Case Report

Cerebral aneurysms associated with von Recklinghausen's neurofibromatosis: Report of a case and review of the literature

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The authors report a case of an intracranial aneurysm associated with von Recklinghausen's neurofibromatosis. A 34-year-old woman presented with a history of headaches, unconsciousness and neck rigidity. Widespread cutaneous neurofibromas were found. Investigations revealed an aneurysm of the anterior communicating artery. The authors discuss this case and review the relevant literature.

Key Words: Intracranial aneurysm, neurofibromatosis-1

von Recklinghausen's neurofibromatosis type I (vRNF) is an autosomal dominant disorder caused by mutations in the neurofibromatosis-1 (NF-1) gene on chromosome 17. This hereditable systemic disease affects approximately 1 in 3500 individuals.[1] Typical dysplasias in NF-1 patients involve the skeletal system (sphenoid wing dysplasia, tibial pseudarthrosis), the skin (café-au-lait spots), and the nervous system (optic pathway gliomas, neurofibromas, astrocytomas, meningeomas). Vascular abnormalities are well recognized in NF-1 and seen in the renal, gastrointestinal and coronary vessels.[2-5] Cerebral vascular manifestations include stenosis or occlusion of major vessels, AV-fistulae, arteriovenous malformations, and aneurysms.[6] Pathological changes in vessels in NF-1, in some cases, have radiographic similarities to moya–moya disease and intracranial aneurysms are mostly saccular or fusiform.[7] We report a case of vRNF associated with an intracranial aneurysm and compare it to similar cases found in the literature.

Case Report

A 34-year-old right-handed female with known vRNF presented with a history of sudden onset of headaches, unconsciousness and neck rigidity. Physical examination revealed that there were neurofibromas and café-au-lait spots distributed over the entire body. There was Grade 4 right hemiparesis, left-sided protrusio bulbi combined with a chemosis of the conjunctiva and loss of vision [Figure 1].

The patient had no family history of NF-1. An additional molecular diagnosis of the NF-1 gene was not performed at our clinic. A cranial computerized tomography (CCT) scan and magnetic resonance images (MRI) of the brain revealed diffuse subarachnoid hemorrhage (SAH) predominantly in the basal cisterns as well as in the left parietal region with an intraventricular hemorrhage (Fisher Kissler Grade 4). Additionally, a left intraorbital mass was recognized. Digital subtraction angiography (DSA) demonstrated an aneurysm of the anterior communicating artery (A-com) [Figure 2].

The aneurysm was clipped via a right peritoneal approach and the intraorbital tumor on the left side was removed with orbital bony wall decompression via a left frontal approach on the same session. Neuropathological/immunohistological examination verified the tumor as an orbital neurofibroma. After 3 and 6 months follow up, significant improvement in consciousness and mental deterioration was seen.

Discussion

Intracranial aneurysms are rare in cases with NF-1. Including our case, we identified 28 cases of intracranial aneurysms in the literature [Table 1]. Predominantly, the aneurysms were

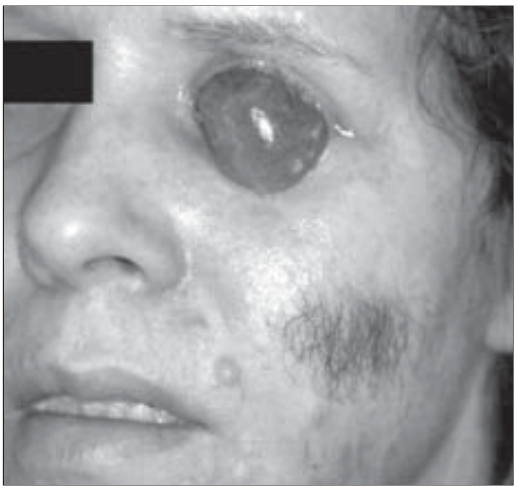

Figure 1: Orbital neurofibroma in neurofibromatosis Type 1

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Table 1: Summary of cases with intracranial aneurysms in von Recklinghausen's neurofibromatosis

References	Age/sex	Clinical manifestation	Aneurysm
8	17/M	Convulsion	AcoA
	60F	SAH, rt. third nerve palsy	rt. Pca ICA
9	32/F	SAH	AcoA
10	50/F	SAH	Location?
11	24/F	Hypertension	blt. ICA
12	52/F	SAH+ICH	PchA
13	36/F	Hypertension	lt. ICA
14	56/F	lt. orbital neurinoma	lt. VA-PICA
15	60/F	SAH	AcoA
16	28/F	Mass in the neck	rt. oa ICA
17	18/F	Asymptomatic	rt. ICA
18	52/F	Mass in left neck	lt. ICA; lt.PCA; lt.VA
	19/M	SAH, diplopia (fourth nerve palsy)	rt. ICA
	36/M	SAH	rt. MCA
19	37/M	Headache, hypertension	blt. MCA; BA
20	27/M	Left-side weakness	rt. BA; rt. ICA; lt. ICA
21	42/F	SAH, hypertension	rt. A sylvii, ACoA, rt. VA
22	55/F	SAH, fourth nerve palsy	rt. ICA
23	60/F	Mass brain stem and suprasellar cistern, disturbance of consciousness	lt. VA; lf.ICA
	40/M	SAH, disturbance of consciousness	rt. ICA-PCA
24	55/M	ICH, coma	Heubner's artery
25	29/F	SAH, cranial nerve palsy	Basilar artery
26	30/F	SAH, orbital neurofibroma	lt. MCA
27	28/M	Disturbance of consciousness	PCA
28	30/M	SAH	rt.+lt. MCA; lt. ICA
	62/M	SAH	AcoA
29		Wallenberg's syndrome	Basilar artery
30	55/F	Coma	AcoA, rt. ICA
31	1	Incidental finding	lt. ICA
32	36/F	Incidental finding	rt. ICA, lt. ICA
	56/F	Incidental finding	rt. ICA
33	34/F	SAH, orbital neurofibroma, right-side weakness, disturbance of consciousness	AcoA

