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(CASE REPORT)

Longitudinal extensive transverse myelitis with sixth nerve palsy post ChAdOx1 nCov-19 vaccine: A case report and literature review

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Abstract

Concurrently with the quick development of COVID-19 vaccines globally, concerns about vaccination efficacy and safety are rising. Neurological complications such as transverse myelitis (TM) are major worries because they can cause lifelong disabilities, which may require long term care. Here, we report a case of longitudinal extensive transverse myelitis (LETM), with sixth nerve palsy in a young female occurring shortly after ChAdOx1 nCov-19 vaccine. The patient recalled developing strabismus, progressive ascending bilateral lower limb weakness, along with upper extremity paresthesia, abnormal sensation below T6 dermatomes, and difficulty in urination. She presented to the hospital with complete paralysis below the neck associated with urinary retention. Extensive diagnostic studies were performed to rule out alternative etiologies, including but not limited to demyelinating diseases, para-post infectious agents, paraneoplastic syndromes, tumors, and autoimmune diseases. She was treated with corticosteroids and discharged upon clinical improvement. However, the patient clinically deteriorated and intravenous immunoglobulin was administered. Unfortunately, the patient is still suffering from physical impairment. We suggested that LETM could be induced by an autoimmune process triggered molecule mimicry. In conclusion, safety monitoring of the COVID-19 vaccines is of great importance in the post marketing surveillance, particularly for rare adverse events.

Keywords: COVID-19; SARS-CoV-2; Vaccine; Adverse event; Acute transverse myelitis; Abducens nerve palsy

1. Introduction

Transverse myelitis (TM) is a very rare disease with an incidence of 3 per 100,000 patients years [1]. It causes motor, sensory, and autonomic dysfunction due to a focal or extensive inflammation in the spinal cord [1]. Common causes include infectious agents and demyelinating illnesses, and around 30% of cases are of unknown etiology [2]. TM after vaccination is even a rarer entity that was reported in 37 cases between 1970 and 2009 with the majority appearing during the first month after vaccines, such as hepatitis B, measles mumps rubella (MMR), and influenza immunizations [3]. Similarly, newly emerged Coronavirus disease 2019 (COVID-19) vaccines were reported to be associated with TM. According to ANA investigates, 9 cases over 51,755,477 vaccinated individuals suffered from TM, [4] and a recent published review by Garg et al, [5] delineated 7 cases of TM post COVID-19 vaccines found in the literature.

Palsy of sixth (abducens) cranial nerve results in strabismus due to abduction deficit. It is usually precipitated by microvascular diseases or tumors and less likely vaccines [6]. Neurological adverse events of COVID-19 vaccines encompass abducens nerve palsy as shown in a previous report [7]. However, to our knowledge, there is no reported cases of TM jointly with abducens nerve palsy post-COVID-19 vaccination. Thus, herein, we present a case of longitudinal extensive transverse myelitis (LETM) and sixth nerve palsy seen in a previously healthy young woman after receiving ChAdOx1 nCov-19 vaccine.

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2. Case details

2.1. Clinical presentation

A 37 years old previously healthy female admitted to our hospital 4 weeks after her first dose of ChAdOx1 nCov-19 vaccine complaining of complete paralysis below the neck (quadriplegia) associated with urinary retention.

2.2. Patient's history

Patient reported having fever on the 2nd day following vaccination that lasted for 12 days. Few days after her shot, the patient also developed left eye esotropia accompanied by decreased visual acuity. She was diagnosed with abducens nerve palsy for which she received vitamin B12 and modified her eyeglasses. The strabismus resolved within 2 weeks. Concomitantly, the patient started having lower back pain that increased in intensity with days, along with upper extremities paresthesia and progressive ascending lower limbs weakness, which caused her gait disturbance and multiple falling down. She remarked that her symptoms were more prominent on the left side of her body. In addition, she complained of an abnormal sensation below T6 dermatomes and difficulty in urination. She started then physiotherapy without physician referral, however, her condition got worse over the days, so she consulted a neurologist. At that time she was no longer ambulatory. Figure 1 summarizes clinical presentation of the patient.

