

Single Case – General Neurology

Intracerebral Hemorrhage in Patients with Neuromyelitis Optica: Case Report with Literature Review for Possible Pathological Association

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Keywords

Neuromyelitis optica · Intracerebral hemorrhage · Subarachnoid hemorrhage · Pathophysiology

Abstract

Neuromyelitis optica (NMO) is an autoimmune demyelinating disorder of the central nervous system which is characterized by attacks of optic neuritis and transverse myelitis. An association between NMO and intracerebral hemorrhage (ICH) has been rarely recognized, having been reported only 3 times before. Here we report on a patient with NMO who eventually developed subarachnoid hemorrhage, in order to emphasize that the association between NMO and ICH is mostly not incidental and that the pathological basis for this association should be investigated thoroughly.

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Published by S. Karger AG, Basel

Introduction

Neuromyelitis optica (NMO) and NMO spectrum disorders (NMOSD) are inflammatory disorders of the central nervous system characterized by immune-mediated demyelination and axonal damage predominantly affecting the spinal cord and optic nerves. Currently, NMO

is considered as an independent disorder and not a variant of multiple sclerosis, as it was previously believed. Whereas multiple sclerosis is mostly a cell-mediated disorder, the pathophysiology of NMO is thought to be primarily mediated by the humoral immune system [1, 2], as proved by the identification of a specific autoantibody against aquaporin 4 (AQP4).

Case Description

Our patient was a 37-year-old female who had initially been diagnosed with multiple sclerosis at the age of 16 years based on recurrent attacks of motor and sensory symptoms. At that time, she was commenced on interferon; however, it was discontinued after 3 months because of the side effects, and she remained on no maintenance therapy. Over the course of the disease, she lost her bladder control as well as vision in the left eye.

At the age of 29 years, she sought another opinion at our hospital; clinically, she had complete quadriplegia with a blind left eye. Her diagnosis was revised with repetition of laboratory testing and imaging, and she was diagnosed with NMO on the basis of positive AQP4 in her cerebrospinal fluid (CSF) as well as magnetic resonance imaging (MRI), which demonstrated atrophy of the cervical cord (Fig. 1–3). Further workup including CSF examination revealed positive IgG bands and negative oligoclonal bands. Also autoimmune serology results, including anti-JO and lupus, ANCA, anti-CCP, and anti-smooth muscle antibodies, were negative, while ANA and anti-RO were positive, but there was no supportive clinical evidence of other forms of vasculitis or connective tissue diseases. In reference to the new diagnosis, the patient was managed with pulse steroid 1 g daily for 5 days followed by 5 sessions of plasma exchange, with no significant improvement, and she was maintained on azathioprine.

During the next 7 years, she had a stable course regarding motor power of her limbs, but she had recurrent attacks of right optic neuritis, for which she received many courses of intravenous methylprednisolone (IVMP) for 3–5 days. At the age of 36 years, she developed a sudden-onset headache with normal blood pressure, and her CT and MRI confirmed a rim of subarachnoid hemorrhage (SAH) in the left frontal cortical sulci (Fig. 4a, b), while CT angiography and MR venography (Fig. 4c) excluded arteriovenous malformations or aneurysms.

The patient was managed conservatively, and repeated CT after 6 months indicated the resolution of the SAH (Fig. 5). With continuation of relapses of visual affection in the right eye, the patient was started on rituximab 2 months back and received 2 doses with no significant clinical improvement. Currently, the patient is bedridden with spastic paraplegia and a blind left eye.

Literature Review

Regarding cerebral hemorrhage in patients with NMO, apart from our case, a literature review revealed only 3 previous case reports and a fourth case of hemorrhagic encephalitis. The first case was described by Shirai et al. [3], who reported on a 48-year-old man who was admitted because of intractable hiccups, nausea, and orthostatic hypotension, and who then developed respiratory failure. Brain MRI showed SAH in addition to enlarged medullary lesions with positive serum anti-AQP4 antibody.

