

Case Report

# Brain stem infarction in a 6-year-old boy with Down syndrome

Toru Imagi<sup>a</sup>, Tomonaga Matsushita<sup>b</sup>, Miyuki Matsushita<sup>a</sup>, Yukako Yae<sup>a</sup>,  
Takaoki Yokochi<sup>a</sup>, Go Kawano<sup>a</sup>, Yukihiko Akita<sup>a</sup>, Keizo Ohbu<sup>a</sup>,  
Toyojiro Matsuishi<sup>a,c,\*</sup>

<sup>a</sup> Department of Pediatrics, St Mary's Hospital, Japan

<sup>b</sup> Department of Neurology, St Mary's Hospital, Japan

<sup>c</sup> Research Center for Children and Research Center for Rett Syndrome, St Mary's Hospital, Japan

Received 25 December 2018; received in revised form 12 February 2019; accepted 25 February 2019

## Abstract

Infarct locations in children with arterial ischemic stroke have primarily been reported to be lobar or in the basal ganglia, and those in patients with Down syndrome (DS) and antiphospholipid syndrome (APS) are typically wide and multiple. No solitary brain stem infarctions have ever been reported in children with DS until now. Here, we report a case of brain stem infarction in a 6-year-old boy with DS who had no cardiac, renal, or intestinal complications. He exhibited ataxic gait and medial longitudinal fasciculus (MLF) symptoms at first presentation. Neuroimaging revealed a localized and isolated lesion in the midbrain. Although he did not satisfy the diagnostic criteria of APS, he showed persistently elevated levels of anticardiolipin antibody (21 U/mL; normal value <10 U/mL). Although he had the risks of a multiple vascular systems disorder, DS, and persistently elevated levels of antiphospholipid antibodies, his lesion was not similar to any of the previously reported cerebral infarctions in DS or in APS. To our knowledge, this is the first report of limited solitary brain stem infarction in a child with DS.

© 2019 Published by Elsevier B.V. on behalf of The Japanese Society of Child Neurology.

**Keywords:** Down syndrome; Brain stem infarction; Anti-phospholipid syndrome

## 1. Introduction

The risk of cerebrovascular events in patients with Down syndrome (DS) is high for both ischemic and hemorrhagic strokes in all age groups. Risk of ischemic stroke in DS is mainly attributed to cardioembolic risk. Moyamoya disease is also one of the causes of brain infarction in DS [1]. In children suffering from ischemic stroke, the primary damage is reported to be mostly lobar or in the basal ganglia [2]. Several reported cases

of antiphospholipid syndrome (APS) have detailed wide regions of ischemic stroke-related impairments in cerebral regions [3]. Pediatric case reports of ischemic stroke limited to the brain stem have been associated with HHV-6 virus infection [4], radiation-induced vasculopathy, resection of medulloblastoma, vascular disorder with or without traumatic episode [5], or coagulation disorder. We examined a 6-year-old boy with DS who presented with ischemic stroke that was limited to the midbrain. He did not have any of the episodes or conditions mentioned above as a known etiology for the disease. He also showed elevated anticardiolipin antibody (aCL). His lesion was different from those previously seen in childhood stroke, APS, or DS. To our

\* Corresponding author at: Department of Pediatrics, St Mary's Hospital, 422 Tsubukuhonmachi, Kurume, Fukuoka 830-8543, Japan.  
E-mail address: [toyojiro@st-mary-med.or.jp](mailto:toyojiro@st-mary-med.or.jp) (T. Matsuishi).

knowledge, this is the first report of ischemic stroke in a child with DS that was limited to the brain stem without any known etiology. Additionally, he presented with an eye movement disorder of the medial longitudinal fasciculus (MLF), which was especially indicative of a brain stem lesion. The written consent was obtained from his parents regarding publishing the information. This research was approved by the institutional ethic committee at St. Mary's Hospital. There are no conflicts of interest to disclose.

