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**Case Report**

# The Development of Indirect Carotid Cavernous Fistulas after Microvascular Ischemic 4th Nerve Palsies

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Dural fistula · Carotid cavernous fistula · Oculomotor nerve · Microvascular ischemic nerve palsy · Risk factor

**Abstract**
An indirect carotid cavernous fistula (CCF) is an abnormal connection between the cavernous sinus and internal or external carotid artery. Indirect CCFs often occur spontaneously, particularly in the setting of vascular risk factors such as hypertension, diabetes, and atherosclerosis. Microvascular ischemic nerve palsies (NPs) share these vascular risk factors. However, to date, no temporal relationship between microvascular ischemic NP and indirect CCF occurring sequentially has been reported. We describe the cases of 64- and 73-year-old women who developed indirect CCFs within 1–2 weeks after spontaneous resolution of a microvascular ischemic 4th NP. Both patients had complete resolution and an asymptomatic period between the 4th NP and CCF. This case highlights the shared pathophysiology and risk factors between microvascular ischemic NPs and CCFs, and emphasizes that CCFs should be kept in the differential diagnosis for red eye or recurrent diplopia in patients with previous microvascular ischemic NP.



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## Introduction

An indirect carotid cavernous fistula (CCF) is an abnormal arteriovenous communication between the cavernous sinus and branches of the internal carotid artery, external carotid artery, or both [1]. Indirect CCFs often occur spontaneously. Their pathogenesis is not completely understood, but a widely supported theory states that they form as an alternate outflow path from the cavernous sinus following a primary thrombosis [2, 3]. Indirect CCFs are seen most frequently in postmenopausal women [4]. Risk factors for indirect CCF include hypertension, diabetes, atherosclerosis, connective tissue disorders (e.g., fibromuscular dysplasia, Ehlers-Danlos type IV), or dissection of the internal carotid artery [2].

Many of the risk factors for spontaneous CCF formation, including hypertension and atherosclerotic or diabetic vascular disease [2, 5], are also risk factors for microvascular ischemic nerve palsies (NPs) [6]. However, despite these shared risk factors, to our knowledge no prior cases of sequential microvascular ischemic NPs followed by spontaneous indirect CCF formation in the same patient have been reported. Here, we report two cases of indirect CCF development shortly after the resolution of microvascular ischemic 4th PSs.

## Case Presentation

*Case 1*

A 64-year-old woman was seen in neuro-ophthalmology clinic for new vertical binocular diplopia of 1 week duration. She had no known medical problems and did not take any medications. There was no prior head trauma. Prior to the referral, she had an MRI brain and orbits with contrast that was normal, and sedimentation rate and C-reactive protein were normal. Neuro-ophthalmic examination revealed a visual acuity of 20/20 in the right eye and 20/20 in the left eye, pupils were equal sizes, and there was no relative afferent pupillary defect. External exam showed no ptosis, and conjunctiva was normal in both eyes. She had a left hypertropia of 3 PD that was worse in right gaze and left head tilt, and excyclotorsion confirmed by Maddox rod testing. Ocular ductions were full apart from a mild limitation of depression in adduction. Cranial nerve function was otherwise normal. She was diagnosed with a left 4th NP, presumed microvascular ischemic in origin, and observation was recommended. Old photographs were reviewed, and she did not have a longstanding right head tilt. Her double vision resolved spontaneously after 6 weeks. She had 1 week where she was asymptomatic, but then developed horizontal binocular diplopia and redness in both her eyes. Repeat examination showed normal visual acuity and intraocular pressure, but she had a mild limitation of abduction in both eyes (90% of normal) and had a comitant esophoria of 6 PD. She was suspected to have an indirect CCF. A computed tomography angiogram showed enlargement of bilateral cavernous sinuses, intercavernous sinus, and retroclival venous plexus. There was also enlargement of the bilateral superior ophthalmic veins and facial veins. She underwent a cerebral angiogram which showed bilateral cavernous sinus dural arteriovenous fistulas supplied by branches of the internal and external carotid arteries bilateral with drainage into bilateral superior ophthalmic veins, left interior petrosal sinus, and bilateral cortical venous reflux. The absence of signs of the CCF on MRI at the time of initial presentation with 4th NP was confirmed by a neuro-radiologist. She underwent successful endovascular transvenous coil embolization. This was complicated by worsening of the 6th NPs, and she had worse limitation of abduction in both eyes (right 50% of normal and left 0% of normal). This gradually improved, and at 6 months, she had a mild limitation of abduction (75% of normal) with an alternating esotropia of 18 PD.