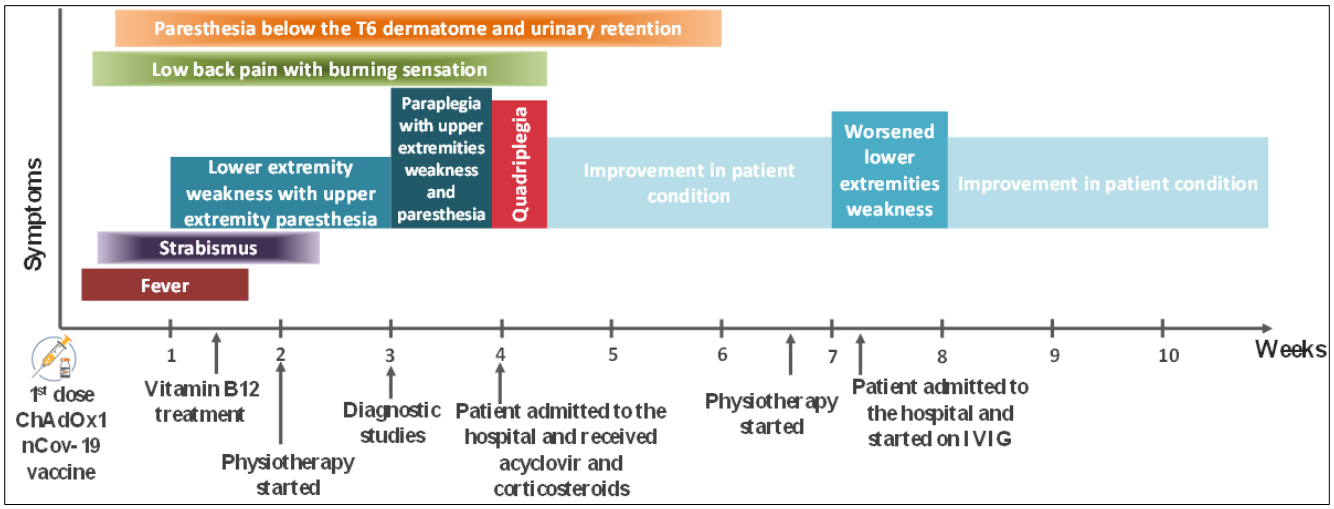

Figure 1 Clinical course and treatment timeline

2.3. Investigation

On admission, patient was afebrile and her vitals were within normal ranges. Patient denied having headaches, vertigo, neck rigidity, nausea, vomiting, or difficulty swallowing. Physical exam revealed diffusely inhibited deep tendon reflex, lack of proprioceptive, pain and light touch sensation below T6 dermatome, and motor strength grade of 0/5 in the lower limb and 1/5 in the upper limb, according to medical research council.

Blood investigation, renal and liver function test were normal, except for an elevated CRP level of 8 mg/L. Real time polymerase chain reaction (RT-PCR) of a nasopharyngeal swab testing Sever Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) RNA was negative. Cerebrospinal fluid analysis showed mild pleocytosis 35 /µl, high RBC, normal protein and glucose levels, and no growth was obtained from CSF. Viral disease of the central nervous system was ruled out by RT-PCR for 9 DNA and RNA neurotropic viruses. Mycobacterium tuberculosis and nontuberculous mycobacterium RT-PCR turned negative. Serum anti-aquaporin 4 antibodies were negative as well. All laboratory parameters are summarized in Table 1.

Electromyography (EMG) and nerve conduction studies were in favor of moderate bilateral neuropathy of the lower limb. There was no abnormal findings on the EMG of the upper limbs. Neuroimaging of the brain and the spine using magnetic resonance imaging (MRI) was performed with and without contrast. Brain MRI turned normal with no post-contrast enhancement, (Figure 2) while spine MRI demonstrated cervical and dorsal cord swelling with extensive

intramedullary signal hyper-intensity on T2-weighted and Stir images at C1 to C6 levels, and D1 to D7 levels involving the entire diameter of the cord without contrast enhancement.(Figure 3&4).

