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Wallenberg syndrome in a young female with Neurofibromatosis type 1

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A diagnosis of neurofibromatosis type 1 (NF 1) was clarified after Wallenberg syndrome in an 18-year-old female. The long segment of the right internal carotid artery was stenotic; however, the vertebral-basilar system was intact. Wallenberg syndrome was likely due to the vasculopathy caused by NF 1. While ischemic attacks are not common in normal teenagers, they do occur in cases with NF 1 because they have a high probability of both developmental abnormality of the vascular system and vasculopathy. We conclude that it is always necessary to take latent disease into consideration in a younger patient with symptoms of ischemic attack.

Key words: Wallenberg syndrome, Neurofibromatosis type 1, vasculopathy

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1. Introduction

Neurofibromatosis type 1 (NF 1) is a common autosomal dominant multisystem genetic disorder caused by a mutation in the NF 1 gene on chromosome 17 q 11.2, affecting 1 in 3000 individuals [1]. Its most frequent manifestations include café-au-lait spots and dermal neurofibromas, which result from abnormalities in neural crest-derived cell types. Many non-neural crest-derived tissues, including bone, brain, and blood vessels, may also be affected. Vascular abnormalities are a well recognized, but rare feature. Of these, vascular lesions of renal arteries are relatively common, but lesions in cerebrovascular arteries are rarer [2–5].

The term NF 1 vasculopathy has been adapted to describe a wide spectrum of the abnormalities of the vascular systems occurring in patients with NF 1, including aneurysms, arterial stenoses and arteriovenous malformations of the aortic, renal,

mesenteric and carotid-vertebral arteries [3]. It is difficult to define the frequency of the intracranial vasculopathy, because most NF 1-associated vascular lesions in the brain are likely to be asymptomatic. Nevertheless, intracranial vasculopathy appears to contribute to excess mortality of young patients with NF 1. Though it may need further discussion that we should inform all NF 1 patients and their families of the provability of having higher risk of ischemic attack in the patients' young ages, clinical physicians at least should always recognize the underlying condition of the disease, which helps early diagnosis and therapy for the best strategies for the prognostic stage.

Here we report a case of a young woman of Wallenberg syndrome, who did not know her existing disease, NF-1, with abnormalities of the vascular system in the head and neck area.

Figure 1 1 a, 1 b: MR imaging of T2 weighed (1 a), diffusion weighed (1 b) at noon of the first disease day.
2 a, 2 b: MR imaging of T2 weighed (2 a), diffusion weighed (2 b) the next morning.
The arrows indicate high signal intensity in the left-lateral portion of the medulla oblongata.

2. Case presentation

An 18-year-old female was admitted to an otolaryngology department by an ambulance after a sudden onset of “dyspnea because of sore throat”. She claimed an odd feeling in her throat, followed by an inability to swallow and dyspnea. She also felt “electricity running-like feeling” in her right hand and foot. She mentioned no past history of any disease. On physical examination at around 9:00 am, there was no sign of inflammation in the organs in the head and neck area, or neurological sign. Endoscopically, however, laryngeal paralysis of the left side was present. Laboratory data, computed tomography (CT) scans, and magnetic resonance (MR) imaging of the brain at noon were within normal limits. She showed no hypertension. However, MR angiography revealed a highly thinned internal carotid artery on the right side from the bifurcation, but no abnormality in the vertebral-basilar system (Figure 2 a). At around 5:00 pm, she complained of dizziness and vomited. Right-beating nystagmus was observed. Horner’s sign appeared and both left facial temperature sensations and right sensations of the body were decreased, which confirmed Wallenberg syndrome. T2-weighted image of MR imaging

taken in the next morning showed slight high signal intensity in the left-lateral portion of the medulla oblongata (Figure 1 a, b).

She had more than ten café-au-lait spots over 15 mm in greatest diameter on her trunk, but no dermal neurofibroma. Her mother was her only caretaker and did not recognize her existing disease. CT angiography showed stenosis of the right internal carotid artery over the long segment; however, no abnormality in the vertebral-basilar system was observed (Figure 2 b). Additional examination of cerebrospinal fluid was normal, and laboratory data did not suggest congenital abnormality of the coagulation system or collagen diseases. Lisch nodules were observed (Figure 3), which confirmed the diagnosis of NF-1. Her symptoms were, therefore, thought to be related to vasculopathy caused by NF-1 though the manifestation of the disease was rather atypical. Two weeks later, she recovered from her symptoms, and was discharged.

