Child's Nervous System (2024) 40:1617–1621
https://doi.org/10.1007/s00381-024-06293-z

CASE REPORT

Neurovascular considerations in patients with Down syndrome and moyamoya syndrome

Arevik Abramyan[1] · Allen Ye Fu[2] · Khushi Patel[1] · Hai Sun[1] · Sudipta Roychowdhury[3] · Gaurav Gupta[1]

Received: 5 December 2023 / Accepted: 15 January 2024 / Published online: 25 January 2024

Abstract

In this article, we describe a rare and complex case of moyamoya syndrome in a 7-year-old boy with Down syndrome and atlantoaxial subluxation. The patient presented with an ischemic stroke in the left hemisphere and cervical cord compression with increased cord edema. Diagnostic digital subtraction angiography revealed unique patterns of vascular involvement, with retrograde flow through the anterior spinal artery, ascending cervical artery, occipital artery, and multiple leptomeningeal arteries compensating for bilateral vertebral artery occlusion. This case underscores the underreported phenomenon of upward retrograde flow through the anterior spinal artery in bilateral vertebral artery occlusion. We address the rare manifestation of posterior circulation involvement in moyamoya syndrome, highlighting the importance of considering atlantoaxial instability as a contributing factor, as the absence of atlantoaxial stability is a risk factor for vertebral artery dissection. This study contributes valuable insights into the intricate relationship of moyamoya syndrome, Down syndrome, and atlantoaxial instability, urging clinicians to consider multifaceted approaches in diagnosis and treatment. It also emphasizes the potential significance of the anterior spinal artery as a compensatory pathway in complex vascular scenarios.

Keywords Moyamoya disease · Vertebral artery occlusion · Down syndrome · Atlantoaxial instability · Pediatric stroke

Introduction

Moyamoya disease (MMD) is a rare cerebrovascular disorder marked by internal carotid artery (ICA) stenosis. Patients with characteristic moyamoya vasculopathy plus associated conditions are categorized as having moyamoya syndrome (MMS) [1]. We present a case involving a 7-year-old boy with MMS and Down syndrome (DS) who was admitted with an ischemic stroke and worsening atlantoaxial subluxation. The digital subtraction angiography (DSA) demonstrated MMD and bilateral vertebral arteries (VAs) occlusion with upward retrograde flow through the anterior spinal artery (ASA), ascending cervical artery, occipital artery, and multiple leptomeningeal arteries. We report this unique case due to its rarity and discuss its mechanism, considering MMD and atlantoaxial instability (AAI) as potential causes of the VA occlusion.

Case description

The patient, a 7-year-old boy with DS, presented with a change in mental status, right-sided facial twitching, and right upper extremity weakness. Previous spinal imaging had revealed an increased atlantodental interval of almost 9 mm in flexion, indicating atlantoaxial stenosis. Magnetic resonance imaging (MRI) revealed a large infarct in the left fronto-temporo-parietal region, a small infarct in the left temporal lobe posteriorly (Fig. 1), and worsening atlantoaxial subluxation with cervical cord compression and increased cord edema (Fig. 2).

✉ Gaurav Gupta
guptaga@rwjms.rutgers.edu

Arevik Abramyan
dr.arevik.abramyan@gmail.com

[1] Department of Neurosurgery, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA

[2] Department of Cell Biology and Neuroscience, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA

[3] Department of Interventional Radiology, University Radiology, Robert Wood Johnson Medical School, New Brunswick, NJ, USA

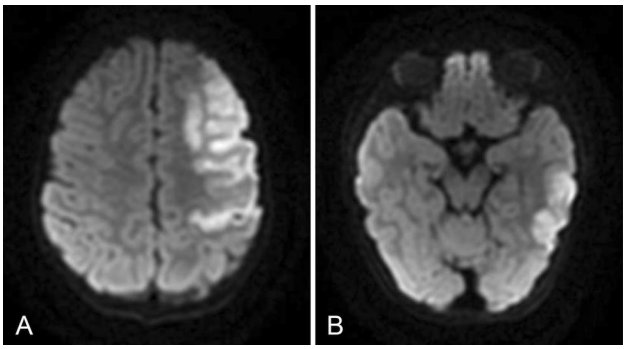

Fig. 1 Axial view of a diffusion-weighted magnetic resonance imaging (DW-MRI) showing a large infarct in the left fronto-temporo-parietal region (**A**) and a small infarct in the left temporal lobe posteriorly (**B**)

