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Clinical Profile and Outcomes of COVID-19–Associated Transverse Myelitis: A Case Report and Review of Literature

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Abstract

Purpose of review

To evaluate demographics, clinical profiles, and outcomes of Transverse Myelitis(TM) in the setting of COVID-19 infection(iTM) or vaccination(vTM), and to describe a case of spontaneous resolution of iTM.

Recent findings

Out of a total of 158 articles that met our search criteria, 30 articles detailing 65 unique cases were included, out of which 48 (73.8%) were iTM and 17(26.2%) were vTM. The mean age of the iTM group was significantly lower as compared to vTM (43±2.9 years vs. 56.3±4.5 years; p=0.02).). There were no gender differences between the groups. There were no significant differences in time to symptom onset (9.9 ± 2.2 days iTM vs. 7.6±1.7 days vTM, p=0.2) between the groups. There were no significant differences between iTM and vTM with respect to imaging features or laboratory abnormalities. The most common pharmacotherapy that was administered was intravenous (i.v.) corticosteroid (n=56, 87.5%) followed by oral corticosteroids (n=20, 31.2%), plasmapheresis (n=19, 29.7%) and intravenous immunoglobulin(n=14, 21.9%). The majority of the cases reported a good outcome (n=51, 79.7%) with no significant differences between the groups (77.1% in iTM vs. 87.5% in vTM; p=0.37).

Summary

There are no significant differences with respect to time to presentation, clinical and radiological features, and in outcomes between iTM and vTM, suggesting a common pathogenesis.

Approximately 80% of cases have a good outcome. Hence, early recognition and treatment are important. Our case demonstrates that treatment should be based on the clinical presentation rather than laboratory or imaging features.

Key words: Transverse myelitis, COVID-19, infection, vaccination, SARS-CoV-2, myelopathy, adverse events

Introduction

Transverse myelitis (TM) is an inflammatory condition affecting the spinal cord and often presents with rapid onset of bilateral focal neurological signs including motor, sensory, and bladder/bowel dysfunction. Clinically, it may be a complete or partial transaction of the spinal cord and if it involves more than three segments, it is called longitudinally extensive. It may occur as part of a continuum of other neuroimmune disorders such as multiple sclerosis, neuromyelitis optica, acute disseminated encephalomyelitis, and neurosarcoidosis. Systemic immune disorders have also been associated with TM. Several infections can also trigger a TM, which presents as a post-infectious syndrome [1]. Direct viral infection of the spinal cord is rare but has been shown with poliovirus, rabies, and is suspected to also occur with other enteroviruses and arboviruses where there is preferentially gray matter involvement of the spinal cord implying neuronal spread.

Since the start of the COVID-19 pandemic more than 2 years ago, numerous neurological manifestations of the infections have emerged in the literature. The prevalence of neurological disorders associated with COVID 19 infection has been estimated to be about 35-85% in the

acute and subacute phases. One of the less common but devastating neurological complications of COVID 19 has been transverse myelitis(TM)[2]. Numerous theories regarding the same have been proposed, including direct neuronal injury by the virus and a host hyperinflammatory response[3]. Additionally, during the pandemic, para-infectious TM arising from COVID-19 vaccinations has also been noticed[3]. Although most reported cases of COVID-19 infection-associated TM(iTM) and COVID-19 vaccine-associated TM(vTM) have been treated with immunotherapy with a positive clinical outcome[4–7], there remains a paucity of data regarding the pathophysiology, clinical presentation, and best course of management for iTM and vTM. We illustrate this by presenting a case of iTM with spontaneous resolution without any immunosuppressive therapy. We also discuss a brief review of the literature on demographics, clinical features, and outcomes of cases with iTM and vTM since the start of the pandemic.

Methods

Case report:

Informed consent was obtained from the patient to present our case report. CARE 2020 guidelines for case reports were adhered to. ENTREQ guidelines were adhered to for the literature review.

Literature review:

A review of the published literature in PubMed was conducted between January 10, 2017, to January 10, 2022 using the search words: “covid 19”, and “transverse myelitis”. Studies were selected if they had at least one reported case of transverse myelitis in an individual with a recent

history of COVID infection or vaccination. Cases with alternate causes of transverse myelitis such as multiple sclerosis (MS), Neuromyelitis Optica Spectrum Disorders (NMOSD), and anti-Myelin Oligodendrocyte Glycoprotein (MOG) disorder were excluded. Cases with uncertain diagnoses or alternate diagnoses of myeloradiculoneuropathy and encephalomyelitis were excluded as well. The exclusion was done on a case-by-case basis. Thus, a single published case series could have a case that was included but another case that was excluded. If two or more studies described the same case, the case from only one study was included.

