CASE REPORT

Adult-onset adenosine deaminase-2 deficiency presenting with recurrent juvenile cerebral infarction : A case report

Ryohei Nakao[1], Yuki Yamamoto[1], Ryosuke Miyamoto[1], Konoka Tachibana[1], Masaki Kamada[2], Hiroyuki Morino[2], and Yuishin Izumi[1]

[1]Department of Neurology, University of Tokushima Graduate School of Biomedical Sciences, Tokushima, Japan, [2]Department of Medical Genetics, Tokushima University Graduate School of Biomedical Sciences, Tokushima, Japan

Abstract : Background : Adenosine deaminase 2 (ADA2) deficiency is a rare autosomal recessive autoinflammatory disorder characterized by systemic vasculitis, recurrent stroke, and immunodeficiency. This results from the biallelic loss-of-function variants of *ADA2*, leading to enzymatic dysfunction and endothelial impairment. Although it is commonly diagnosed during childhood, adult-onset cases with milder phenotypes have also been reported. Objective : We report a case of adult-onset ADA2 deficiency that presented with recurrent juvenile stroke and systemic vasculitis. Case : A 42-year-old female with recurrent juvenile stroke and systemic vasculitis symptoms was diagnosed with ADA2 deficiency by genetic testing. The patient had a known pathogenic variant, c.139G>C (p.Gly47Arg), in a homozygous state. Given the mild phenotype and stable condition, the patient continued long-term aspirin therapy without additional immunosuppressive treatment. Conclusion : This case highlights the importance of considering ADA2 deficiency in patients with unexplained stroke and recurrent vasculitis, particularly those with a history of parental consanguinity. Measurement of serum ADA activity may serve as a potential screening tool for ADA2 deficiency, especially in settings in which genetic testing is not readily available. J. Med. Invest. 72 : 430-433, August, 2025

Keywords **:** *ADA2 deficiency, juvenile stroke, vasculitis, genetic testing*

INTRODUCTION

Adenosine deaminase 2 (ADA2) deficiency is a rare autoinflammatory disease characterized by systemic inflammation, vasculitis, and early onset stroke. It is caused by biallelic loss-of-function variants of *ADA2*, leading to impaired enzymatic activity and endothelial dysfunction (1). Initially described in pediatric patients with vasculopathy resembling polyarteritis nodosa (2, 3), the disease spectrum has since expanded to include immunodeficiency, hematologic defects, and neurological manifestations, including ischemic and hemorrhagic stroke (4). Herein, we report a case of ADA2 deficiency presenting with recurrent juvenile stroke, diagnosed via genetic testing in a 42 year of female.

CASE REPORT

The patient 42 year old female patient an unremarkable birth or developmental history. Her family history revealed parental consanguinity ; however, no similar symptoms were observed in her younger brother. The patient was diagnosed with hypertension at 20 years of age. At 23 years of age, she developed right-sided hemiparesis and dysarthria and was diagnosed with cerebral infarction. Diffusion-weighted brain magnetic resonance imaging (MRI) at the age of 28, because of right oculomotor nerve palsy revealed a high-intensity lesion in the right medial midbrain (Figure 1B). Further evaluation suggested central nervous system vasculitis, which prompted the initiation of oral steroid therapy, which resulted in symptom and imaging improvement. However, treatment was discontinued owing to steroid-induced psychosis, and only low-dose oral aspirin was continued. Subsequently, the patient experienced recurrent episodic symptoms including fever, abdominal pain, visual field defects, finger joint pain, and numbness in the extremities. These symptoms were transient and resolved within a few days after administration of nonsteroidal anti-inflammatory drugs.

At the age of 42, the patient exhibited mild livedo reticularis in both hands (Fig 1A), while other findings were unremarkable. Neurological examination revealed a positive Barré sign in the right upper limb and mild hyperreflexia in the right upper and lower limbs. The sensory examination results were normal. Although the patient was able to walk independently, her gait was slow. Laboratory tests revealed no significant abnormalities in the blood cell counts or inflammatory markers. Serum IgM levels decreased slightly (39 mg/dL). Additionally, MRI at the age of 42 showed no new lesions over time, and MR angiography showed no stenosis or occlusion of the large vessels (Fig 1C, D).

