


# Stroke During Norovirus Infection as the Initial Episode of Antiphospholipid Syndrome

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## Introduction

Antiphospholipid syndrome (APS) is a rare disorder characterized by thrombosis, pregnancy morbidity, and the presence of antiphospholipid antibodies (aPL), which inhibit phospholipid-dependent coagulation reactions.<sup>1</sup> APS develops either solely (primary APS) or in association with autoimmune disease such as systemic lupus erythematosus (secondary APS). Infection of virus, bacteria, and mycoplasma often precede development of APS.<sup>1</sup> We report a patient with primary APS that developed during norovirus gastroenteritis.

## Case Report

A 6-year-old Japanese boy was admitted to a hospital because of headache, staggering, and vomiting, all of which developed in the same morning. Although the diagnosis of norovirus gastroenteritis was made by detection of the antigen in his stool, there was no apparent dehydration at the admission. Although his staggering and vomiting subsided by the next day, mild headache persisted. On the fourth day of illness, he was diagnosed as having cerebellar infarction by magnetic resonance imaging (MRI) of the brain and referred to our hospital for further investigation. On admission to our hospital, there was no skin rash, lymphadenopathy, or injury. Physical examination demonstrated no abnormal findings in his chest, abdomen, or extremities. Neurological examination revealed only mild right foot dysmetria on heel-to-shin test but no other cerebellar signs such as dysidiadochokinesis, ataxia, or coordination disturbance. T2 and diffusion-weighted MRI showed a high-intensity area of his cerebellum, suggesting recently developed infarction (Figure 1), although magnetic resonance angiography (MRA) showed no apparent obstructive lesions (Figure 2A and B). He and his family had no history of ischemic stroke. Echocardiography showed no intracardiac embolic sources or congenital heart diseases.

Laboratory examinations demonstrated the following: white blood cell count 9100/ $\mu$ L with normal

differentiation, hemoglobin 120 g/L, platelet count  $38.7 \times 10^4$ / $\mu$ L, erythrocyte sedimentation rate 14 mm/1 hour, C-reactive protein 0.1 mg/L. There were no abnormal findings in his liver and renal function or serum levels of total cholesterol and triglyceride. Coagulation study showed the following: activated partial thromboplastin time 37.4 seconds, fibrinogen 1.9 g/L, fibrin degradation products 1.8 mg/mL, protein C 86% (reference range = 64% to 146%), protein S 71% (reference range = 65% to 135%). Immunological studies gave the following results: serum IgG 10.7 g/L, IgA 1.3 g/L, IgM 1.0 g/L, C3 1.0 g/L, C4 0.16 g/L, CH50 45.2 U/mL, and positive for anticardiolipin IgG antibodies at 50 U/mL (reference range < 10) but negative for anti-proteinase-3 antibody, anti-myeloperoxidase antibody, antinuclear antibody, anti-double strand DNA antibody. Because MRI showed only residual infarction, he was discharged from our hospital on the 10th hospital day.

Six months later, however, follow-up MRA showed right vertebral artery occlusion (Figure 2C and D), although he had no symptoms. Laboratory examinations showed positive anticardiolipin IgG antibodies at 55 U/mL and anti- $\beta$ 2 glycoprotein-I antibodies at 18.4 U/mL (reference range < 3.4). The diluted Russell viper venom test for lupus anticoagulant was negative. He was diagnosed as having antiphospholipid syndrome. Following the commencement of aspirin 60 mg in combination with cilostazol 50 mg per day, there has been no relapse of infarction or arterial obstruction during 2 years of follow-up.

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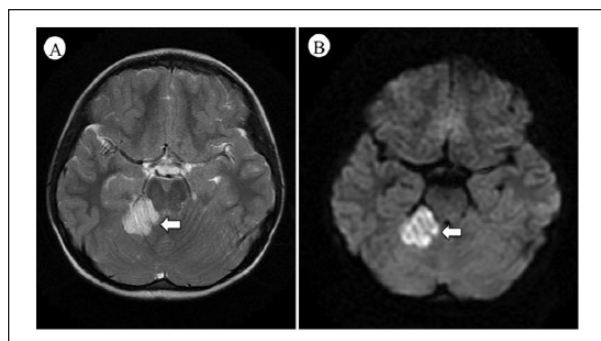
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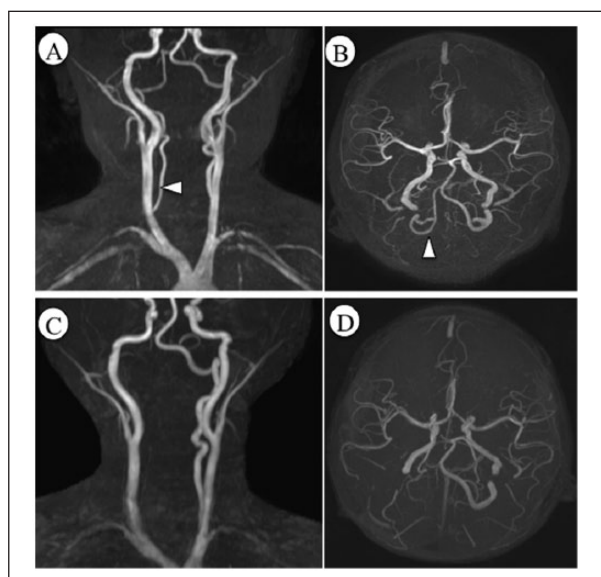
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**Figure 1.** T2 and diffusion-weighted magnetic resonance imaging of the brain showed a high-intensity area of his cerebellum as acute stroke (arrows).



