ISSN: 2755-9890

Journal of Spine Research & Reports

SCIENTIFIC Research and Community

Case Report

Open Access

A Patient with Brainstem Infarction and Recurrent Fever a Case Report

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ABSTRACT

Introduction: Bilateral medulla oblongata infarction (BMOI) is a rare subtype of all ischemic strokes often leading to tetraplegia including autonomic dysregulation. Underlying infection occurring concomitantly during initial treatment might be underdiagnosed due to overlapping symptomatic.

Case Presentation: We present a case of an immunocompetent patient with pulmonary tuberculosis, who developed acute tetraplegia following a BMOI. The patient started experiencing daily episodes of high fever shortly after the insult. After numerous initial negative screenings for tuberculosis, the recurrent fever of unknown origin pointed towards an autonomic nerve system in connection with the recent medullary lesion. However, an atypical pulmonary tuberculosis radiological presentation with a diffuse tree-in-bud sign on a Computer Tomography-scan, absent meningeal involvement in the lumbar puncture, but finally the presence of Mycobacterium Tuberculosis in tracheal secretion confirmed the diagnoses of Tuberculosis. The patient was successfully treated with quadruple therapy for two months followed by dual therapy (Rifampicin and Isoniazid) for an additional four months. This case highlights the diagnostic challenges of Mycobacterium Tuberculosis infection in an immunocompetent patient with rapid onset of tetraplegia, showing symptoms resembling autonomic dysreflexia, typically observed in patients with spinal cord injuries at/above the T6 level, but also existent in those with ischemic medullary lesions.

Conclusion: In patients with recent BMOI and recurrent fever, tuberculosis should be always a key consideration in the differential diagnosis during the initial treatment besides the diagnoses of autonomic dysregulation.

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Received: August 18, 2025; **Accepted:** August 25, 2025; **Published:** September 15, 2025

Keywords: Medulla Oblongata, Tetraplegia, Stroke, Autonomic Dysregulation, Fever Unknown Origin, Mycobacterium Tuberculosis

Abbreviations
BMOI: Bilateral Medulla Oblongata Infarction
CSF: Cerebrospinal fluid
DWI: Diffusion- Weighted Imaging
SCIM: Spinal Cord Independence Measure
TB: Tuberculosis

Introduction

Bilateral medulla oblongata infarction (BMOI) is a rare subtype of all ischemic strokes, involving occlusion of the anterior spinal artery and vertebral artery, which usually presents with hypoglossal palsy, tetraplegia, loss of deep sensation and bulbar dysfunction with or without respiratory failure [1-3]. The primary culprit for BMOI is large-artery atherosclerosis, but thromboembolic events, mainly from atrial fibrillation or hypercoagulable states, vascular malformations, cervical trauma, and vertebral artery dissection as well as cerebral vasculitis, in particularly secondary to infections,

have been also reported as causal mechanisms [4]. Pathognomonic magnetic resonance imaging (MRI) findings of BMOI reveal a bilateral infarction at levels of the medial medulla, which is well known as the "heart appearance" on diffusion-weighted imaging (DWI) [5]. The medulla oblongata is the lowest segment of the brain stem, located adjacent to the spinal cord, with a complex anatomical structure. Bilateral medulla oblongata infarction comes with complex and often severe neurological impairments. Clinical findings often show tetraplegia, respiratory failure, and autonomic dysfunctions. Patients in the acute phase are often managed in intensive care and later transferred to specialized rehabilitation centres.