Considering the patient's history of stroke, parental consanguinity, and recurrent vasculitis symptoms, genetic testing was performed to evaluate the hereditary vasculitis and establish a definitive diagnosis. Exome sequencing revealed a homozygous c.139G>C (p.Gly47Arg) variant of *ADA2* (NM_001282225.2), which is an established loss-of-function mutation. Serum ADA activity was significantly decreased to 3.2 U/L (reference range : 8.6–20.5). Based on these findings, the patient was diagnosed with an ADA2 deficiency. Considering the mild phenotype and stable condition of the patient, the low-dose aspirin therapy was continued.

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Address correspondence and reprint requests to Yuki Yamamoto, MD, PhD, Department of Neurology, Tokushima University Graduate School of Biomedical Sciences, 3-18-15 Kuramoto-cho, Tokushima, 770-0035, Japan and Fax : +81-88-633-7208. E-mail : yuki.yamamoto412@gmail.com

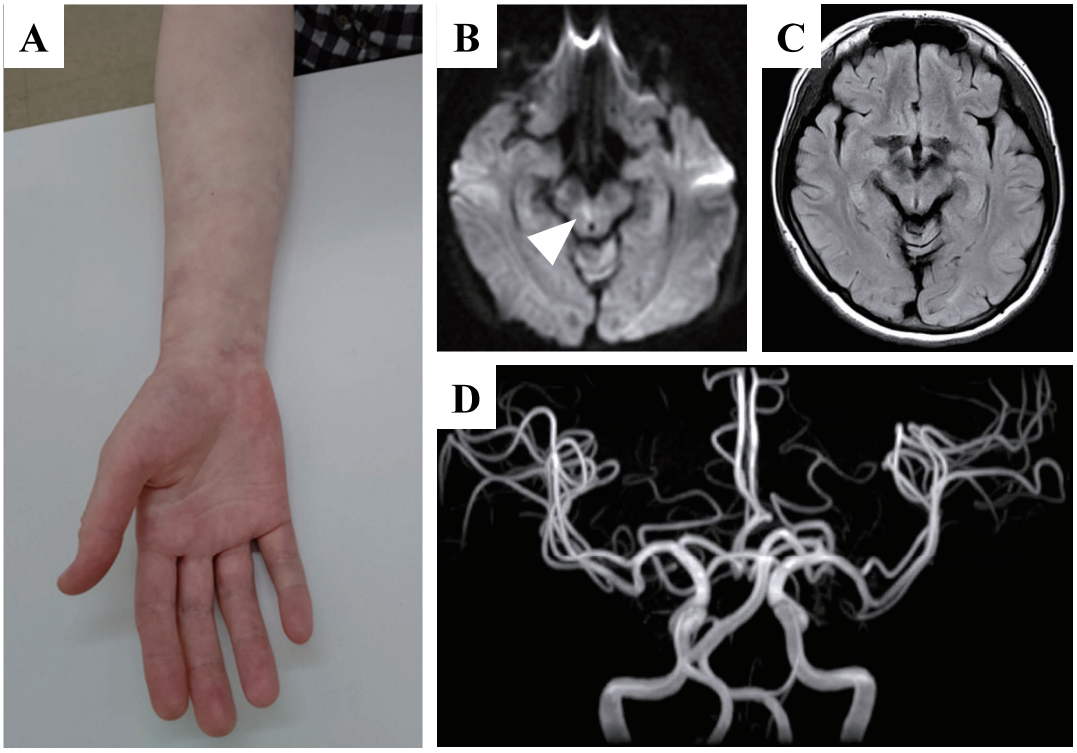

Figure 1. (A) The patient's right forearm at the age of 42 years showing a mild livedo-like rash. (B) Diffusion-weighted brain MRI at the age of 28 years demonstrating a high-intensity lesion in the right medial midbrain. (C) Fluid attenuated inversion recovery imaging of brain MRI at the age of 42 years, showing no apparent increase in lesion size or quantity. (D) MR angiography at the age of 42 years, showing no significant stenosis or occlusion of the major intracranial arteries.