**Figure 2.** Magnetic resonance angiography showed no occlusion of the right vertebral artery on admission (A and B, arrowheads). Right vertebral artery occlusion was observed 6 months later (C and D).

## Discussion

We report a case of cerebellar infarction associated with APS during norovirus gastroenteritis. Our case fulfilled one clinical (arterial thrombosis) and one laboratory (anti-cardiolipin antibodies) criteria of APS.<sup>2</sup> Our case had no symptoms or autoantibodies related to collagen vascular disease, and was accordingly classified as primary APS. Pediatric APS is rare and accounts for only 2.8% of the total number of primary APS.<sup>3</sup> Arterial thrombosis occurs in about 30% of pediatric APS, whereas deep vein thrombosis is the initial presentation in 60%. The frequency of arterial thrombosis is particularly high in primary APS.<sup>4</sup> Because

15% to 75% of pediatric ischemic stroke is associated with APS, aPL should be tested in any case of pediatric arterial or deep vein thrombosis.<sup>5,6</sup>

Coexisting hereditary thrombophilic disorders such as protein C and protein S deficiency are risk factors of thrombosis in APS.<sup>4</sup> However, our patient had normal levels of both proteins. Another hereditary risk of thrombosis, factor V Leiden, has not been reported in Japan. Also, there was no hypercholesterolemia or hypertriglyceridemia on several examinations.

Although aPL is a hallmark of APS, development of thrombosis requires priming of procoagulant cells, that is, endothelial cells, platelet, and monocytes, in patients positive for the antibodies.<sup>1</sup> Surgical injury and infection are major triggers of thrombosis in APS patients. Indeed, 10% of pediatric APS develops in association with infection such as infection of parvovirus B19, varicella-zoster virus, HIV, streptococcus, staphylococcus, gram-negative bacteria, and mycoplasma.<sup>1</sup> In our patient, staggering, headache, and vomiting developed simultaneously, suggesting that cerebellar infarction had occurred around the onset of norovirus gastroenteritis. This is supported by a high-intensity lesion on both diffusion- and T2-weighted MRI taken 2 weeks after the onset of cerebellar symptoms. To our knowledge, there has been no report describing APS associated with norovirus infection. Dehydration is a trigger of thrombosis in adult patients with APS.<sup>7</sup> However, lack of apparent dehydration suggests involvement of other factors in the development of thrombosis in our patient.<sup>8</sup> In murine models, norovirus is recognized by melanoma differentiation-associated protein 5, a sensor of viral RNA, of the immunocompetent cells and induces type I interferon, a potential activator of procoagulant cells.<sup>8</sup> In humans, norovirus-associated encephalopathy is accompanied by elevated levels of cytokines in the cerebrospinal fluid.<sup>9</sup> In addition, recent studies have demonstrated viral RNA in the sera from patients with norovirus gastroenteritis suggesting extraintestinal spread of the virus.<sup>10</sup> Platelet expresses human histo-blood group antigens, receptors of norovirus, although at a lesser extent than red blood cells.<sup>11</sup> Thus, the virus may trigger thrombosis by direct or indirect priming of platelet membranes and/or other procoagulant cells at a site distant from the intestine. Indeed, disseminated intravascular coagulation has been reported in a case of norovirus gastroenteritis.<sup>12</sup>

There has been no relapse of thrombosis following commencement of antiplatelet therapy in our patient after the second event. Patients with APS who suffered from arterial thrombosis as an initial attack tend to repeat arterial

thrombosis.<sup>1,4</sup> The Japanese guideline of APS recommends low-dose aspirin in combination with antiplatelet agent for the prevention of relapse according to the American Heart Association guideline for prevention of ischemic stroke,<sup>13</sup> because platelets possibly play a critical role in the development of arterial thrombosis. Twenty-one percent of pediatric APS patients with initial arterial thrombosis develop recurrent thrombosis mostly after cessation of therapy.<sup>4</sup> Thus, a long-term careful follow-up is necessary in such cases.

In conclusion, norovirus infection could be a trigger of thrombosis even in the absence of apparent dehydration. Low-dose aspirin in combination with antiplatelet agent is a choice for the prevention of recurrent arterial thrombosis in such cases.

### Author Contributions

SN: Contributed to conception and design; contributed to management of patient and analyses; drafted the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

DS: Contributed to conception and design; contributed to management of patient and analyses; critically revised the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

KU: Contributed to conception and design; contributed to management of patient and analyses; critically revised the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

IK: Contributed to conception and design; contributed to management of patient and analyses; drafted the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

### Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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