## 2. Case report

A 6-year-old boy with DS who was confirmed after birth as trisomy 21 on the G-band and was otherwise healthy was referred to our hospital because of persistent ataxic gait. Two days before visiting our hospital, he began falling down toward the right side when walking and drooling when eating. He had not had any infections, vaccinations, or neck or head trauma within the 3 months before this episode. Upon arrival, his vital signs were normal. His neurological examination revealed a wide-based and unsteady gait with cerebellar ataxia, particularly when turning around. His level of consciousness was normal. Spontaneous gaze position was slightly abducted in the right eye, and the same eye exhibited impaired adduction when he attempted to look to the left. Convergence was preserved. These findings led to a diagnosis of MLF. Nystagmus was not seen. He also had difficulty controlling the lower part of the right side of his face. Other neurological findings such as increased deep tendon reflexes, muscle weakness, or sensory disturbance were not seen. A blood test, including a blood coagulation test, was normal except for increased low-density lipoprotein and IgG aCL (21 U/mL; normal value: <10 U/mL). He showed continuously elevated levels of aCL for 8 months (Table 1). Electrocardiogram showed no arrhythmia,

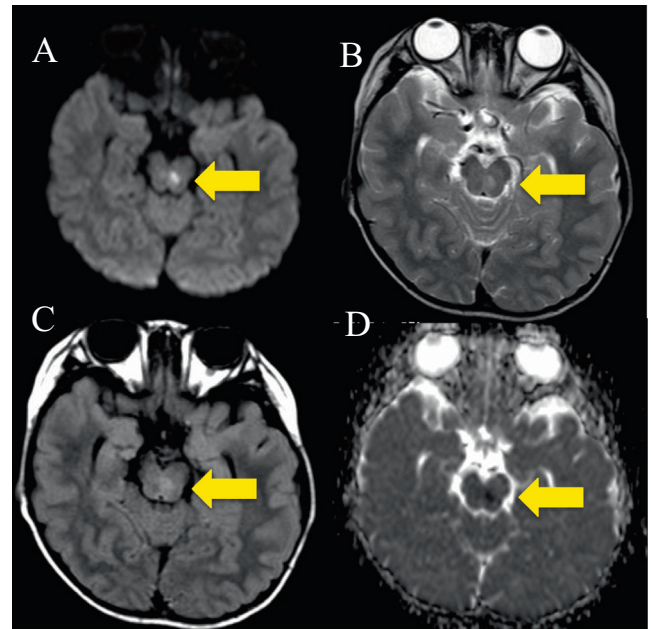


Fig. 1. Different magnetic resonance imaging (MRI) scans taken at the same level on the first hospital day. (A) Diffusion-weighted imaging (DWI). (B) T2-weighted MRI imaging (T2WI). (C) Fluid attenuated inversion recovery (FLAIR). (D) Apparent diffusion coefficient (ADC). DWI (A, arrow), T2WI (B, arrow), and FLAIR (C, arrow) showed a hyperintense lesion in the left midbrain. ADC (D, arrow) showed hypointense lesion in the same region. These findings are strongly suggestive of acute ischemic stroke.

including atrial fibrillation. Transthoracic echocardiography revealed no abnormal findings such as thrombus or congenital heart disease. Carotid ultrasonography (duplex) also revealed no abnormal findings. Magnetic resonance imaging (MRI) scans on the first hospital day, including Diffusion Weighted Image (DWI) (Fig. 1A), T2 Weighted Image (T2WI) (Fig. 1B), and Fluid Attenuated Inversion Recovery (FLAIR) (Fig. 1C) revealed a hyperintense lesion in the left

Table 1  
Table Laboratory Examination (normal value).