The DSA demonstrated stenosis of the right supraclinoid ICA beyond the ophthalmic artery and stenosis of the right proximal anterior cerebral artery (Suzuki stage III, Fig. 3A and B). Extensive neovascularization and collateral flow were seen from the branches of the intracranial ophthalmic artery to the skull base and from the branches of the right external carotid artery (occipital artery, proximal branches of the middle meningeal artery, superficial temporal artery, internal maxillary artery, Fig. 3C). The same branches of the left external carotid artery also demonstrated extensive intracranial collateral circulation and neovascularization with blood perfusion of the left ICA distribution (Fig. 3F). Left ICA was completely occluded in the cavernous segment (Suzuki stage IV, Fig. 3D and E).

Notably, there was an occlusion of both the right VA (Fig. 4C and D) and left VA (Fig. 4E and F) in the region of C2-C4 vertebrae with multiple collaterals from the thyrocervical and costo-cervical trunks which communicated with the ASA. Eventually, the retrograde flow from the ASA, ascending cervical artery, occipital artery, and multiple leptomeningeal arteries reconstituted the intracranial VAs for posterior fossa blood perfusion (Fig. 4).

Due to the patient's lateral axial stenosis and subluxation with AAI, and physical findings concerning for decreased head and upper extremity movement, structural compromise was also investigated. The patient underwent surgery for cord decompression and posterior spinal fusion from the occiput to C2 cervical spine with right iliac crest bone graft, removal of the posterior arch of C1 for decompression, and insertion of a halo vest. The patient tolerated the procedure well.

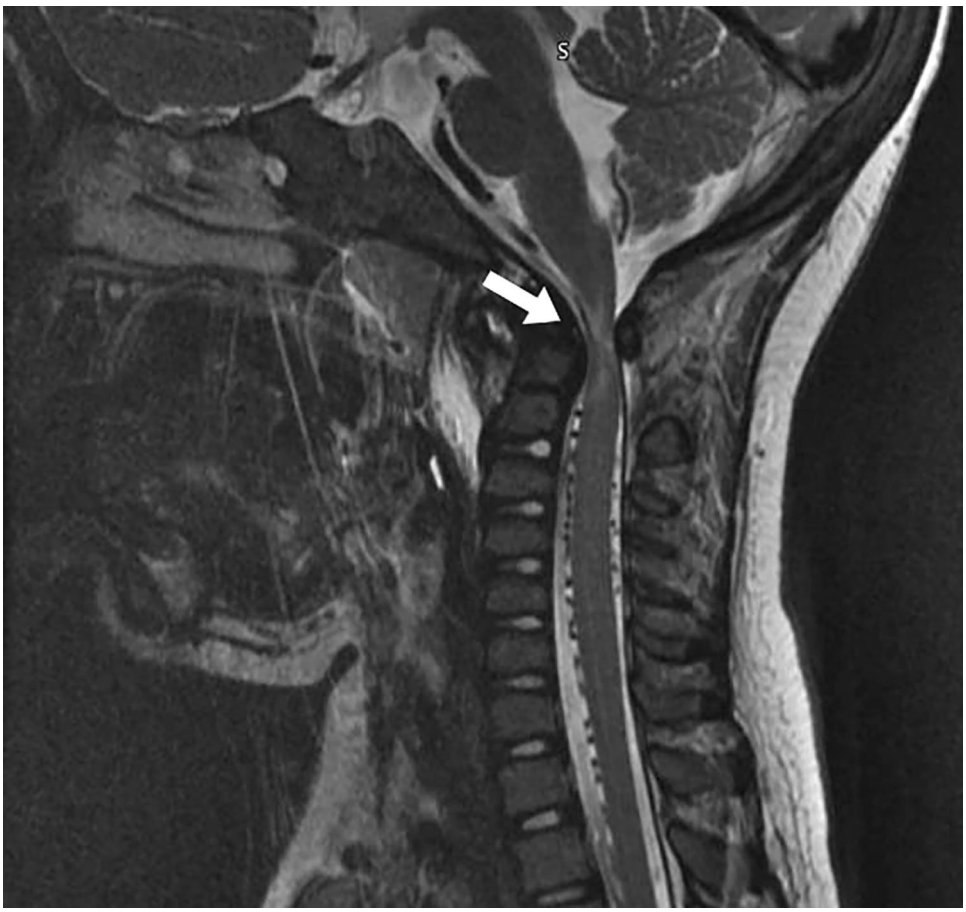

Fig. 2 Sagittal view of a T2 cervical magnetic resonance imaging (MRI) showing atlanto-axial subluxation with cervical cord compression and increased cord edema (white arrow)