F, female; M, male; ICA, internal carotid artery; MCA, middle cerebral artery; VA, vertebral artery; PCA, posterior cerebral artery; AcoA, anterior communicating artery; pcaICA, ICA at posterior communicating artery origin; VA-PICA, VA at posterior inferior cerebellar artery origin; PChA, posterior choroidal artery; oaICA, ICA at ophthalmic artery origin; ICH, intracerebral haematoma; SAH, subarachnoid hemorrhage; rt, right; lt, left; blt, bilateral.

located in the ICA circulation. In three cases, the aneurysms was in the vertebrobasilar circulation, and eight patients had multiple aneurysms.[12,34] A female predominance could be observed.[34,35]

The pathogenesis of vascular abnormalities in neurofibromatosis is unclear. Intracranial aneurysms in NF-1 might occur as a result of the radiation therapy of gliomas of the optic chiasm.[21] The first histological studies of vascular lesions in vRNF were done by Reubi in 1944.[36] He classified the changes in the arterial walls depending on their diameter (50-400 pm, 100-700 pm, 0.5-1 mm) into three groups: pure intimal form, nodular form, and intimal aneurysm form. At least the intimal aneurysm form was typical for cerebral aneurysms and had marked, eccentric, fibrous intimal proliferation, a small number of sparsely distributed spindle cells in the intima and media, smooth muscle fibrosis, and elastica fragmentation. Other reports by Feylter *et al* added new or similar features of histological changes including irregular smooth muscle loss or nodular proliferation of epitheloid and spindle cells.[34,37] Using electron microscopy studies, Greene *et al*. found that the spindle cells had characteristics of smooth muscle cells, with myofilaments, pinocytotic vessels, and electron dense plaques associated with the plasma membrane and free within the cytoplasm.[3]

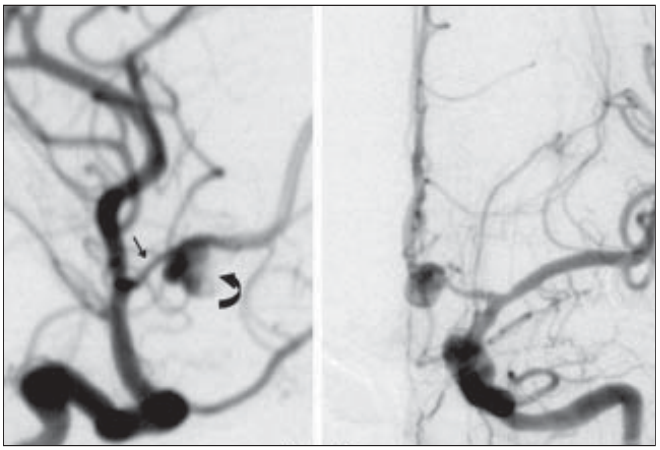

Figure 2: Lateral and anteroposterior views of the left internal carotid angiography (ICAG) showing a multilobulated aneurysm of the anterior communicating artery (curved arrow) and a vasospasm of this artery (straight arrow)

There seems to be no link for a neural cause of vessel malformations in NF-1. Changes in the walls of vessels may depend on primary defects of myocytes inside these walls, and probably pericytes play an important role.[35]

New publications asked for the expression of the NF-1 gene product neurofibromin and its association with blood ves-

sels.[26,38-40] Neurofibromin is believed to have a regulatory role in the development of various connective tissues.[1] Norton *et al* demonstrated by immunochemical studies the expression of NF-1 in the endothelial cell layer of rat and bovine renal and cerebral arteries as well as in the aorta.[40] In addition, Western blotting confirmed neurofibromin expression in bovine aorta and cerebral blood vessels. To follow the role of neurofibromin as a negative growth regulator (tumor suppressor gene), Norton concluded that in individuals with NF-1, it is possible that the loss (or reduction) of neurofibromin expression results in vascular abnormalities. Conway *et al* analyzed autopsy series of NF-1 and aneurysm patients statistically and found no significant relation between the prevalence of intracranial aneurysms and NF-1.[41] In their own series, they found 25 NF-1 cases in 50 000 autopsies. Autopsy revealed an intracranial hemorrhage in four patients (16%) without the verification of an aneurysm. Schievink *et al*. studied 39 patients with NF-1 and detected two patients with associated intracranial aneurysms.[32] They found a significantly higher detection rate of cerebral aneurysms in NF-1 than in a population consisting of 526 matched controls. In conclusion, they suggested that there is an increased risk of developing intracranial aneurysms in NF-1 patients. This is in accordance with the work of Rosser *et al*., who analyzed 353 children with NF-1.[31] Cerebrovascular abnormalities including intracranial aneurysms were found in 2.5% of the cases. The pathophysiology of the vascular changes is not fully understood and needs to be analyzed on a cellular level in the future.

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