Case Presentation

A 28-year-old male patient presented initially to an acute hospital abroad in October 2022 with sudden right-sided, followed shortly after by left-sided body weakness associated with slurring of speech and loss of balance. Symptoms progressively worsened within a few hours resulting in tetraplegia with sign of airway compromise, subsequently leading to elective intubation. His neurological evaluation included MRI of the brain and magnetic resonance angiography and computed tomography (CT) angiography of the head and neck, which revealed BMOI with associated reduced overall posterior circulation perfusion (Figure 1a). An MR Angiography showed no evidence of atherosclerotic changes or vasculitis. The only additional finding was a hypoplasia of the right vertebral artery (Figure 1b). The short and 24-hour electrocardiogram and the thoracal echocardiogram showed no abnormalities. No fever was observed. Cerebrospinal fluid (CSF) studies turned out unremarkable. A single antiplatelet treatment with Clopidogrel (due to patient-reported acetylsalicylic acid allergy) and statin was promptly started. The patient was repatriated to the intensive care unit in a hospital in Switzerland, partly ventilator dependent without a tracheostoma, a persistent incomplete tetraplegia fully orientated. Several tests were conducted to investigate the etiology of the stroke, all resulting inconclusive (Table 1). Notably, the patient tested positive for Acinetobacter baumanii tracheal colonization and was consequently isolated for droplets. In the coming days, the patient experienced several bouts of fever with increasing inflammatory parameters, whereas blood cultures and tracheal secretions did not show any relevant growth. A CT-scan of the thorax revealed an enlarged mediastinal lymph node but no other abnormalities. A fine needle biopsy of the lymph node was performed but turned out inconclusive. In the absence of a clear infectious focus in a cardiopulmonary stable patient, no antibiotic therapy was administered to the patient.

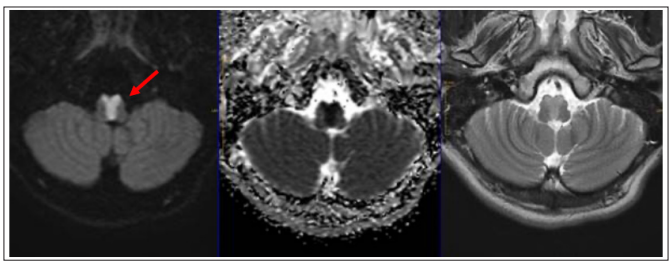

Figure 1a: MRI T2 and DWI sequence, showing the heart-shaped cortical infarction.

The patient was transitioned to a specialized rehabilitation center for post-acute rehabilitation with the continuation of the pre-established antiplatelet therapy. Upon arrival, we proceeded to perform a dilatative tracheostomy due to insufficient respiratory capacity. The interprofessional rehabilitation included individually adopted interventions to stimulate recovery, strengthen force, optimize respiration and swallowing, and prepare independent mobility and self-care.

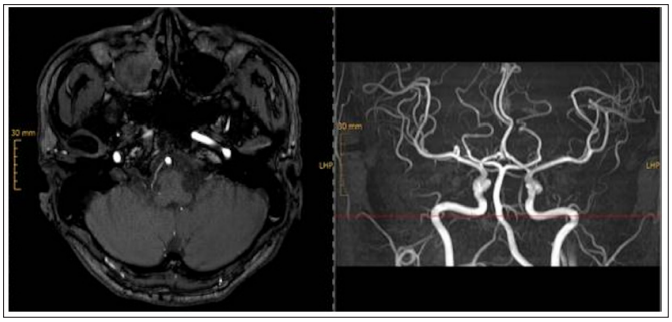

Figure 1b: MRI T2 showing hypoplasia of the right vertebral artery.

This patient had no history of communicable diseases, including human immunodeficiency virus and sexually transmitted diseases. He also denied any high-risk behavior and consumption of intravenous drugs or others. A COVID-19 infection was diagnosed one year before the ischemic event. His family history was notably positive for strokes but negative for other relevant neurological disorders. He also had no prior treatment with immunosuppressants.

At the age of 3 years, due to a positive Mantoux Test by his pediatrician after a trip to Vietnam, the patient was treated for 9 months with Isoniazid. His social history was pertinent to work as a flight engineer. During the first phase of rehabilitation at our center, he again suffered recurring bouts of febrile temperatures, typically in the morning and evening, as well as sweating abnormalities. Due to its regularity and in lack of other obvious causes we associated these with autonomic dysreflexia, typically occurring in patients with spinal cord lesions above T6 as well as medullary lesions.