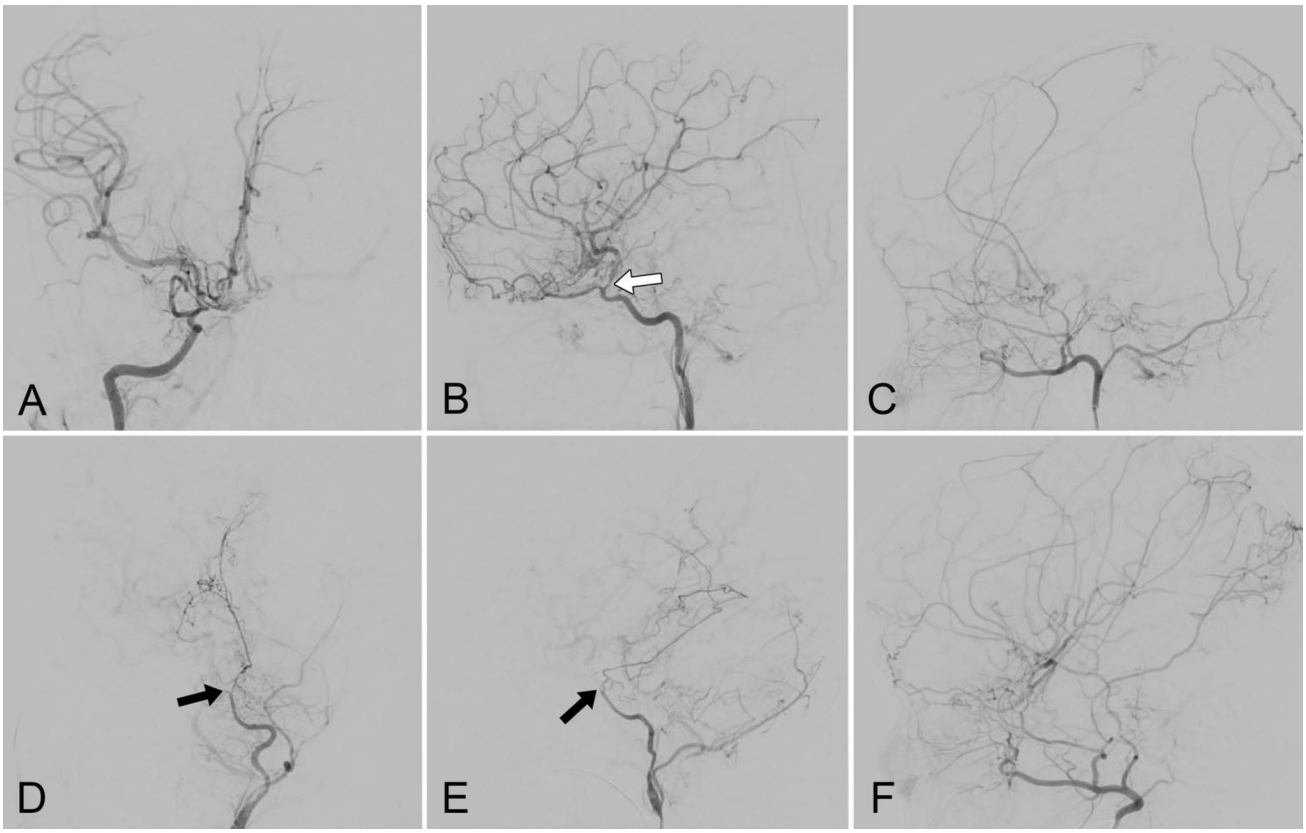

Fig. 3 **A**, **B** Right ICA angiogram in frontal (**A**) and lateral view (**B**) showing severe stenosis (white arrow) of the right supraclinoid ICA and right proximal A1/ACA (Suzuki stage III). **C** Right ECA angiogram in lateral view showing collateral flow from the branches of occipital artery, middle meningeal artery, superficial temporal artery, and internal maxillary artery. **D**, **E** Left ICA angiogram in frontal (**D**) and lateral view (**E**) demonstrates occlusion of the ICA in the cavernous segment (Suzuki stage IV, black arrow). **F** Left ECA angiogram in lateral view showing extensive neovascularization and collateral flow from the branches of middle meningeal artery, superficial temporal artery, and internal maxillary artery

Also, due to the patient's extensive history of MMS, previous ischemic stroke, and noted bilateral VA occlusion, vascular compromise remained high on the differential. Surgical revascularization was considered a viable option to establish alternative blood supply to the brain, reducing the risk of future recurrent ischemic events. Typically planned at least 3to 6 months later, the revascularization procedure was delayed due to increased risks of perioperative strokes and complications when performed within the initial months following the last stroke in MMD patients, as well as considering the post-operative recovery after posterior spinal fusion surgery.