Coagulation Study		Immunological Study	
PT	12.2 s	C3	90 mg/dL (86–160)
PT (ACT)	89.0%	C4	22 mg/dL (17–45)
PT (INR)	1.05	CH50	45 U/mL (25.0–45.0)
APTT	28.0 s	Antinuclear antibody	< 40 (<40)
AT-3	93.9%	Rheumatoid factor	7 IU/mL (≤15)
Fib	222.4 mg/dL	Anti-DNA antibody	2.0 IU/mL (≤6.0)
D-Dimer	0.9 μg/mL	Anticardiolipin-β2GP1 antibody	≤1.2 U/mL (<3.5)
Lupus anticoagulant	1.05 (0.00–1.29)	Anticardiolipin-IgG	
Protein C activation	95% (64–146)	on admission	21 U/mL (<10)
Protein S activation	72% (60–150)	3 months later	14 U/mL (<10)
		8 months later	10 U/mL (<10)

PT: prothrombin time, APTT: activated partial thromboplastin time.

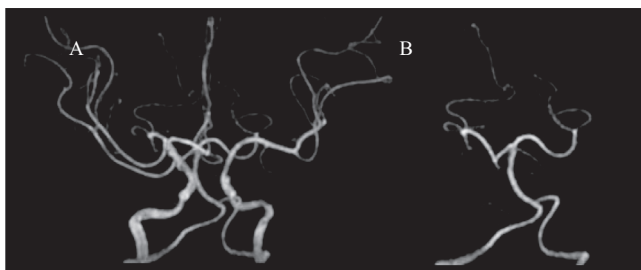


Fig. 2. Magnetic resonance angiography (MRA) on the first hospital day. No abnormal findings were observed, including stenosis or obstruction of the arteries, arteriovenous malformation, or evidence of moyamoya disease.

midbrain (arrow). Apparent Diffusion Coefficient (ADC) imaging showed a hypointense area in the same region (Fig. 1D, arrow). These findings were strongly suggestive of an acute ischemic stroke. Magnetic resonance angiography (MRA) on the same day showed no abnormal findings, including stenosis or obstruction of the arteries, arteriovenous malformation, or evidence of moyamoya disease (Fig. 2A, B). He was diagnosed as having acute ischemic stroke in the left midbrain, and was treated with the free radical scavenger, edaravone (Radicut<sup>R</sup>) at 18 mg/day for 6 days and with acetylsalicylic acid (aspirin<sup>R</sup>) at a dosage of 5 mg/kg/day. No recurrence of ischemic stroke or hemorrhage was observed during the hospital stay, and his symptoms gradually improved. He was discharged on the 15th hospital day without any symptoms, except for lingering MLF, which lasted 6 months. Antiplatelet therapy with acetylsalicylic acid was continued for 24 months. Abnormal findings on MRI disappeared after 6 months.

### 3. Discussion

We examined a 6-year-old boy with DS and elevated aCL who experienced an ischemic brain stem stroke that was confined to the left midbrain. This location was unusual for a pediatric patient with stroke, and the lesion was also unusual for strokes that occur in DS.

To our knowledge, infarctions localized to the brain stem are quite rare in both children and adults. MRI findings showed the lesions were confined to the paramedian area of the midbrain and the affected blood vessel was considered to be the posterior cerebral artery (PCA). However, obvious stenosis or obstruction was not confirmed by MRA. According to a previous report regarding cerebral infarction lesions in children, lesions affecting anterior circulation are more common than those affecting posterior circulation [2]. While PCA infarction was reported in 6.8% of all adult patients who were hospitalized for cerebral infarction, few reviews or case reports have focused on PCA infarction in children. The most common etiology of PCA infarc-

tion in adults has been reported to be lacunar infarction, followed by infarction due to atherosclerosis and cardio-genic thrombosis [6]. In addition, the paramedian area was the most affected region in 13 of 21 patients with pure midbrain infarctions [7].