The second case was described by Yaguchi et al. [4], who reported on a woman without hypertension who had previously experienced intracranial hemorrhage twice, at 48 and 56

years of age, after which she was diagnosed with NMOSD at the age of 59 years based on the presence of a brain stem lesion and the detection of anti-AQP4 antibodies.

Most recently, the third case was described by Kamo et al. [5], who reported on a 51-year-old Japanese woman with a history of hypertension and dyslipidemia and recurrent episodes of left visual acuity disorder related to AQP4-positive NMOSD. She developed blindness in the left eye, and brain MRI showed a hyperintense lesion in her pons, so she was initially diagnosed with recurrence of NMOSD and 1,000 mg of IVMP was administered for 3 days. After the third course of IVMP, she developed left-sided sensory disturbance, and the blood pressure had increased to 202/127 mm Hg; brain CT showed pontine hemorrhage. She was diagnosed with posterior reversible encephalopathy syndrome associated with NMOSD recurrence, along with development of pontine hemorrhage induced by the increase in blood pressure resulting from IVMP.

In April 2019, Du et al. [6] reported on a case of a patient with NMO who presented with hemorrhagic encephalitis during the course of the disease.

Discussion

While the pathogenesis of NMO is not fully understood, it is believed that AQP4-IgG is of great importance in triggering the pathology of the disease. AQP4 is a transmembrane protein expressed by astrocytes and controls the flow of water in cells [7]. Upon penetration through the blood-brain barrier (BBB) and binding with AQP4 on perivascular astrocyte end-feet, AQP4-IgG activates the classic complement pathway which causes astrocyte damage, followed by marked NK cell, granulocyte and monocyte infiltration, along with BBB breakdown, oligodendrocyte death and demyelination, microglia activation, and even neuronal apoptosis [8]. Thus, in the CNS, AQP4 immunoreactivity is expressed around the capillary blood vessels and foot processes of astrocytes beneath the pia mater, and serum from NMO patients disrupts the BBB [9]. Unfortunately, the mechanism of AQP4-IgG generation remains unclear; predictions include AQP4 molecular mimicry and infection [10, 11]. Th17 cells and follicular helper T cells [12] significantly increase during the relapse period, which are critical for breaking down the BBB and antibody production.

Link between NMO and Vascular Pathology

A study involving 31 NMO patients found various Th2-related cytokines such as interleukin (IL)-1 receptor antagonist, IL-5, IL-10, and IL-13, as well as the Th17-related cytokines IL-6, IL-8, and granulocyte colony-stimulating factor, to be elevated in the CSF [13]. Epidemiological studies have found an increased vascular risk in association with increased basal levels of cytokines such as IL-6 and tumor necrosis factor- α .

Tumor necrosis factor- α is an important cytokine in the injured vasculature, where it may function to regulate the expression of platelet-derived growth factor, vascular endothelial growth factor, fibroblast growth factor, adhesion molecules, cytokines, and extracellular matrix (ECM)-degrading matrix metalloproteinases, as well as directly affecting vascular smooth muscle cell growth and migration. Other cytokines such as IL-1 β and IL-6 contribute to the pathogenesis of specific vascular diseases [14]. Thus, these cytokines induce vascular cell growth and migration, induce apoptosis, promote adhesion of immune cells to endothelial cells (ECs), and cause an increase in vascular permeability [15]. Many of the effects of cytokines on vascular cells could also involve increases in reactive oxygen species, which in high

concentrations cause cellular injury and death. ECs are a major target of oxidative stress, which plays a critical role in the pathophysiology of vascular disease. Cytokines may have additional specific effects on the vascular ECs, vascular smooth muscles, and ECM. Such effects could affect the mechanism of vascular tone and the signaling pathways of vasoconstriction and vasodilation, as well as vascular cell growth and proliferation, and could also lead to structural changes in vessel wall architecture and the ECM [16].