Table 1 Summary of laboratory parameters of the patient

Laboratory parameters	**Value**	**Reference range**
Hematology		
WBC $x10^9$/L	7.4	4.5-10.5
Neutrophils %	75	43-76
Lymphocytes %	18	17-48
Monocytes %	8	0-10
Eosinophils %	1	0-10
Basophiles %	0	0-2
RBC $x10^{12}$/L	4.89	3.8-5.8
Hemoglobin g/dl	13	12-16
Hematocrit %	43	36-48
MCV fL	83.6	80-93
MCH pg	27	26-32
MCHC g/dl	32.3	31-35
Platelets $x10^9$/L	330	150-450
Coagulation		
PT sec	13.3	13.2
PT activity %	85	70-100
INR	1.00	
Chemistry		
Glucose mg/dL	92	76-100
Urea mg/dL	17	6-24
Creatinine mg/dL	0.8	0.5-1.35
SGOT U/L	26	<35
Alkaline phosphatase U/L	67	44-147
Sodium mEq/L	136	135-145
Potassium mEq/L	4.1	3.5-5.5
Chloride mEq/L	104	100-108
Lipid panel		
Cholesterol mg/dL	191	Desirable <200
HDL mg/dL	64	Desirable >60
Triglyceride mg/dL	89	Desirable <150
LDL mg/dL	75	Desirable <130
Serology		
CRP mg/L	8*	0.8-1.0
CMV IgM	0.20	Negative<0.70
		Positive>=0.9
Endocrinology		
Procalcitonin ng/ml	<0.1	0.0-05
C.S.F.		
RBC /µl	2750*	Adult:0-10

WBC /µl	35	Adult:0-5
Protein mg/dl	25	0-6 days:70
Glucose mg/dl	87	60-70% of glycemia
Culture CSF	No growth after 48 h	
Neuro9 Viral Panel by Real-time PCR in CSF		
Adenovirus	Negative	
Cytomegalovirus	Negative	
Epstein-Barr Virus	Negative	
Herpes Simplex Virus 1	Negative	
Herpes Simplex Virus 2	Negative	
Varicella-Zoster Virus	Negative	
Enterovirus	Negative	
Parechovirus	Negative	
Human Herpes Virus 6	Negative	
Human Herpes Virus 7	Negative	
Parvovirus B19	Negative	
Detection of Tuberculosis DNA by Real-time PCR in CSF		
MTB	Negative	
NTM	Negative	
Immunology		
Aquaporin4 (neuromyelitis optica NMO) CSF IgG antibodies detected by I.F.	<1/10	Negative:<1/10

CRP: C -reactive protein; CSF: Cerebrospinal fluid; INR: International Normalized Ratio; MCH: Mean Corpuscular Hemoglobin; MCHC: Mean Corpuscular Hemoglobin Concentration; MCV: Mean Corpuscular Volume; MTB: Mycobacterium Tuberculosis; NTM: Non Tuberculous Mycobacteria; RBC: Red Blood Cell; WBC: White Blood Cell