STATA 14.0 was used for statistical analysis. Frequency tabulation, chi-square, and unpaired t-test were used for included cases when appropriate. If information was not available regarding a specific variable, the case in question was excluded from the comparative analysis between groups(iTM and vTM).

Case Report

A 68-year-old woman with no pertinent past medical history developed bilateral lower extremity weakness, numbness, and tingling. These symptoms evolved over a period of one day. She was diagnosed with COVID-19 based on a SARS-CoV-2 PCR positive test 19 days prior to the onset of neurological symptoms, at which time she was asymptomatic. PCR testing was performed as she was a contact of a confirmed patient. At the time of presentation, she had a normal mental status and cranial nerve examination, intact strength (MRC grade 5) in both upper extremities, weakness in the proximal muscles of both lower extremities (Iliopsoas and quadriceps MRC grade 4+), and reduced pain sensation in the entire right lower extremity with no clear sensory level. Deep tendon reflexes were normal in the upper extremities. The knee jerks were hyperreflexic and plantar responses were upgoing on both sides.

Blood tests showed a normal metabolic panel and complete blood cell count. Cell-based assays for antibodies to MOG and aquaporin- 4 (NMO) were normal. MRI of the brain with and without contrast was normal. However, MRI of the cervical and thoracic spine with and without contrast showed a non-enhancing patchy abnormality on T2/STIR sequences extending from C1 through

T10 levels, predominantly sparing the gray matter. The image is shown in Figure 1. Lumbar puncture was slightly traumatic.

Opening pressure was normal (13 cm H_20). CSF showed lymphocytic pleocytosis (27 WBCs with 7 RBCs/ mm^3, 79% lymphocytes), elevated protein (120 mg/dL), and borderline low glucose (50 mg/dL). Oligoclonal bands were absent. The patient elected to defer immunosuppressive therapy as she felt that the symptoms were relatively mild. Evaluation 3 months later showed improvement in strength and sensation. A repeat MRI of the cervical and thoracic spine with and without contrast showed near-complete interval resolution of the T2/STIR abnormalities.

Results of the literature review

The search was conducted between January 10, 2017 to January 10, 2022, and resulted in 158 articles. Out of these, 78 articles describing 138 cases of relevance, i.e. articles containing descriptions of cases with TM associated with COVID 19 infection or vaccination, were selected. Of these articles, 50 (78 cases) were excluded due to either uncertain diagnoses or an alternative diagnosis of Multiple Sclerosis (MS), Neuromyelitis Optica Spectrum Disorders (NMOSD), anti-Myelin Oligodendrocyte Glycoprotein (MOG) disorder, encephalomyelitis or myeloradiculoneuropathy. In the final review, 30 studies detailing 65 unique cases were included. The search strategy is detailed in Figure 2. The selected studies are detailed in eTable 1.Out of a

total of 65 included cases, 48 (73.8%) were iTM and 17 (26.2%) were vTM. The mean age (± SD) of all cases was 46.5±20.6 years. The mean age of the iTM group was significantly lower as compared to vTM (43±2.9 years vs. 56.3±4.5 years; p=0.02). There was no statistically significant difference in the sex composition between the two groups (55.3% males in the iTM group vs. 58.8% males in the vTM group, p=0.74). Table 1 shows cases reported with COVID-19 vaccination. Out of a total of 17 cases of vTM, 6 cases (35.3%) were associated with ChAdOx1 nCov-19 (Astrazeneca), 4 cases (23.5%) each with BNT162b2(Pfizer) and mRNA-1273 (Moderna), and 1 case (5.9%) each with Ad26.COV2.S (Johnson and Johnson), BBIBP-CorV(Sinopharm) and CoronaVAC. A comparison of clinical, radiographic and laboratory features between iTM and vTM are shown in Table 2. There was no statistically significant difference in clinical, imaging or laboratory features between the groups.

Duration after infection/vaccination

TM occurred after 9.9 ±2.2 days (mean ±SD) after infection and 7.6±1.7 days after vaccination. There was no difference between the groups.

MRI findings

In iTM, the most common site of involvement was both cervical and thoracic spine (42.6%), followed by thoracic spine (38.3%). In vTM, the most common site of involvement was the thoracic spine (47.1%) followed by both cervical and thoracic spine (29.4%).
Longitudinally extensive transverse Myelitis (LETM) occurred in 82.9% of iTM cases vs. 62.5% of vTM cases. Contrast enhancement was present in 34% of cases of iTM as compared to approximately 59% of cases in vTM. There was no statistical difference between the two groups.

