- Of the 57 reported cases in the literature, 16 harbor aneurysms and 5 have associated arterio-venous malformations
- The presence of the posterior primitive hypoglossal artery is often associated with hypoplasia or aplasia of the vertebral artery
- Carotid artery stenosis is reported in 15 of the 57 cases
- 6 of the 57 patients presented with a subarachnoid haemorrhage

**Abbreviations**

WFNS= World Federation of Neurosurgical Societies

PPHA= Persistent Primitive Hypoglossal Artery

PACS = Picture Archiving and Communication System

ICA= Internal Carotid Artery

ECA= External Carotid Artery

CCA= Common Carotid Artery

AVM= arterio-venous malformation

SAH= subarachnoid haemorrhage

BA= Basilar Artery

VA= Vertebral Artery

PICA= Posterior Inferior Cerebellar Artery

PCA = Posterior Cerebral Artery

MCA= Middle Cerebral Artery

AICA= Anterior Inferior Cerebellar Artery