After a few weeks, increasing liver parameters were also observed, and an abdominal ultrasound revealed no signs of cholecystitis. 3-months after the onset of the tetraplegia, we ran a head and whole-spine MRI as part of our organization-specific developed protocol ("Nottwiler Standard"), an assessment standard for use in the rehabilitation of persons after newly acquired spinal cord injuries according to the guiding principles [6]. As an incidental finding, a significant pleural effusion with possible adjacent partial atelectasis of the left lung tissue was detected. A follow-up CT-Scan was performed, confirming the diagnosis (Figure 2A). A pleural puncture under sonographic control was attempted but the effusion was already too consolidated to be aspirated.

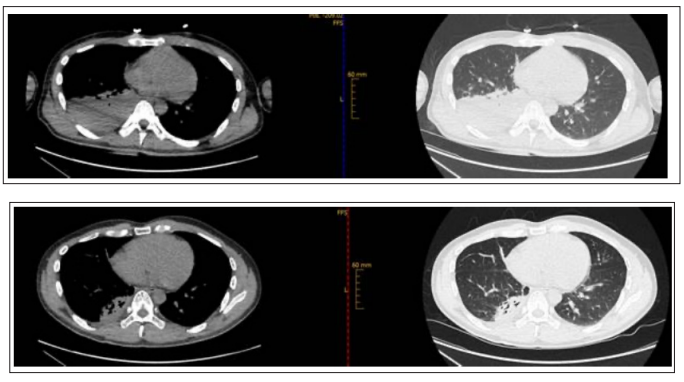

Figure 2: CT-Scan of the thorax (Parenchymal Window) at A) time of diagnosis of TB and B) 6 months post-diagnosis

An analysis of tracheal secretions was performed, and empirical antibiotic treatment was started. Tracheal aspirates came back positive for pan-sensitive Mycobacterium tuberculosis. A lumbar puncture to exclude leptomeningeal involvement turned out negative. Standard treatment for tuberculosis (TB) (rifampicin, isoniazid, pyrazinamide, ethambutol) was initiated. After two weeks of treatment, we could observe a marked reduction in inflammatory parameters and remission of fever. One month after the patient was completely symptom-free, and the laboratory parameters had returned to baseline levels. After two months, treatment was switched to dual therapy with rifampicin and isoniazid. The patient could be efficiently decannulated in March 2023. An MRI control 3 months post-stroke showed already significant cystic degeneration of the infratectal area, whereas the degree of peduncular atrophy reflects the extent of damage in the corticospinal tract [7]. At 6 months, the patient partially recovered his neurological functions: his speech was without dysarthria or aphasia and motor examination revealed strength M1 to M2 in all key muscles, with marked spasticity. He was able to breath independently and to use a powered wheelchair for mobility. The Spinal Cord Independence Measure (SCIM III) increased from initially 0 to finally 49 points. He remained dependent on self-care. All laboratory tests returned in the normal range (Table 1) [8-11].

Table 1: Summary Of Pertinent Laboratory and Diagnostic Studies Results at Presentation And 6 Months Later

Cerebrospinal Fluid	**at Initial Presentation**	
Colour and appearance	Clear and colourless	
Opening pressure	N	
Glucose level, mmol/L	3.3	
Protein level, mg/L	149	
WBC count, /mm3	0	
RBC count, / mm3	1	
Diagnostic Tests		
Transthoracic Echocardiogram	Normal	
Transoesophageal Echocardiogram	Absence of PFO	
Holter	Absence of Arrhythmia	
Chemistry Tests	**at Initial Presentation**	**6 Months Later**
RBC count 1012/l	3.89	4.52
WBC count 109/l	11.84	4.73
Differential:		
Segmented neutrophils 109/l	9	3.03
Lymphocytes 109/l	0.91	0.79
Monocytes 109/l	0.76	0.38
Eosinophiles 109/l	0.46	0.3
Basophiles 109/l	0.06	0.01
Hemoglobin g/l	100	142
Hematocrit %	0.32	0.42
Platelet count 109/l	629	233
Ferritin µg/l	1308	288
C-Reactive Protein mg/l	71	5
Sodium mmol/l	138	140
Calcium mmol/l	3.18	4.16
Bilirubin total µmol/l	3.2	2.2
AST U/l	17	16
ALT U/l	20	18
AP U/l	183	73
Gamma-GT U/l	215	28
Pancreatic Amylase U/l	60	39
Lipase U/l	74	58
LDH U/l	166	123
ANCA	negative	
ANA	negative	
Vasculitis	negative	
Anti-Phospholipids	negative	