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*Case 2*

A 73-year-old woman was referred for new vertical binocular diplopia. She had a past medical history of pre-diabetes and osteoporosis. Her only medication was risedronate. She presented to the emergency room and had a computed tomography angiogram that was normal. An MRI brain and orbits with contrast were also performed, which was normal. She was referred to neuro-ophthalmology and had a visual acuity of 20/20 in both eyes, equal and reactive pupils, a right hypertropia of 3 PD that was worse in left gaze and right head tilt, and right eye excyclotorsion confirmed by Maddox rod testing. There was a mild limitation of depression in adduction in the right eye, but ocular ductions were otherwise full. Cranial nerve function was otherwise normal. She was diagnosed with a right 4th NP, presumed microvascular ischemic in nature. Sedimentation rate and C-reactive protein were normal. Her double vision spontaneously resolved after 6 weeks. She had a period without symptoms for 2 weeks, but then noticed redness in her right eye. Repeat examination at that time showed right corkscrew episcleral vessels, elevated intraocular pressure in the right (25 OD and 13 OS), right ptosis and miosis related to a right Horner's syndrome, pharmacologically confirmed with apraclonidine. Ocular ductions were full. These new developments were concerning for a right indirect CCF, and computed tomography angiography showed an enlarged right superior ophthalmic vein and enlargement of the right cavernous sinus. Cerebral angiogram showed a right-sided dural arteriovenous fistula of the right cavernous sinus with supply from the branches of the right internal maxillary artery including the artery of the foramen rotundum with a small amount of supply from dural branches of the internal carotid arteries, most prominently the left MHT. Drainage was from a dilated right superior ophthalmic vein and then into the right superficial temporal vein and external jugular vein. There was no intracranial venous reflux. The original MRIs were reviewed by a neuro-radiologist for signs of a CCF at initial presentation with 4th NP, and none were observed. She underwent transvenous endovascular embolization, and her eye redness resolved. However, this was complicated by a right 6th NP as she had a limitation of abduction (25% of normal), which spontaneously resolved at 6 months. The right Horner's syndrome persisted.

## Discussion

Here, we report 2 patients who developed CCFs in close temporal relationship to a microvascular ischemic 4th NP (4 NP). Though it is possible that a posteriorly draining CCF mimicked a microvascular ischemic NP [7], this is unlikely since both patients had spontaneous improvement and were asymptomatic between the microvascular ischemic NP and the CCF. The signs and symptoms of an indirect CCF can be dynamic with the pattern of drainage [8, 9], which may switch from posterior to anterior if the former pathway becomes thrombosed [3, 10]. However, an isolated 4 NP is an uncommon presentation for cavernous sinus lesions [8, 11, 12], and while two previous reports of 4 NP evolving into a red-eyed CCF exist [13, 14], the time course of the present cases does not conform to the expected natural history of a CCF with changing drainage. The clinical course of the 4 NP is most consistent with a microvascular ischemic etiology, given that it was relatively stable and resolved spontaneously within 6 weeks [15, 16]. A distinct process then resulted in the indirect CCF. The shared constellation of events in these cases indicates that underlying vascular risk factors may have contributed to both the ischemic NP and indirect CCF formation.

Microvascular ischemic ocular motor NPs are strongly associated with vasculopathic risk factors including hypertension, diabetes, dyslipidemia, smoking, and history of coronary artery disease, myocardial infarction, or stroke [17]. Relatively little is known about the

pathophysiology of microvascular ischemic NP, but common features from three available autopsy studies [18–20] include hyalinization of the vasa nervorum and myelin loss with relatively preserved underlying axons [6, 16]. Evidence of focal ischemia was present particularly in watershed territories. It therefore appears that chronic vascular changes lead to hyalinization and narrowing of intraneural arterioles, causing focal hypoxia of the endoneurial space and eventual demyelination, which leads to the nerve conduction deficit [6].

Indirect CCF is similarly associated with vasculopathic risk factors. In individuals without predisposing genetic conditions or cavernous aneurysms, spontaneous CCFs most often occur in the setting of arterial hypertension and atherosclerotic or diabetic vascular disease [5]. The pathophysiology of spontaneous CCF formation, and in particular the initial insult that leads to arterial wall rupture, is not agreed upon. Indirect CCFs may develop after microscopic disruption of thin-walled dural arteries, causing dilation of existing dural arterial anastomoses [1, 5, 21], or alternatively may develop following thrombosis of one or more principal outflow pathways from the cavernous sinus [2, 3, 22].

Recently, a hypercoagulable state was reported in the majority (64%) of patients with history of an indirect CCF [23]. However, a comprehensive coagulopathy workup showed no evidence of a hypercoagulable state in these 2 patients. Normal or negative results were obtained for anti-phospholipid antibodies, antithrombin assay, complete blood count, C-reactive protein, factor V mutation by PCR, fibrinogen, homocysteine, lupus anticoagulant assay, protein C assay, protein S assay, protime (PT/INR), partial protime, prothrombin gene mutation, erythrocyte sedimentation rate, and serum protein electrophoresis. Furthermore, neither patient has known risk factors for hypercoagulable state, such as cancer, or hereditary vascular disorders [23], nor do they have any known history of thromboembolic events. These laboratory results and clinical history reduce the likelihood that multiple thrombotic events caused the 4NP and the indirect CCF. Moreover, the flow pathway of the CCFs in both cases suggests that they did not result from a micro-thrombosis in the supply to the 4th nerve, which comes predominantly from the inferolateral trunk [24].

In conclusion, both microvascular ischemic NP and spontaneous CCF are more likely in the setting of chronic pathological changes to the microvasculature. Microvascular damage associated with hypertension, diabetes, and atherosclerosis can begin before these conditions become clinically apparent. For this reason, it is encouraged to investigate for vasculopathic risk factors if not already known in patients with microvascular ischemic NP [16]. Given their shared risk factors, spontaneous CCF should be considered on the differential for diplopia and recurrent diplopia or red eye in patients with a history of microvascular ischemic NP. Both may occur in the same patient in a sequential manner.

## Statement of Ethics

Written informed consent was obtained from the patient for publication of the details of their medical case and accompanying images. The need for Research Ethics Approval was waived by the University of Toronto Research Ethics Board. The study complies with the guidelines for human studies and was conducted in accordance with the World Health Organization Declaration of Helsinki.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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## Author Contributions

Lauren Pickel contributed to conception and design, preparation of the manuscript, and final approval of the manuscript. Jonathan Micieli contributed to conception and design, data collection, critical revisions, and final approval of the manuscript.

## Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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