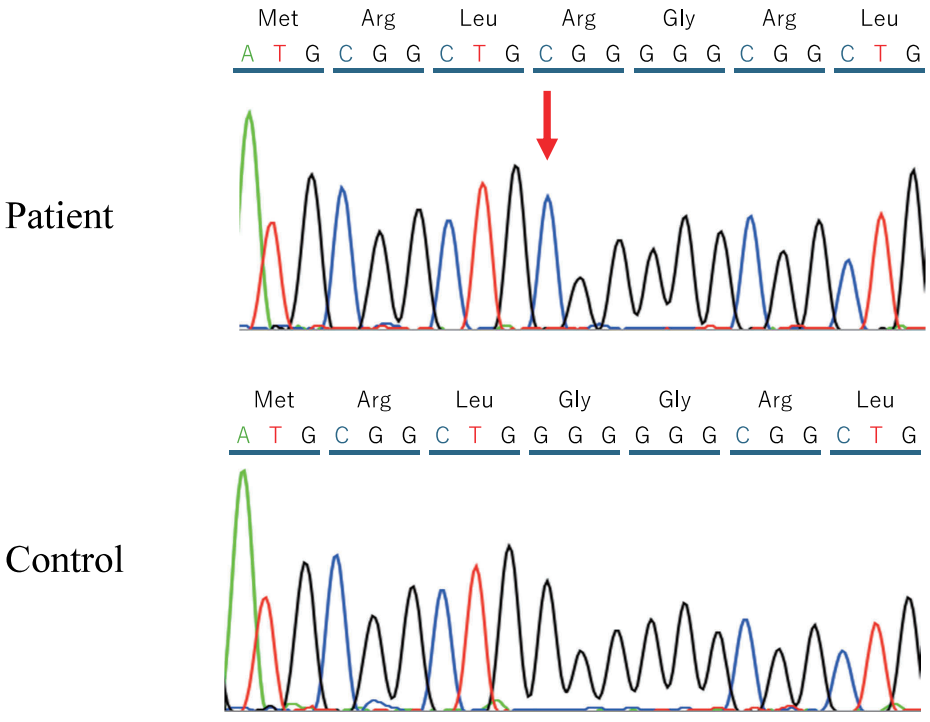

Figure 2. Sanger sequencing results for the identified variants (upper panel : patient ; lower panel : control). The red arrow indicates a homozygous c.139G>C substitution.

DISCUSSION

ADA2 deficiency is an autosomal recessive autoinflammatory disease caused by ADA2 variants. More than 60 pathogenic variants with significant genotypic and phenotypic variability have been identified (1). The disease manifests as systemic vasculitis, vascular abnormalities, immunodeficiency, and hematological disorders. Typical vasculitis-related symptoms include periodic fever, livedo reticularis, cerebral infarction, and cerebral hemorrhage. Immunodeficiency primarily presents as hypogammaglobulinemia, particularly low IgM levels, and recurrent infections, whereas hematological abnormalities include lymphopenia, neutropenia, pure red cell aplasia, pancytopenia, or bone marrow failure in some cases. Diagnosis relies on clinical presentation, with measurement of plasma ADA2 activity as a screening tool and confirmatory genetic testing.