Beta-HCG	negative	
alpha-Fetoprotein	negative	
Infectious Disease Laboratory Tests	**at Initial Hospitalization**	
Bacterial culture, serum	negative	
Fungal culture, serum	negative	
HIV	negative	
Hepatitis panel, A, B, C	negative	
Lues Serology	negative	
Lyme Abs IgG	negative	
TB QuantiFERON Gold test	negative	
Genetic Testing	**at Initial Hospitalization**	
Factor-V-Leiden Mutation	negative	
M. Fabry	negative	
JAK2 Mutations	negative	
Immunophenotyping (Paroxysmal Nocturnal Hematuria)	negative	

A CT-Scan performed at 6 months (Figure 2B) showed bronchiectasis in the originally consolidated lung segments with possible small caverns along this bronchiectasis, which we interpreted as post-specific changes but not in relationship with an active TB. Repeated sputum cultures were all negative. Therefore, the antituberculotic treatment was stopped.

Discussion

We present a case of pulmonary tuberculosis in an immunocompetent patient presenting with ischemic medullary stroke without meningeal involvement. While common stroke triggers include higher ager, atherosclerosis and atrial fibrillation, infections can increase the risk by leading to cerebral vasculitis. Our patient's condition might stimulate the differential diagnostic thinking integrating several causative factors on the one side and the differential diagnostic of TB in cases of fever of unknown origin. Recent data suggests higher ischemic stroke risk in TB survivors [9]. In a series of retrospective studies investigating ischemic stroke in patients with pulmonary TB, an increased risk of ischemic stroke was observed within 3 months after the diagnosis of TB [10,11]. Notably, most patients showed radiological signs of meningeal involvement. Pulmonary TB patients often exhibit thrombocytosis, with TB inducing platelet hyperaggregation [12]. Furthermore, raised plasma fibrinogen, fibrin degradation products, tissue plasminogen activator, and depressed antithrombin III levels were seen in TB patients [13]. Stroke risk, though rare in TB, can be from meningeal invasion or vasculitis, amplified by the severe prognosis of BMOI. Central nervous system TB often results in fatal brain damage from intracranial vessel alterations, involving infiltrative, proliferative, and necrotizing processes of small and medium intracranial vessels [14,15]. Our patient had no history to suggest an immunosuppressed state. The patient tested negative for human immunodeficiency virus (HIV) 1 and 2. Vasculitis screening (antinuclear antibodies, antineutrophil cytoplasmic antibodies, and rheumatoid factors) revealed negative results. Furthermore, initial cerebral vessel imaging studies did not suggest primary CNS vasculitis, and echocardiography excluded any thromboembolic event of cardiac origin. A lumbar puncture turned out negative, excluding meningeal involvement, as typically seen in neuro- tuberculosis. The diagnosis was made challenging due to consistently several negative QuantiFERON tests performed at various time points in all hospitals. One possible explanation for this repeated negative testing can be that the TB-specific lymphocytes migrate into the tuberculomas during active TB or that the specific cells are anergized by mycobacterial humoral factors [16]. However, considering the patient's childhood positive Mantoux test and subsequent treatment, we deduce the recent TB is a new occurrence, not a reactivation.

During the phase of recurrent fever and altered blood pressure, this patient showed features seen in autonomic dysreflexia, a significant autonomic reaction with high impact on morbidity and mortality. Autonomic dysreflexia cannot only occur 70 to 90% of patients with spinal cord injury injuries at or above T6, but also arise in individuals with ischemic-origin medullary lesions [17-19]. Notably, stroke patients might experience similar symptoms to those with high spinal cord lesions, ranging from autonomic dysregulation to severe arrhythmias and myocardial infarction, a syndrome recently described as the stroke-heart syndrome [20,21].