Laboratory Testing

CSF abnormalities were found in 75% of the cases (n=48) and serological abnormalities were found in 35.5% of the cases in total. There was no significant difference in CSF abnormalities between iTM and vTM. Serological abnormalities included SARS-COV2 IgG antibody, SARS-COV2 PCR, SSA antibody, GdM2/3 IgG antibody CBC (anemia, lymphopenia and leuckocytosis), elevated CRP, LDH, ferritin, IL-6, troponin T, ESR, D dimer; low Vitamin B12 and calcium. There was no difference in the frequency of serological abnormalities between iTM and vTM.

Outcomes

Response to treatment was noted in 79.7% of the cases with a similar distribution among the subgroups of iTM and vTM. A comparison between outcomes and different clinical, radiologic and laboratory factors is shown in Table 3. There was no difference in outcomes in iTM and vTM. Cases with lesions in the cervical spine were more likely to show improvement than not (77.1 % showed improvement and 22.9% did not show an improvement, p=0.048). Improvement did not seem to depend on whether the lesion was short segment or LETM, whether the lesion was contrast-enhancing, or whether there were any abnormalities in the serum or CSF. Administration of intravenous corticosteroids was associated with improvement in 83.9%. Use of a combination of corticosteroids, IVIG and PLEX was associated with a poor outcome, although there were only two such reported cases (100% showed no improvement, p=0.004). This may represent a selection bias as combination therapy is usually reserved for severe cases.

Discussion

A unique feature of our study is that we incorporated both COVID infection-related and COVID

vaccine-related cases associated with transverse myelitis. There was no significant difference in the interval between onset of symptoms and exposure to vaccination or to infection (Table 1) In both groups, the mean duration of onset was between 7-10 days. This suggests that TM may be a final common pathway of autoimmune inflammation regardless of the nature of the triggering agent (COVID infection vs. COVID vaccine).

TM associated with COVID infections presents a unique opportunity to learn about the natural history of TM from a confirmed viral/immunological trigger to the development of clinical symptoms. A prior similar opportunity presented with the Zika virus epidemic, which also resulted in cases of TM.[33] Case reports suggested onset of symptoms within 7-15 days of suspected infection.[34,35] Similar patterns have also been reported with Dengue infection and Chikungunya virus.[36,37]

As hypothesized with TM associated with Zika virus infection, it is likely that iTM with COVID is a parainfectious presentation.[33] Although direct infection could not be ruled out in cases with COVID infection related TM, the significant improvement with immunosuppressive therapy (Table 2) and similar time delay between exposure and symptom onset between iTM and vTM suggests a parainfectious pathogenesis.

The type of vaccine administered did not seem to be associated with vTM. All of the approved vaccines had cases where TM was reported. The higher incidence with ChAdOx1 nCoV-19, BNT162b and mRNA-1273 as compared to CoronaVAC, Ad26.COV2.S and BBIBP-CorV likely reflects the greater frequency of administration of the former three vaccines as compared to the latter three. A detailed review of the vaccine administration data would be needed to

determine if a specific class of vaccines predisposes to vTM, similar to the analysis for Guillan Barre syndrome published by Hanson et al in 2022, which suggested a higher risk with Johnson and Johnson vaccine as compared to the mRNA vaccines.[38] Rare case reports of TM have also been reported following influenza vaccine and a variety of other vaccinations. [39,40]Importantly, these complications are rare, and there are no distinguishing features between those associated with vaccinations or the infections, suggesting similar pathophysiological processes.

We also reviewed the VAERS (Vaccine Adverse Event Reporting System) data from the CDC which showed a total of 290 cases of transverse myelitis linked to COVID-19 vaccine administration in the United States until 5/13/2022 which were reported to the database. [41] The vaccines administered included Johnson and Johnson, Pfizer and Moderna. Pfizer and Moderna vaccines comprised approximately 75% of the cases, again likely reflecting increased frequency of administration of these vaccines as compared to Johnson and Johnson. The VAERS relies on self-reporting and hence, the data may not reflect the true incidence of vTM. Due to the self-reporting nature, the data is usually incomplete from a clinical standpoint, and hence the cases were not used for analysis in our study.