ADA2 functions as an extracellular enzyme predominantly produced by monocytes and macrophages. Unlike ADA1, which primarily catalyzes intracellular adenosine deamination, ADA2 operates in the extracellular environment and converts adenosine to inosine (5). In addition to its enzymatic activity, ADA2 plays a crucial role in immune regulation by regulating endothelial cell and leukocyte development and differentiation (6). Deficiency of this enzyme leads to endothelial dysfunction, increased vascular permeability, and dysregulated inflammatory responses, all of which underlie the vascular manifestations observed in affected individuals. We identified a homozygous c.139G>C (p.Gly47Arg) variant in a 42-year-old patient in the present case who presented with recurrent stroke and parental consanguinity. This variant was frequently observed in early reports of ADA2 deficiency, with an estimated carrier frequency of 10% in the Georgian Jewish population (2, 7). Since then, it has been identified in many cases of ADA2 deficiency and is recognized as a loss-of-function variant (1). ADA2 deficiency exhibits significant clinical variability even among family members with identical variants. Although the disease typically manifests in childhood, adult-onset cases have been reported, often with mild or asymptomatic presentation (8). To date, there have been 628 cases of this disease reported in the literature worldwide ; however, in Japan, there are no reports except for a case series of 8 pediatric patients (9, 10). However, with increased awareness of this disease entity, proper diagnosis and treatment may become more accessible to the affected individuals.

Approximately half of patients with ADA2 deficiency experience neurological events, including cerebrovascular disease, most commonly lacunar infarctions in the brainstem and deep gray matter (11). This is consistent with the present case, which showed ischemic lesions in the midbrain. The localization of these brain lesions suggests pathological involvement of deep penetrating arteries in ADA2 deficiency. Increased neutrophil extracellular traps and tumor necrosis factor (TNF)-α are thought to contribute to vascular endothelial damage and subsequent cerebrovascular events ; however, the exact mechanism underlying this pathophysiology remains unclear (12). TNF-α inhibitors, such as etanercept, are the primary treatment for ADA2 deficiency and have been reported to significantly reduce event recurrence, particularly in patients with inflammatory or vasculitic phenotypes (13-15). Although aspirin and other antiplatelet agents are commonly used for stroke prevention, their use in patients with ADA2 deficiency remains controversial owing to their unclear benefits and the risk of brain hemorrhage (11, 14). In the present case, low-dose aspirin therapy was continued because the patient was relatively young, had a low risk of bleeding, and maintained low disease activity for a long period. However, stronger immunosuppressive therapy may be needed if the disease progresses.

In this case, the serum ADA level markedly decreased to below the lower limit of the reference range. Serum ADA comprises two isoenzymes : ADA1 (approximately 80%) and ADA2 (approximately 20%) (16). While patients with ADA2 deficiency exhibit significantly reduced or absent ADA2 activity, the total ADA levels may remain within the normal range because of preserved ADA1 activity. This necessitates specific ADA isoenzyme fractionation using erythro-9-(2-hydroxy-3-nonyl) adenine (EHNA), an ADA1-specific inhibitor, to accurately detect ADA2 deficiency ; however, it is testing modality is only available in a limited number of laboratories worldwide (17). Additionally, certain genetic variants may retain partial enzyme activity, potentially yielding false-negative results. In other words, even if ADA2 activity levels are normal or borderline, genetic testing should still be performed if clinical suspicion remains highly suggestive of ADA2 deficiency. Therefore, although it has some limitations, serum ADA levels, when combined with clinical findings, may serve as a useful tool for assessing the need for further testing, especially in settings in which genetic testing or ADA2 fraction analysis is not readily accessible.

In conclusion, we describe the case of a 42-year-old female with adult-onset ADA2 deficiency who presented with a juvenile stroke. ADA2 deficiency should be considered in patients with unexplained juvenile stroke, particularly when symptoms of recurrent vasculitis and parental consanguinity are present. Increased awareness of this disease, especially among neurologists and rheumatologists, is important for timely diagnosis and appropriate management of this treatable cause of juvenile strokes. When combined with clinical findings, the measurement of serum ADA activity may serve as a useful tool for determining the need for genetic testing.

CONFLICTS OF INTEREST

The authors have no disclosures relevant to the manuscript to declare.

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