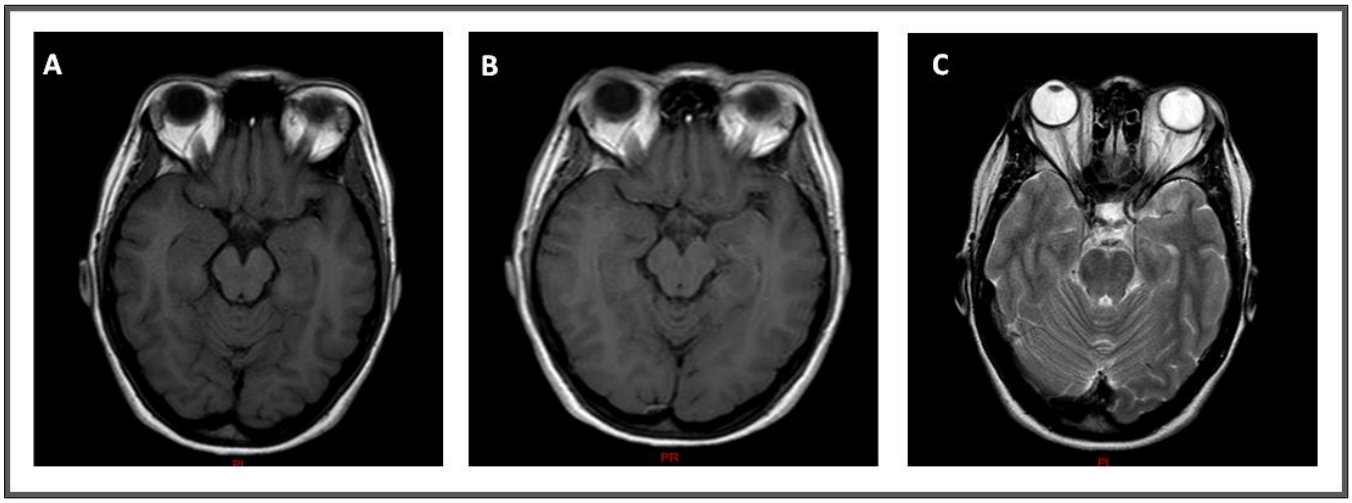

Figure 2 T1-weight (A), T1-weight with contrast (B), and T2-weight (C) magnetic resonance imaging (MRI) scan of the brain showing no abnormal findings and no uptake of the contrast

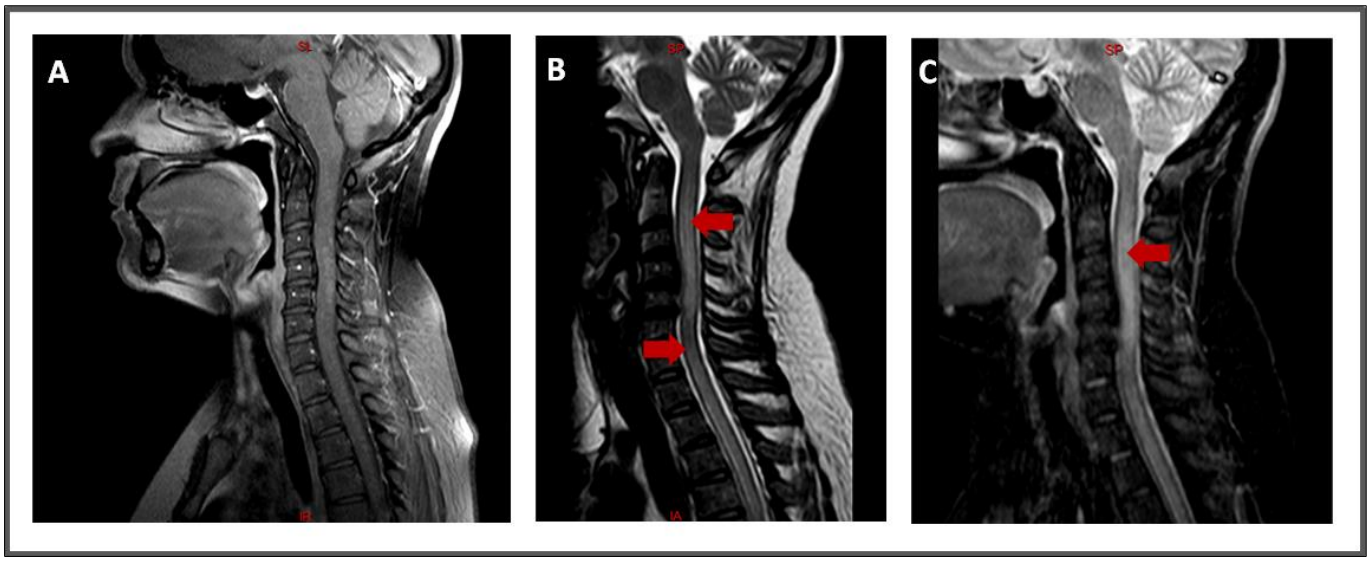

Figure 3 Sagittal Cervical T1-weight with contrast (A), cervical and dorsal T2-weight (B), and cervical Stir (C) MRI of the spine showing spinal cord swelling at cervical and dorsal levels (arrows). We noted narrowed anterior and posterior subarachnoid spaces secondary to intramedullary signal hyper-intensity on T2 (B) and Stir (C) at C1-C6 levels, and T1-T7 levels with no post contrast enhancement changes. Disc diseases can be noted at C4-C5 and C5-C6 can be noted.