Evidence of Vascular Pathology in NMO

Data regarding (1) the presence of these cytokines in NMO patients [13], (2) the earliest pathological descriptions of NMO which highlighted the frequent occurrence of necrosis with cavitation, hyalinization of small vessels, and perivascular inflammatory infiltrates which distinguish NMO from multiple sclerosis, and (3) also the more recent work which has indicated the importance of perivascular deposition of immunoglobulin and complement [17] and its localization to the vascular glial limiting membrane [18], with infiltrate consisting of macrophages, granulocytes, and eosinophils with a general paucity of lymphocytes [19], all confirm the vascular pathology that occurs in NMO, resulting in fragile blood vessels which might cause SAH. Also, modern histopathological techniques have demonstrated the specificity of acute fragmentation and loss of perivascular GFAP-positive astrocyte foot processes and their cell bodies as an early and consistent feature of NMO [20, 21]. These mechanisms could explain the possibility of occurrence of many types of vascular disorder in NMO patients, predisposing them to the hemorrhage observed in our cases.

Conclusions

An association between NMO and cerebral hemorrhage could be suggested in the context of our understanding of NMO pathology and the role of the different cytokines in the disease pathogenesis. We believe that further research is needed to confirm the relation between NMO and the development of vascular disorders.

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding was received from any governmental or nongovernmental sources.

Author Contributions

H.S. Elshony: study design, manuscript writing, literature review, and editing. A. Idris: manuscript reviewing and editing. A. Al-Ghamdi: manuscript reviewing and editing. R. Muddassir: literature review and manuscript writing.

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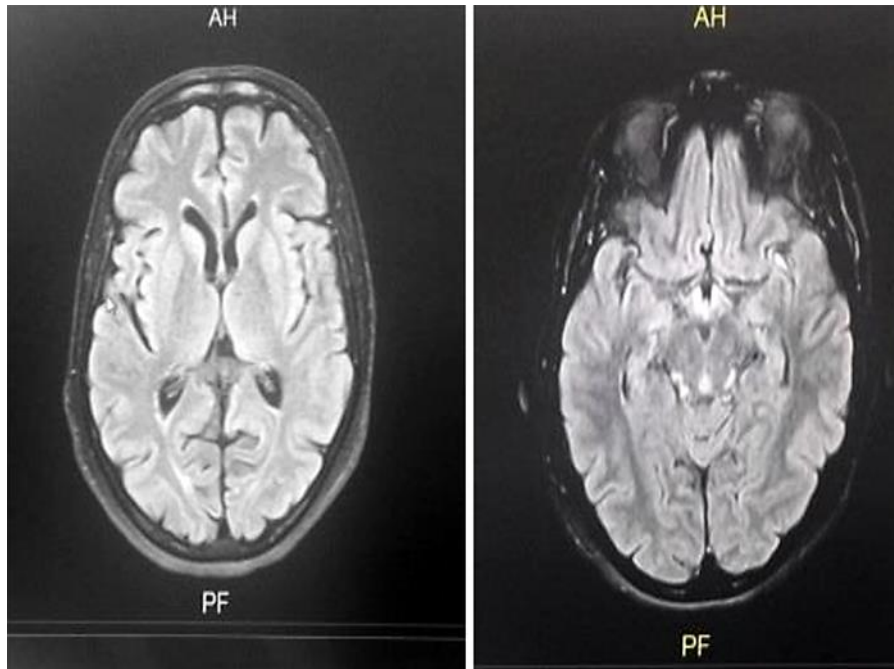


Fig. 1. Axial FLAIR MRI showing no supra- or infratentorial areas/foci of abnormal signals.