The impaired function of the autonomic nerve system becomes apparent through symptoms range from low or elevated blood pressure, changed sweating, and fever to bowel and bladder functioning. Without prompt intervention, autonomic dysreflexia with elevated blood pressure can have severe systemic effect [22]. Thermo-dysregulation following acute spinal or medullary insult is often underestimated and overlooked. In these patients, the heightened fever risk could therefore also result from thermoregulatory abnormalities due to autonomic system dysfunction [19]. Though fever in patients with spinal cord injury typically traces back to infections, thromboembolism, or medicines with urinary infections being most frequent some cases lack a discernible cause. These "fever of unknown origin" incidents might be deemed neurogenic, suggesting autonomic function impairment [23]. TB symptoms include coughing, shivering, fever, night sweating and weight loss [24]. These infective symptoms are cloth to those of autonomic dysreflexia and can therefor mislead the diagnostic processes. This overlap is especially pronounced in patients with newly diagnosed tetraplegia undergoing early rehabilitation, where weight loss and reduced appetite on the other side are often present. The patient had a notable family history of stroke, increasing the risk for CVI. Most common genetic studies nevertheless were inconclusive (Table 1). Several other rare genetic disorders which lead to a hypercoagulable state could also have played a role in pathogenesis of this ischemic event. We further interpreted the increase in liver parameters because

of the pleural effusion and the TB related liver pathologies, as antituberculotic treatment rapidly normalised liver parameters.

In our case, the relation between BMOI and TB remains unclear. We conclude that in young patients with ischemic cerebrovascular events, multifactorial aetiologies should be considered. Familial history of stroke remains a significant risk factor, despite the absence of identifiable genetic mutations. Infections, notably tuberculosis, predispose to stroke, with enhanced risk in cases of meningeal involvement absent in our patient. Furthermore, hypoplasia of the right vertebral artery might have predisposed to a bilateral thromboembolic event. Such interplaying factors potentially contributed to the thromboembolic event.

In case of Fever of unknown origin, recurrent diagnostic circles should be repeated to not oversee relevant and potentially dangerous diagnoses even if a reasonable explanation as an impaired autonomic nerve system exist. In Switzerland, with 600 TB cases diagnosed annually, it's imperative for clinicians to include TB in the differential diagnosis when assessing unexplained fevers, underscoring the need for thorough clinical and radiological evaluations [25]. Therefore, in developed countries clinicians should include TB in the differential diagnosis for patients with unexplained fevers, considering its delayed onset.

Data Availability Statement
The authors confirm that the data supporting the findings of this study are available within the article.

Declarations
Ethics approval and Consent to Participate
Written consent to publish was obtained from the patient and can be asked on demand. The local ethical committee (Ethical Committee Northern West Switzerland: EKNZ) confirmed the declaration of no objection.

Consent for Publication
Written informed consent was obtained from the patient for publication of this case report and accompanying images. All authors gave their consent for publication of the final version.

Availability of Data and Materials
All data are available from the corresponding author on request.

Competing Interests
None reported.

Funding
There was no funding for the study.

Authors' Contributions
A.O. F. contributed to conceptualization, methodology, visualization, conducting the literature review, data analysis, writing the original draft, and writing and reviewing the manuscript. A.S.S. contributed to conceptualization, supervision, methodology, and writing and reviewing the manuscript. P.K. contributed to data analysis, interpretation of the results and writing the original draft. R.V. contributed to data analysis, selecting the radiological images, interpretation of the results and writing the original draft. P.K.B., G.L. and M.M. contributed to writing and reviewing the manuscript. M.H. contributed to conceptualization, project administration, supervision, methodology, and writing and reviewing the manuscript.

Acknowledgements
We thank the patient for valuable feedback on the manuscript and the permission to publish the case report.

Care Checklist
This Case Report was written according to the CARE Checklist Guideline.

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