Discussion

MMD is a rare cerebrovascular condition characterized by the progressive stenosis of the distal ICAs. An understanding of the etiology of MMD as well as the best treatments for this disorder have remained elusive, although several genes such as RNF213 [2], ANO1 [3], and DIAPH1 [4] have been associated with the risk of developing MMD.

Although rare, some case reports and case series have described patients with both DS and MMS [5–8]. Kainth et al. determined the estimated prevalence of DS as 3.8% (3760 per 100,000) among patients admitted with MMD and 9.5% (9540 per 100,000) among moyamoya patients younger than 15 years of age [9]. It has been hypothesized that overexpression of a gene on chromosome 21 could lead to the onset of MMS, although no such association has been discovered yet [6, 7]. Some studies report the RNF213 gene may interact with the genes on chromosome 21 that influence vascular physiology and elasticity in patients with DS, resulting in the picture of MMS [5].

MMD is most often known as a disorder of the anterior circulation. However, in rare cases, the involvement of the posterior circulation has been reported. Cramer et al. reported occlusion of the posterior cerebral artery to be present in 1 out of 7 patients with MMD and DS [6]. Studies estimate that occlusion of at least one of the VAs in MMD

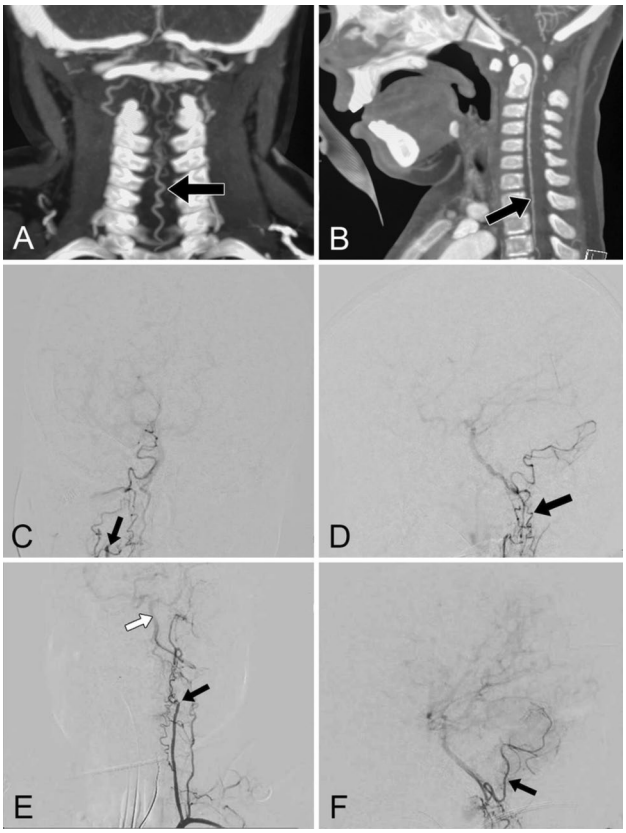

Fig. 4 **A**, **B** Neck computed tomography angiography showing the tortuous and dilated ASA (black arrow). **C**, **D** Right VA angiogram in frontal (**C**) and lateral view (**D**) demonstrates occluded right VA (**C**, black arrow) and multiples collaterals (**D**, black arrow) which reconstituted the intracranial VAs. **E**, **F** Left VA angiogram in frontal (**E**) and lateral view (**F**) demonstrates occluded left VA (**E**, black arrow) with reconstituted by multiple collaterals basilar artery (**E**, white arrow) and posterior inferior cerebellar artery (**F**, black arrow)

occurs in approximately 3% of patients, with bilateral occlusion being even rarer [10, 11]. Although unilateral presentations of MMD have been reported [12], bilateral involvement is a more common presentation in patients with DS, possibly reflecting the difficulty in making an early diagnosis rather than a vascular pathology specific to these patients [6]. In our case, the patient presented with right-sided facial twitching and upper extremity weakness, most likely attributed to a large ischemic stroke in the left fronto-temporo-parietal region of the left hemisphere. Additionally, the patient's reduced head and upper extremity movement were possibly associated with atlantoaxial subluxation causing cervical cord compression.