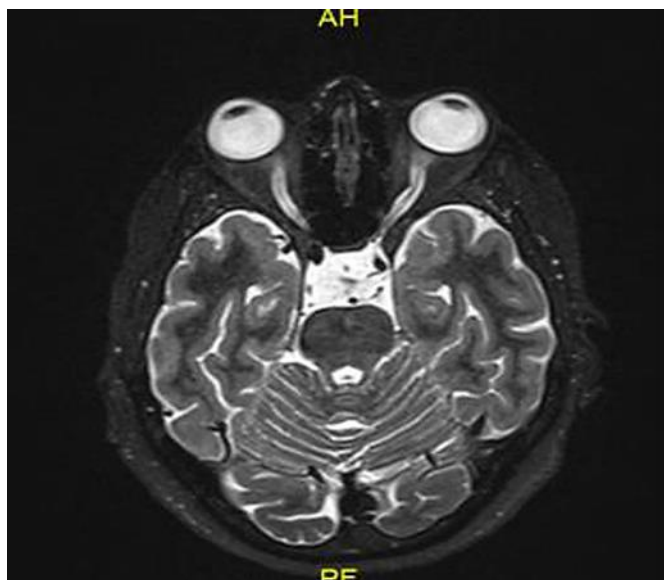


Fig. 2. Axial high-resolution T2-weighted MRI showing atrophic changes affecting the optic nerve bilaterally, with prominent CSF in the optic sheath, with no infratentorial abnormal signal intensity.



Fig. 3. Sagittal T1-, T2-, T1-weighted post-gadolinium-enhanced cervical MRI and sagittal T2-weighted dorsal MRI showing atrophic changes with prominent CSF with no areas of abnormal signal intensity.