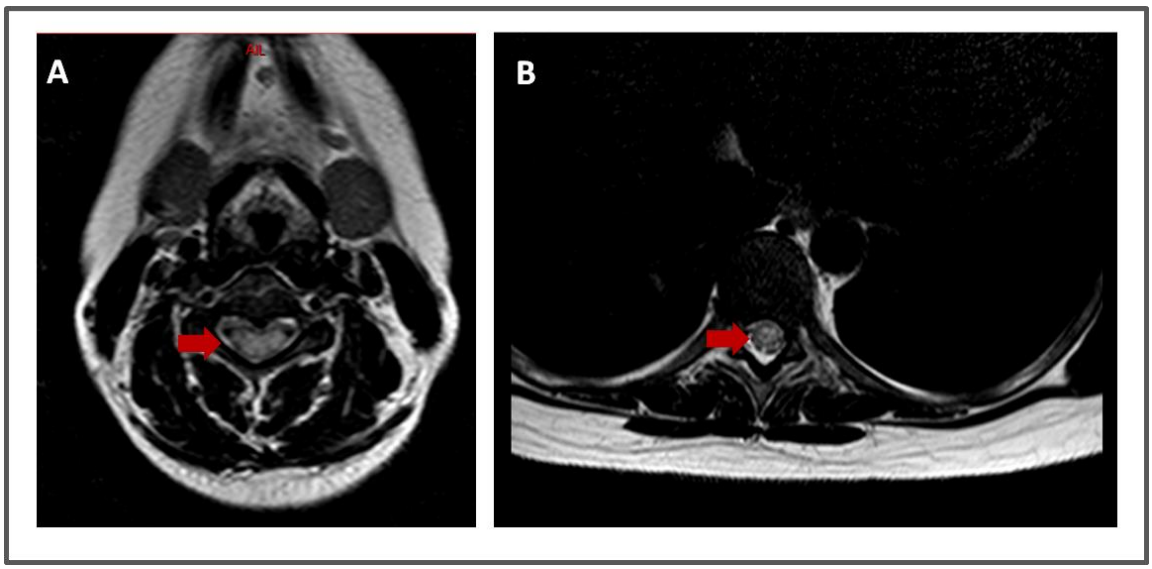

Figure 4 Cervical axial (A) and dorsal axial (B) T2-weighted images showing extensive hyper-intensity (arrows) reflecting a total transverse involvement of the diameter of the cord

2.4. Differential diagnosis

In this context of acute onset of progressive ascending paralysis associated with hypoesthesia and esotropia, a differential of Guillain-Barré syndrome, neuromyelitis optica, multiple sclerosis, acute disseminated encephalomyelitis (ADEM), traumatic spine injury, autoimmune diseases such as systemic lupus erythematosus, neurosarcoidosis, and Sjögren syndrome, paraneoplastic syndromes, post or para-infectious myelitis including viral, bacterial, fungal and parasitic agents, spinal cord tumor and current COVID-19 infection were considered. Our patient had long (≥ 3vertebral segments) transversal segment involvement leading to bilateral lower limb weakness with no evidence of compression on imaging, and symmetric sensory deficit below specific dermatome accompanied by urinary retention. Based on the Brighton case definition for TM, [8] level 1 diagnostic certainty of TM requires histopathology identification of acute

cord inflammation, level 2 diagnostic certainty requires the presence of myelopathy symptoms, along with 2 or more of the following indicators:

- Fever up to 38˚C
- CSF pleocytosis (WBC >5/µl)
- Neuroimaging findings demonstrating acute inflammation or demyelination of spinal cord.

Level 3 diagnostic certainty requires the presence of myelopathy symptoms and 1 of the indicators previously mentioned.

Accordingly, our patient was diagnosed with LETM with level 2 diagnostic certainty.