The patient's atlantoaxial and subaxial spinal instability may contribute to bilateral VA dissection and occlusion, given the assumed risk factor of instability induced by AAI [13]. AAI is a common co-morbidity among patients with DS, resulting from ligament laxity and odontoid dysplasia. About 10–30% of patients having trisomy 21 will traditionally develop AAI, yet some reports mark the risk to be more than 60% in adult population [14–16]. The incidence may vary in the pediatric population. Takeoka et al. and Alfhmi et al. both noted an incidence of AAI in the pediatric population ranging from 14.6 to 22.2%, with the majority being asymptomatic [17, 18]. Instability in the atlantoaxial joint, crucial for head rotation, can potentially lead to VA compression, dissection, and subsequent occlusion. It is essential to perform not only cranial but also cervical MRI for a patient with DS presenting neurological complications [8].

In patients with VA occlusion, spontaneous flow reversal may occur in the ASA as a source of compensatory blood supply to the posterior circulation. Although rarely reported, our case observed upward retrograde flow through the ASA, feeding the basilar artery through collateral vessels from the ASA, ascending cervical artery, occipital artery, and multiple leptomeningeal arteries. The possible etiology of the VAs occlusion could vary because of the patient's MMD and DS with AAI. ASA is found to be an important potential source of posterior fossa perfusion if blood supply from the VAs is tenuous or absent, and the degree and extent of contribution from the ASA to the intracranial blood perfusion depends on presence or absence of another source of collateral supply (such as posterior communicating artery), and on the patency of the adjacent vertebrobasilar junction as a route for the further flow.

Conclusion

The rare pattern of upward retrograde flow through the ASA in the case of the bilateral VA occlusion is underreported in the literature. In the presented case, the unique combination of MMS, DS, AAI, and bilateral VA occlusion highlights the need for comprehensive understanding and individualized management strategies. The observation of upward retrograde flow through the ASA emphasizes its potential significance as a compensatory pathway in complex vascular scenarios.

Author contributions 1. Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data: A.A., A.F., K.P. 2. Drafting the article or revising it critically for important intellectual content: H.S., G.G. 3. Final approval of the version to be published: S.R., G.G. All authors reviewed and approved the final version to be published.

Availability of data and materials No datasets were generated or analysed during the current study.

Declarations

Ethical approval Not applicable.

Conflict of interest The authors declare no conflict of interest.