The CSF profile was abnormal in most cases of vTM and iTM. In cases where the CSF was abnormal (n=48), The most common abnormality included elevated protein (81.2%), followed by lymphocytosis (47.9%). These findings are supportive of a viral/post viral etiology of TM. In contrast, serological testing was normal in most cases. A similar finding was noted in our case as well. Our case showed extensive white matter involvement of the spinal cord with sparing of the

gray matter. This pattern of spinal cord involvement has been poorly described in the literature. However, enteroviruses such as polio virus and EV71 or EVD68 may predominantly affect the gray matter. This distinction may be important since demyelinating processes with white matter involvement may be suggestive of an immune mediated process while gray matter involvement may suggest direct infection of the neurons. These cases often occur in children, have a more rapid onset with less than 10 days from the onset of infection. The term acute flaccid myelitis is often used to describe them due to the predominant anterior horn cells involvement which leads to a flaccid paralysis. [42]

Analysis of the outcomes revealed improvement with treatment in approximately 80% of all cases, suggesting an optimistic prognosis. Treatment data was available for all cases except one. Most cases received i.v. corticosteroids (87.5%), followed by oral corticosteroids, plasmapheresis and IVIG (31.2%, 29.7% and 21.9% respectively). Most cases were treated with only one modality (corticosteroids/IVIG/plasmapheresis), possibly suggesting low severity or a favorable/rapid response. Cases requiring >2 modalities had a poorer outcome, reflecting the severity of the disease. Thus, early and aggressive treatment may be warranted even if the trigger is an infectious agent.

Our case is unique as it reflects resolution of iTM despite significant cord involvement. This likely suggests a transient parainfectious inflammation with COVID-19 infection without significant axonal/cytotoxic damage and complete resolution. Hence, clinical symptoms are likely a better indicator of prognosis rather than the degree, or type of cord involvement, and all cases of iTMmay not require treatment. Larger, prospective studies are required to enable physicians to prognosticate iTM cases and individualize therapy (supportive treatment vs. immunomodulatory

therapies).

Since TM is a rare manifestation that can be triggered by a wide variety of infections and immune conditions and has very similar clinical presentations no matter what the triggering event is, it suggests that the patients likely have a genetic susceptibility. In fact, rare familial cases of TM have been reported and a rare missense mutation in a gene VPS37A has been implicated.[43] Hence further genetic studies maybe useful in these populations.

Our study has several limitations. SARS-CoV-2 polymerase chain reaction (PCR) in the CSF was unavailable and hence a direct infection could not be confirmed in our case. However, given the temporal relationship of the patient's symptoms and recent COVID-19 infection, iTM is the most likely diagnosis. The patient did not receive any pharmacotherapy, and hence it is difficult to ascertain whether the lesion present in the imaging would have resolved sooner with therapy. We only selected cases from one database (PubMed) for analysis and may have missed cases in other databases, and those that have not been published. Additionally, the possibility that they may have recovered spontaneously despite undergoing treatment, cannot be completely excluded.

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Figure Legends

Figure 1: **MRI of Thoracic Spine**: An T2 Axial and sagittal section of the thoracic spinal cord with and without contrast shows a high signal intensity lesion through C1-10 levels sparing the grey matter.

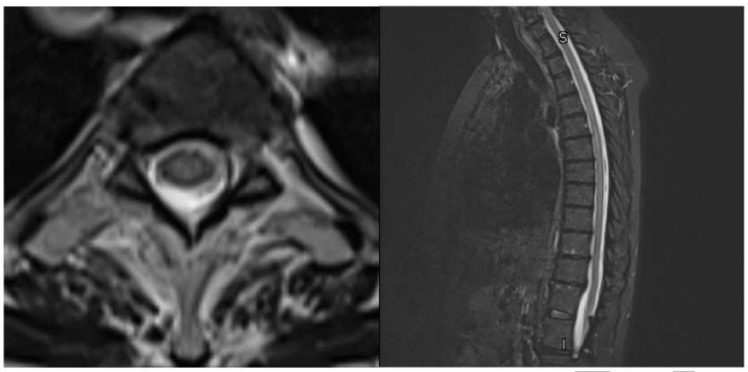

Figure 2: **Search strategy for literature review**: Out of a total of 158 articles, our search strategy resulted in a total of 30 studies (65 unique cases) which were included in the analyses.