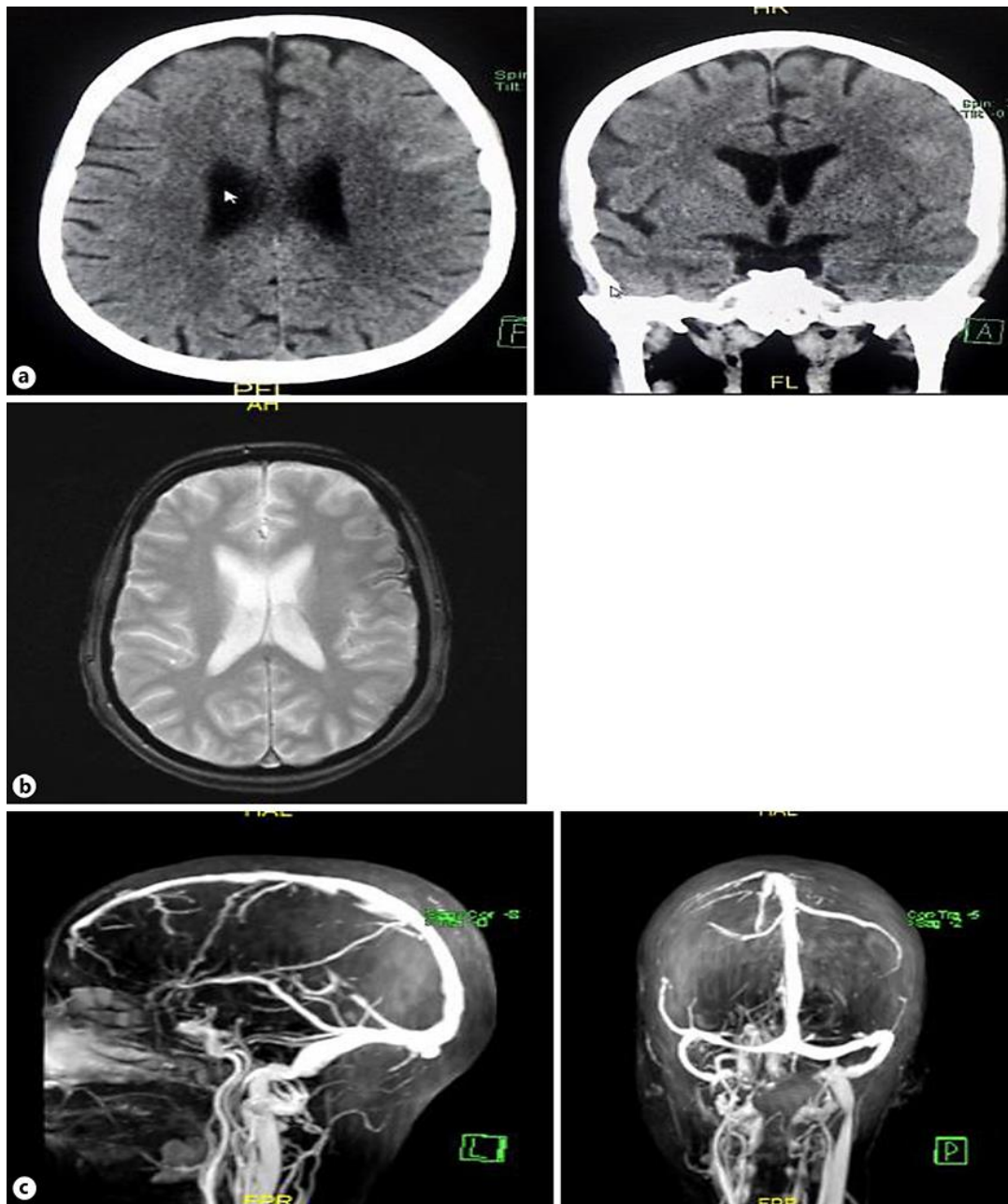


Fig. 4. **a** Axial and coronal noncontrast CT done at the onset of the headache showing high-density blood involving the left cortical sulci (subarachnoid hemorrhage [SAH]). **b** Brain axial gradient MRI showing blooming of the left frontal cortical sulci confirming the diagnosis of SAH. **c** Sagittal and coronal brain MR venography, axial view, showing no filling defect or thrombosed veins.

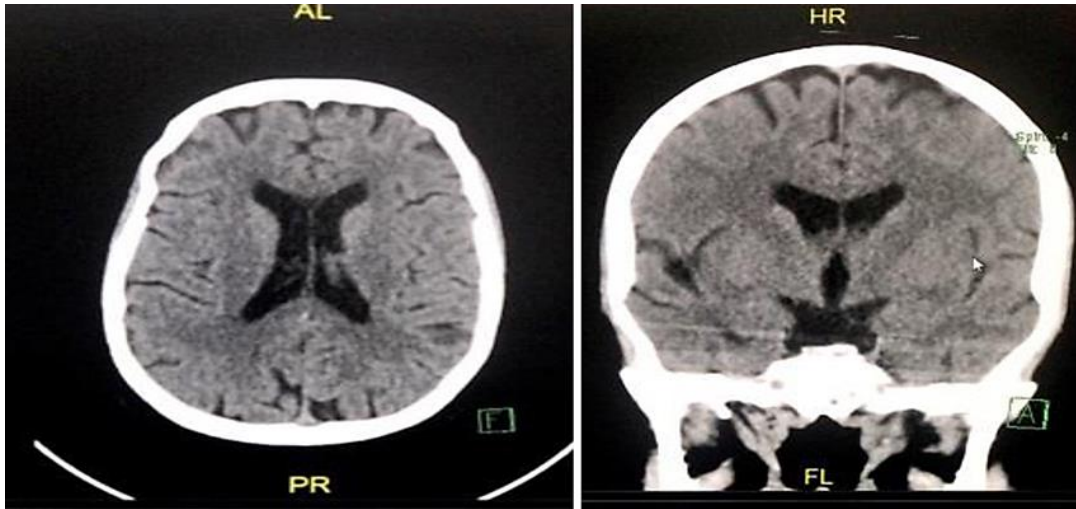


Fig. 5. Axial and coronal noncontrast CT done 6 months after the onset of subarachnoid hemorrhage showing complete resolution of the hemorrhage.