References

1. Scott RM, Smith ER (2009) Moyamoya disease and moyamoya syndrome. N Engl J Med 360:1226–1237. https://doi.org/10.1056/NEJMra0804622
2. Kamada F, Aoki Y, Narisawa A, Abe Y, Komatsuzaki S, Kikuchi A, Kanno J, Niihori T, Ono M, Ishii N, Owada Y, Fujimura M, Mashimo Y, Suzuki Y, Hata A, Tsuchiya S, Tominaga T, Matsubara Y, Kure S (2011) A genome-wide association study identifies RNF213 as the first Moyamoya disease gene. J Hum Genet 56:34–40. https://doi.org/10.1038/jhg.2010.132
3. Pinard A, Ye W, Fraser SM, Rosenfeld JA, Pichurin P, Hickey SE, Guo D, Cecchi AC, Boerio ML, Guey S, Aloui C, Lee K, Kraemer M, Alyemni SO, University of Washington Center for Mendelian Genomics, Bamshad MJ, Nickerson DA, Tournier-Lasserve E, Haider S, Jin SC, Smith ER, Kahle KT, Jan LY, He M, Milewicz DM (2023) Rare variants in ANO1, encoding a calcium-activated chloride channel, predispose to moyamoya disease. Brain 146:3616–3623. https://doi.org/10.1093/brain/awad172
4. Kundishora AJ, Peters ST, Pinard A, Duran D, Panchagnula S, Barak T, Miyagishima DF, Dong W, Smith H, Ocken J, Dunbar A, Nelson-Williams C, Haider S, Walker RL, Li B, Zhao H, Thumkeo D, Marlier A, Duy PQ, Diab NS, Reeves BC, Robert SM, Sujijantarat N, Stratman AN, Chen Y-H, Zhao S, Roszko I, Lu Q, Zhang B, Mane S, Castaldi C, López-Giráldez F, Knight JR, Bamshad MJ, Nickerson DA, Geschwind DH, Chen S-SL, Storm PB, Diluna ML, Matouk CC, Orbach DB, Alper SL, Smith ER, Lifton RP, Gunel M, Milewicz DM, Jin SC, Kahle KT (2021) DIAPH1 Variants in non-East Asian patients with sporadic moyamoya disease. JAMA Neurol 78:993–1003. https://doi.org/10.1001/jamaneurol.2021.1681
5. Abdelgadir A, Akram H, Dick MH, Ahmed NR, Chatterjee A, Pokhrel S, Vaijaya Kulkarni V, Khan S (2022) A better understanding of moyamoya in trisomy 21: a systematic review. Cureus 14:e23502. https://doi.org/10.7759/cureus.23502
6. Cramer SC, Robertson RL, Dooling EC, Scott RM (1996) Moyamoya and Down syndrome. Clinical and radiological features Stroke 27:2131–2135. https://doi.org/10.1161/01.str.27.11.2131
7. Kumar P, Panigrahi I, Sankhyan N, Ahuja C, Goyadi PK (2018) Down syndrome with moyamoya disease: a case series. J Pediatr Neurosci 13:201–204. https://doi.org/10.4103/jpn.JPN_116_17
8. Takanashi J, Sugita K, Ishii M, Iai M, Goto M, Tanabe Y, Niimi H (1993) A girl with Down syndrome complicated by moyamoya disease and symptomatic atlanto-axial instability. No To Hattatsu 25:248–252
9. Kainth DS, Chaudhry SA, Kainth HS, Suri FK, Qureshi AI (2013) Prevalence and characteristics of concurrent Down syndrome in patients with moyamoya disease. Neurosurgery 72:210–215. https://doi.org/10.1227/NEU.0b013e31827b9beb
10. Deng X, Zhang D, Zhang Y, Wang R, Wang B, Zhao J (2017) Moyamoya disease with occlusion of bilateral vertebral arteries and the basilar artery fed by the collateral vessels of vertebral arteries: a rare case report. J Clin Neurosci 42:116–118. https://doi.org/10.1016/j.jocn.2017.03.043
11. Miyamoto S, Kikuchi H, Karasawa J, Nagata I, Ikota T (1984) Moyamoya disease associated with bilateral occlusion of the vertebral artery. Surg Neurol 22:21–28. https://doi.org/10.1016/0090-3019(84)90222-2
12. Matsushima T, Inoue T, Natori Y, Fujii K, Fukui M, Hasuo K, Kuwabara Y (1994) Children with unilateral occlusion or stenosis of the ICA associated with surrounding moyamoya vessels — "unilateral" moyamoya disease. Acta Neurochir (Wien) 131:196–202. https://doi.org/10.1007/BF01808612
13. Hu Y, Du J, Liu Z, Wu H, Ding J, Jian F (2019) Vertebral artery dissection caused by atlantoaxial dislocation: a case report and review of literature. Child's Nervous System 35:187–190. https://doi.org/10.1007/s00381-018-3948-x
14. Alvarez N, Rubin L (1986) Atlantoaxial instability in adults with Down syndrome: a clinical and radiological survey. Appl Res Ment Retard 7:67–78. https://doi.org/10.1016/0270-3092(86)90019-6
15. El-Khouri M, Mourão MA, Tobo A, Battistella LR, Herrero CFP, Riberto M (2014) Prevalence of atlanto-occipital and atlantoaxial instability in adults with Down syndrome. World Neurosurg 82:215–218. https://doi.org/10.1016/j.wneu.2014.02.006
16. Pueschel SM, Scola FH, Perry CD, Pezzullo JC (1981) Atlantoaxial instability in children with Down syndrome. Pediatr Radiol 10:129–132. https://doi.org/10.1007/BF00975185
17. Alfhmi S, Sejeeni N, Alharbi K, Alharbi R, Malayoo B (2023) Atlantoaxial subluxation in a 10-year-old girl with down syndrome: a case report. Cureus. https://doi.org/10.7759/cureus.43955
18. Takeoka Y, Kakutani K, Miyamoto H, Suzuki T, Yurube T, Komoto I, Ryu M, Satsuma S, Uno K (2021) Complications of posterior fusion for atlantoaxial instability in children with Down syndrome. Neurospine 18:778–785. https://doi.org/10.14245/ns.2142720.360