DS is associated with a high risk of stroke at all ages. Ischemic stroke risk in DS is mostly attributed to cardioembolic disorder [1]. Moyamoya disease with DS is also reported as a risk for cerebral infarction, and the incidence of moyamoya disease in people with DS is higher than that in the general population [1]. Patients with DS are known to have elevated levels of aCL [3], and our patient exhibited aCL that was more than 10 U/mL. However, he did not meet the diagnostic criteria for APS (i.e., aCL over 40 U/mL for more than 12 weeks) [8]. Persistently elevated aCL might have played an important role in this case of brain stem infarction because the association between thrombosis and aCL is inconsistent while the significant correlations with thrombotic complications for the IgG aCL isotype were reported [9]. Other case reports of DS with APS presented with cerebral infarctions and lesions that were spread broadly throughout the cerebral hemisphere [3]. Additionally, damage to large extracranial or intracranial vessels by trauma which causes cerebral embolism and minor head trauma have also been reported to be an etiology of childhood stroke [5]. Stretching and distorting forces in intraparenchymal end arteries can cause intimal lesions followed by an occluding thrombus. Thus, the patient might have experienced a minor head injury without witness before the ischemic stroke, or hyperextension or hyperflexion, which could have led to the stroke episode. This is a possibility, even though X-ray examination did not show an extended distance between the rear surface of his frontal arcus of the C1 cervical vertebra and the anterior surface of the C2 cervical vertebra dens (anterior atlanto-odontoid distance). The X-ray data are not decisive because 27% of the population with DS have been reported to have atlantoaxial instability; thus, setting the normal limit of anterior atlanto-odontoid distance is still controversial [10].

Right facial palsy, MLF syndrome, and ataxic gait suggested damage spanning from the inferior colliculus to the upper pons. Ataxic gait is considered to be a disorder of the cerebellar peduncle. A lesion localized to the left midbrain was observed with MRI, and his symptoms and signs were consistent with the MRI findings. When infarctions are localized to the paramedian area of the adult midbrain, ocular movement disorders such as MLF, as well as truncal ataxia and ataxic gait, are frequently observed [7]. The most striking findings in this 6-year-old patient with DS were the limited region of the midbrain infarction and the persistently elevated aCL. MLF syndrome was an important diagnostic sign that suggested a brain stem impairment.

**References**

- [1] Sobey CG, Judkins CP, Sundararajan V, Phan TG, Drummond GR, Srikanth VK. Risk of major cardiovascular events in people with Down syndrome. *PLoS ONE* 2015;10:1–11.
- [2] deVeber GA, Kirton A, Booth FA, Yager JY, Wirrell EC, Wood E, et al. Epidemiology and outcomes of arterial ischemic stroke in children: the Canadian pediatric ischemic stroke registry. *Pediatr Neurol* 2017;69:58–70.
- [3] Hoxha A, Calligaro A, Bortolati M, Tonello M, Guariso G, Ruffatti A. The antiphospholipid syndrome and infections in a child with trisomy 21. *Autoimmun Rev* 2008;8:121–3.
- [4] Wada A, Muramatsu K, Sunaga Y, Mizuno T, Takei M, Ogasawara S, et al. Brainstem infarction associated with HHV-6 infection in an infant. *Brain Dev* 2018;40:242–6.
- [5] Kieslich M, Fiedler A, Heller C, Kreuz W, Jacobi G. Minor head injury as cause and co-factor in the aetiology of stroke in childhood: a report of eight cases. *J Neurol Neurosurg Psychiatry* 2002;73:13–6.
- [6] Arboix A, Arbe G, García-Eroles L, Oliveres M, Parra O, Massons J. Infarctions in the vascular territory of the posterior cerebral artery: clinical features in 232 patients. *BMC Res Notes* 2011;4:329.
- [7] Ogawa K, Suzuki Y, Oishi M, Kamei S. Clinical study of twenty-one patients with pure midbrain infarction. *Eur Neurol* 2012;67:81–9.
- [8] Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost* 2006;4:295–306.
- [9] Kelchtermans H, Pelkmans L, de Laat B, Devreese KM. IgG/IgM antiphospholipid antibodies present in the classification criteria for the antiphospholipid syndrome: a critical review of their association with thrombosis. *J Thromb Haemost* 2016;14:1530–48.
- [10] Mysliwiec A, Postuszny A, Saulicz E, Doroniewicz I, Linek P, Wolny T, et al. Atlanto-axial instability in people with Down's syndrome and its impact on the ability to perform sports activities – a review. *J Hum Kinet* 2015;48:17–24.