2.5. Treatment

The patient was treated with 30 mg/kg 3 times per day Acyclovir until a source of infection was excluded and 1g/day intravenous (IV) methylprednisolone over 5 days. A Foley catheter was inserted for 14 days to relieve her urinary retention. Patient lower limb extremity weakness improved (motor strength 1/5) regained normal function (motor strength 2/5) and sensation of her upper limb. She was discharged home with outpatient physiotherapy.

2.6. Outcome and follow-up

After discharge, she had a slow progressive improvement in function and amelioration in her urinary retention. However, her weakness worsened after her third physiotherapy session, so she was readmitted to the hospital and a total dose of 15g IV immunoglobulin (IVIG) was administered over 3 days, then an additional 10 g was administered later on to complete a full dose of 25 g of IVIG. Although she had significant improvement in her upper limb, patient is still suffering from lower limb weakness and subsequent inability to move in order to complete daily life activity.

3. Discussion

As of November 5th, 2021, 7,180,519,949 doses of COVID-19 vaccines were administered around the world [9]. Following immunization, possible side effects include fever, chills, headache, fatigue, myalgia, arthralgia, and inflammation and pain at the injection site. Serious neurological complications, such as TM, are rare but constitute a major concern, as they can cause physical impairment and lifelong disabilities that necessitate long term care [5]. In transverse myelitis, there is an immune mediated focal inflammatory demyelinating process of the spinal cord resulting in sensory (e.g. paresthesia in the extremities, back pain…), motor (e.g. limb weakness, paraplegia…), and autonomic (e.g. sphincter dysfunction) symptoms that appear as soon as few hours or after several weeks [10]. In addition, once symptoms begin, they tend to worsen over time. When lesion extends over more than 3 vertebral segments, the condition is referred to as LETM [10].

The lack of multiple sclerosis lesion pattern in the brain MRI, the absence of marked CSF pleocytosis, and the extensive transverse spinal cord lesion, all ruled out multiple sclerosis. In addition, MRI effectively excluded ADEM, tumoral and vascular lesions. There was no signs of optic neuritis and Serum anti-aquaporin 4 antibodies were negative, hence neuromyelitis optica was unlikely. Moreover, concurrent negative serology and sterile CSF excluded the possibility of an infectious origin. The diagnosis of Guillain-Barré syndrome was excluded due to the absence of an albuminocytological dissociation in CSF, and specific EMG features. According to Brighton case definition for TM, [8] we diagnosed the patient with vaccination induced LETM with level 2 diagnostic certainty associated with post-vaccinal sixth nerve palsy. An extensive literature review was conducted to identify published case reports on transverse myelitis induced by SARS-CoV-2 vaccines and findings were tabulated. (Table 2).

In addition to our case, TM occurred post-AstraZeneca, in 7 out of 15 cases and the diagnosis of LETM was made in 8 out of 15 cases. Majority had TM alone, however few papers presented TM in association with palsies, [11,12] optic neuritis, [13] or on top of chronic myelitis [14]. Particularly, our patient suffered from LETM jointly with abducens nerve palsy. The later was only described in one patient who developed esotropia 2 days after receiving COVID-19 vaccine [7]. In addition, our affected subject appeared to be younger than the majority of cases and only 1 study reported TM in a 16 years old child in Saudi Arabia after receiving the second dose of Pfizer-BioNTech vaccine [15]. Onset of symptoms varied between 1 day and 3 weeks. Symptoms presentation of our patient also fell in this range. Similarly to our cases, tetraparesis was also described by Pagenkopf et al [16] and Erdem et al [17].

Table 2 Summary of reported case in the literature of transverse myelitis induced by vaccination