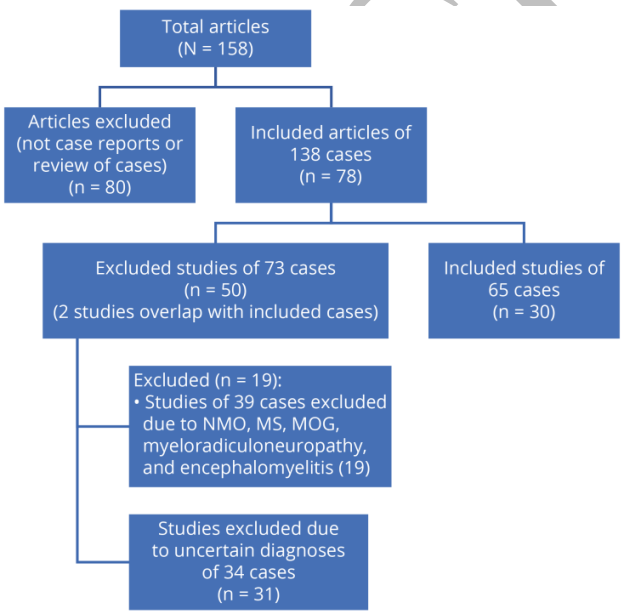

Table 1: Vaccines associated with vTM

Type of vaccine (Commonly used names)	Number of cases (n, %)
ChAdOx1 nCov-19 (AstraZeneca)	6(35.3%)
BNT162b2 (Pfizer)	4(23.5%)
mRNA-1273 (Moderna)	4(23.5%)
CoronaVAC	1(5.9%)
Ad26.COV2.S (Johnson and Johnson)	1(5.9%)
BBIBP-CorV (Sinopharm)	1(5.9%)
Total	17 (100%)

Table 2: Clinical, imaging and laboratory features

Clinical features	All cases	COVID infection	COVID vaccination	P value (comparison between infection vs. vaccination)
Duration since vaccination/infection	N=59 9.2±12.6 days	N=42 9.9±2.2 days	N=17 7.6±1.7 days	0.2
Location of MRI abnormality Cervical (n,%) Thoracic(n, %)	N=64 13, 20.3% 26, 40.6%	N=47 9, 19.1% 18, 38.3%	N=17 4, 23.5% 8, 47.1%	0.64
Multiple(n, %)	25, 39.1%	20, 42.6%	5, 29.4%	
Number of segments	N=57 SS 13, 22.8%	N=41 7, 17.1 %	N=16 6, 37.5%	0.1

	LETM 44, 77.2%	34, 82.9%	10, 62.5%	
Contrast enhancement	N=64 26, 40.6%	N=47 34.0%	N=17 58.8%	0.075
CSF profile Normal Abnormal	N=64 16, 25% 48, 75%	N=47 12, 25.5% 35, 74.5%	N=17 4, 23.5% 13, 76.5%	0.8
Serological testing Normal Abnormal	N=62 40, 64.5% 22, 35.5%	N=45 27, 60.0% 18, 40.0%	N=17 13, 76.5% 4, 23.5%	0.2
Response to treatment No Yes	N=64 13, 20.3% 51, 79.7%	N=48 11, 22.9% 37, 77.1%	N=16 2, 12.5% 14, 87.5%	0.37

Table 3: Comparison of outcomes

Factors	No improvement	Improvement	P value
iTM (n=48) vTM (n=16)	11 (22.9%) 2(12.5%)	37 (77.1%) 14 (87.5%)	0.37
Cervical Spine (n=13) Thoracic spine (n=25) Cervical+thoracic spine (n=25)	1 (7.7%) 9 (36.0%) 3 (12.0%)	12(92.3%) 16(64.0%) 22(88.0%)	0.048
Short Segment (n=12) LETM (n=44)	2 (16.7%) 8(18.2%	10(83.3%) 36(81.82 %)	0.9
Contrast enhancing lesion (n=25)	5 (20%)	20(8%)	0.96
CSF abnormal (n=47)*	9 (19.15)%	38 (80.85%)	0.97
Serological testing abnormal (n=22)	5 (22.7%)	17(77.3%)	0.65
*CSF Abnormalities (n=48, 100%) Elevated protein (n=39, 81.2%) Lymphocytosis (n=23, 47.9%) Pleomorphic leukocytosis			

(n=5, 10.4%) Hypoglycorrhachia (n=2, 4.2%) Hyperglycorrhachia (n=1, 2.1%) Oligoclonal bands			

(n=6, 12.5%)			
Treatment (N=64,100%)			
i.v. corticosteroids (N=56, 87.5%)	9 (16.1%)	47 (83.9%)	**0.03**
IVIG (N=14, 21.9%)	4(28.6%)	10 (71.4%)	0.38
Plasmapheresis (N=19,29.7%)	6(31.6%)	13(68.4%)	0.14
Oral corticosteroids (N=20, 31.2%)	4(20.0%)	16(80.0%)	0.97
Combination therapy (Corticosteroids/IVIG/plasmapheresis)			
2 modalities (N=28)	6 (21.4%)	22 (78.6%)	0.84
3 modalities(N=2)	2(100%)	0 (0%)	**0.004**

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