3. Discussion

NF 1 is a relatively common genetic disorder. The pattern of inheritance is autosomal dominant, but in about 50% of the cases, the disease is due to a new mutation and the patient does not have

Figure 2 2 a: MR angiography of the first disease day. The right internal carotid artery was poorly observed.
2 b: CT angiography. The long segment of the right carotid artery showed smooth narrowing, which were indicated by the arrows. The carotid canal was occlusive, and showed no thickening of the wall of the artery.

familial history of the disease. Vascular involvement is relatively common in NF 1, but most patients are asymptomatic. Nevertheless there are reports in which a younger generation showed fatal ischemic attack in the large cerebral arteries and an older generation showed a hemorrhagic attack. Vascular alterations of NF 1 include stenosis/occlusion, aneurysm, arteriovenous fistula of medium and large diameter arteries, and moyamoya syndrome [4].

In our case, two different facts were present: one was asymptomatic stenosis of the long segment of the right internal carotid artery and the other was symptomatic Wallenberg syndrome. The supraclinoid portion of the internal carotid artery is the segment most frequently involved in

occlusive disorder in heritable connective tissue disorders [6]. Primary involvement of the middle and anterior cerebral arteries is also common [7]. However, stenosis of the long segment of the internal carotid artery as observed in our case has never been reported. CT angiography showed smooth narrowing of the long segment of the internal carotid artery, which suggested the possibility of developmental hypoplasia of the vessels or bone rather than occlusive vascular disease caused by NF 1. Multiple skeletal defects, which are related to the defective development of the mesenchymal tissue, can also occur in NF 1.

The natural course of occlusive cerebrovascular disease with NF 1 is a gradual stenosis of the arteries with complete occlusion of the vessel. This

process progresses slowly, allowing the development of collateral vessels, which provide effective cerebral circulation. Sometimes, however, stenotic/occlusive disorder of intracranial vascular supply may present symptoms of ischemic attack in childhood or adolescence, being the first manifestation of NF 1. MR and CT angiography in our case did not show any evidence of Wallenberg syndrome, nevertheless the ischemic attack was likely to be related to NF 1 vasculopathy. It remains unknown if stenosis of the long segment of the internal carotid artery has anything to do with ischemic attack; however, we may say that latent abnormality of the vascular system is a risk factor for ischemic attack in patients with NF 1 [8].

The protein product of NF 1 gene, neurofibromin, shares sequence and functional homology with a group of Ras-GTPase activating proteins [9]. The Ras pathway transmits mitogenic signals to the nucleus, and neurofibromin acts as a negative regulator in this pathway [9–11]. Loss of neurofibromin produces increased mitogenic signaling, which leads to either cellular proliferation or differentiation. According to Salyer et al [12], the pathology of vascular lesions with NF 1 was characterized by accumulation of cells in the intimal layer of the blood vessel, resulting in hyperplasia that narrows the lumen. They suggested that intimal thickening in NF 1 vasculopathy is the result of proliferation of Schwann cells within the arteries. This implies a pathogenetic relationship between these lesions and the neurofibromas that characterize this disease.

Recent work, however, has shown that the proliferating cells in NF 1 vasculopathy are usually smooth muscle cells rather Schwann cells [13, 14]. Neurofibromin expression has been identified in the heart and in endothelial and smooth muscle cells of blood vessels. Type 2 neurofibromin is the predominant isoform expressed in endothelial and vascular smooth muscle cells. Intrinsic expression of neurofibromin raises the possibility that NF 1 vasculopathy results from a deficiency of neurofibromin function in the normal cellular

Figure 3 The arrows indicate Lisch nodules. Right eye (a), and left eye (b). Horner's sign was also observed.

components of the blood vessel wall [15].

More recent work using neurofibromin-deficient mice showed that peripheral blood from NF 1 patients revealed increased concentrations of inflammatory cells and cytokines previously linked to vascular inflammation and vasculocclusive disease, and provided genetic and cellular evidence of vascular inflammation in NF 1 patients and model mice [8, 16]. Vascular inflammation can induce the accumulation of the cells in the vessels, which might explain temporary or long-existing occlusion of the vessels and eventually hemorrhagic attack.

Our case of Wallenberg syndrome with NF 1 recovered almost completely. The narrowing of the internal carotid artery was thought to be caused by developmental deficit with NF 1. On the other hand, Wallenberg syndrome was considered a manifestation of vasculopathy with NF 1. We must use caution in young patients with ischemic attack and always consider that NF 1 may be present.

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