Author	Country	Diagnosis	Age/ gender	Vaccine type/dose	Onset	MRI findings	Symptoms	Treatment	Outcome
Tahir et al [12]	U.S.A.	LETM+ Bell's palsy	44years/ female	Johnson &Johnson / no infromation	10 days	T2 hyper-intensity at C2-C3 extending to upper thoracic spine	Back pain, paresthesia in neck and abdomen Numbness, weakness and hyperreflexia in the lower limbs Urinary retention	IV prednisolone +plasmapheresis	Improved
Gao et al [20]	Taiwan	LETM+ vitamin B12 deficiency	76 years/ female	Moderna/ 1st dose	2 days	T2 hyper-intensity at C2-C5 with ring enhancement at C3	Right upper and lower limb and sacral paresthesia and thermal analgesia, proprioception sensation loss below T4 Gait disturbance, hyperreflexia in the right limbs	Pulse IV then oral methyl prednisolone+ Hydroxycobalamine	Improved
Hsiao et al [11]	Taiwan	Acute transverse myelitis (ATM)+ facial palsy	41 years/ male	AstraZeneca/1st dose	2 weeks	T2 hyper-intensity at T1-T6 with cord enhancement in early T1 and post contrast T1	Paresthesia below T4, loss proprioception and vibration sensation in both limbs Lower limb weakness, clumsiness and hyperreflexia	Pulse IV then oral methyl prednisolone	Improved
Tan et al [21]	Malaysia	LETM	25 years/female	AstraZeneca/1st dose	5 days	T2 hyper-intensity at T3-T5, T7-T8 and T11-L1 with variable cord enhancement	Numbness and allodynia below T8 Progressive bilateral lower limb weakness then inability to walk, hyperreflexia Urinary retention	IV methyl prednisolone	Improved

Mclean et al [18]	U.S.A.	LETM	69 years/female	Pfizer-BioNTech /1st dose	2 days	T2 hyper-intensity at C3-C4 to T2-T3 involving the anterior and mid cord	Upper and lower limb paresthesia Upper and lower extremity weakness, then inability to walk Urinary urgency and incontinence (on follow-up)	IV methyl prednisolone	Improved
Khan et al [22]	India	ATM	67 years/female	Moderna /1st dose	1 day	Stir hyper-intensity at C1-C3 with patchy post contrast enhancement on T1	Paresthesia right lower limb, loss of vibration sensation up to the ankle Bilateral upper and lower extremity weakness, hyperreflexia	IV methylprednisolone +plasmapheresis	Improved
Albokhari et al [15]	Saudi Arabia	ATM	16 years/female	Pfizer-BioNTech /2nd dose	2 days	T2 hyper-intensity at cervical and thoracic spine	Lower extremity numbness, decrease sensation to fine and pain stimuli Lower extremity then upper extremity weakness, hyperreflexia	IV methylprednisolone	Improved
Alshararni [14]	Saudi Arabia	Acute on top of chronic TM	38 years/male	Pfizer-BioNTech /1st dose	2 days	Sclerotic cord margin, cord enhancement at T11-T12 with hypo-intensity on T1 and hyper-intensity on T2 and Stir	Lower limb pain Lower limb weakness then paraplegia,	No infromation	Improved

Malhotra et al [23]	India	ATM	36 years/male	AstraZeneca/1st dose	8 days	T2 hyper-intensity at C6-C7 in the dorsal aspect of the cord, and moderate peripheral enhancement on T1	Bilateral lower limb abnormal sensation ascending to the trunk Hyperreflexia	Oral then IV methylprednisolone	Improved
Pagenkopf et al [16]	Germany	LETM	45 years/male	AstraZeneca/1st dose	11 days	T2 hyperintensity from C3 to T2 with wide involvement of the cord	Thoracic back pain, sensory level at T9 Generalized weakness, followed by acute flaccid tetraparesis Urinary retention	Pulse IV then oral methyl prednisolone	Improved
Erdem et al [17]	Turkey	LETM	78 years/female	Sinovac-Coronavac/no information	3 weeks	C1-T3 spinal cord involvement	Paresthesia upper limb Tetraparesis Urinary retention	No information	No information
Notghi et al [19]	U.K.	LETM	58 years/male	AstraZeneca/1st dose	7 days	T2 and Stir hyper-intensity from T2 to T10 with enhancing myelitis at T3 and T9/T10 levels	Progressive lower limb numbness, allodynia extending to the chest, hyperesthesia below T7 All four limb hyperreflexia Urinary incontinence	IV methylprednisolone then oral prednisolone+ plasmapheresis	Improvement
Helmshen et al [13]	Germany	LETM with optic neuritis in patient with relapsing-remitting	40 years/female	AstraZeneca/1st dose	2 weeks	T2 increased longitudinal centrally located signal intensity through the thoracic cord	Binocular blindness Back pain, numbness in lower extremity, sensory deficit below T5 Weakness in lower extremity progressed to inability to walk and then	Steroids + plasmapheresis+ immune-adsorption	Partial improvement

		multiple sclerosis				reaching T7-T10.	paraplegia, absent tendon reflex Incontinence		
Vegezzi et al [24]	Italy	ATM	44 years/female	AstraZeneca/1st dose	4 days	T2 hyper-intensity at T7-T8 posterior cord with enhancement on post contrast T1 T2 hyper-intensity at T10-T11	Bilateral lower limb ascending paresthesia, reduced sensation lower back and during micturition, reduced pinprick and light touch sensation up to the ankles Brisk deep tendon reflex in lower limb	IV then oral methylprednisolone	Improved
Fitzsimmons and Nance et al [25]	USA	ATM	63 years/ male	Moderna/ 2nd dose	1 day	T2 hyper-intensity at the distal spinal cord and conus	Lower back pain, lower extremity pain and paresthesia Inability to walk Urinary retention, involuntary erection, constipation	IVIG+IV then oral methylprednisolone	Improved
This case	Lebanon	LETM+ abducens nerve palsy	32 years/ female	AstraZeneca/1st dose	2 days	T2 and Stir hyper-intensity on C1-C6 and T1-T7 involving the entire diameter of the cord	Upper limb and below T6 paresthesia, low back pain. Progressive bilateral lower limb weakness than paraplegia, upper limb weakness Urinary retention	IV methylprednisolone + IVIG	Partial improvement

Contrary to our case with urinary retention, urinary incontinence was observed in 3 reports [13,18,19]. This might be attributed to a detrusor hyperreflexia resulting in urge incontinence, or to an overflow incontinence precipitated by low spinal cord lesion. Comparably, coinciding cervical and thoracic lesions were also reported in several studies.[15–18] Till date, there is no clearly defined consensus regarding the gold standard treatment of vaccine induced LETM, in accordance with the literature, we treated our patient with IV methylprednisolone. Upon clinic deterioration or refractory cases, plasmapheresis was performed in majority of cases [12,19,20]. Due to lack of albumin in our institution, patient received IVIG instead, this therapeutic option was also adopted by Fitzsimmons and Nance et al [25].

The exact mechanism that clarify the causal relation between SARS-CoV-2 and TM is still unknown. We can postulate that autoimmunity resulting in demyelination of the spinal cord in TM could be due to a molecule mimicry process since, vaccine particle similarly to infectious agents could share similar antigen with the host cells. This might trigger several immune reactions that targets the spinal cord [3].

4. Conclusion

Here, we discussed the case of LETM with sixth nerve palsy that occurred shortly after first dose of ChAdOx1 nCov-19 vaccine. The diagnosis was made by MRI and temporal correlation between symptoms and vaccine administration. Blood and CSF work-up were performed to exclude other etiologies. Our report might increase the hesitancy on vaccination for the public population, however we should bear in mind the significant benefit of immunization for personal and collective immunity to fight this pandemic. Furthermore, identifying similar rare adverse events is only possible in post-marketing surveillance, and reporting them should be a global scientific priority to better communicate the risks and benefits of vaccines.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare no conflict of interest.

Statement of informed consent

Written informed consent was obtained from the patient for the publication of this paper.

Abbreviations

ADEM: acute disseminated encephalomyelitis
ChAdOx1 nCov-19 vaccine: Chimpanzee Adenovirus-vector vaccine
COVID-19: Coronavirus Disease 2019
CSF:vCerebrospinal fluid
EMG: Electromyography
IV: Intravenous
IVIG: Intravenous Immunoglobulin
LETM: Longitudinal Extensive Transverse Myelitis
MMR: Measles, Mumps, Rubella
MTB: Mycobacterium Tuberculosis
MRI: Magnetic Resonance Imaging
NTM: Non Tuberculous Mycobacterium
RT-PCR: Real Time Polymerase Chain Reaction
SARS-CoV2: Severe Acute Respiratory Virus 2
TM: Transverse Myelitis

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