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Glial fibrillary acidic protein astrocytopathy in a patient with recent mRNA SARS-CoV-2 vaccination
COVERSHEET

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ABSTRACT

Background: Literature describing triggers of GFAP astrocytopathy (GFAP-A) is limited. We report a case of GFAP-A in a patient with recent messenger ribonucleic acid (mRNA) severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) vaccination and discuss the possible pathogenesis.

Case description: A 45-year-old gentleman presented with features of meningoencephalitis 31 days after the first dose and 4 days after the second dose of mRNA SARS-CoV-2 vaccination. He sequentially developed brainstem/cerebellar, autonomic and cord dysfunction. Cerebrospinal fluid was positive for GFAP autoantibody. Clinical improvement occurred after intravenous methylprednisolone and immunoglobulins.

Conclusion: Although we are uncertain of a causal link of GFAP-A to mRNA vaccine, indirect activation of an underlying dysregulated immune milieu is plausible.

1. Introduction

Glial fibrillary acidic protein astrocytopathy (GFAP-A) is a rare neurological condition, first described in 2016. It has a varied clinical presentation that includes meningoencephalitis, myelitis, ataxia, and autonomic dysfunction, and has been described to occur in association with other autoimmune diseases, or follow viral infections. (Fang et al., 2016, Iorio et al., 2018, Dubey et al., 2018) While viral infections are recognized as triggers of immune-mediated neurological conditions, the association between vaccination and such conditions is inconsistent. (Ribeiro et al., 2021, Chen et al., 2018)

The possibility of novel messenger ribonucleic acid (mRNA) severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) vaccines aberrantly activating the immune system, and triggering an autoimmune condition, has been previously suggested. (Dotan et al., 2021, Akinosoglou et al., 2021) We describe a patient with GFAP-A, and a preceding history of Moderna SARS-CoV-2 (mRNA-1273) vaccination. Our report contributes to the knowledge of this rare entity, and surfaces the possibility of it being triggered by an mRNA vaccine.

2. Methods

We describe clinical details and investigations of a patient diagnosed with GFAP-A, in close temporal association with SARS-CoV-2 mRNA vaccination.

3. Results

A 45-year-old Chinese gentleman, with a past medical history of type 2 diabetes mellitus and hypertension, presented with fever, cough and nausea of 3 days' duration, followed by altered mental status. He had received his first and second dose of Moderna SARS-CoV-2 (mRNA-1273) vaccine 31 and 4 days prior respectively. At presentation, he was febrile, confused (Glasgow Coma Scale 11), and had right focal motor seizures.

Abbreviations: Ab, antibody; Ag, antigen; ALT, alanine transaminase; ANA, antinuclear antibody; AST, aspartate transaminase; B, Bacillus; C, Chlamydia; CT, Computed Tomography; DNA, deoxyribonucleic acid; ds, double stranded; GAD, glutamic acid decarboxylase; HbA1c, glycosylated haemoglobin; HIV, human immunodeficiency virus; Ig, immunoglobulin; L, litre; M, mycoplasma; mmol, millimoles; MRI, Magnetic resonance imaging; ng, Nano gram; PCR, Polymerase Chain Reaction; RSV, Respiratory Syncytial Virus; u, micro; RT, Reverse Transcriptase; TB, tuberculosis; U, units; umol, micromoles; WBC, white blood cells.

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Table 1
Summary of relevant investigations.

Specimen	Laboratory test	Week 1	Week 2-3	Week 4
Blood/Serum	[units; normal]			
	WBC [$10^{9/L}$; 3.8-9.9]	13.3	11.3	
	C-Reactive protein [mg/L; 1-5]	3.3; 12.5; 3.7	2.4	
	Procalcitonin [ng/mL; 0.5-2]	0.46; 1.7	0.08	
	SARS-CoV-2 Antibody [N-antigen]		Non-Reactive	
	SARS-CoV-2 Antibody [Spike protein]			Positive
	HIV Ag-Ab screen	Negative		
Urine	Streptococcus Pneumoniae Ag	Negative		
	Legionella Pneumophilia Serogroup 1 Ag	Negative		
Nasopharyngeal Swabs	SARS-CoV-2 RT-PCR	Negative		
	Film array[#]	Negative		
Cerebrospinal Fluid	Glucose [mmol/L]	9	4.2	3.8
	Protein [g/L]	1.69	1.44	0.75
	WBC [/uL]	178 [95% Lymphocytes; 5% monocytes]	180 [96% Lymphocytes; 3% monocytes]	5
	PCR[**]	Negative	-	
	Enterovirus RT-PCR	Negative		
	Mycobacterium TB complex	Negative		
	GeneXp,	No growth	No growth	
	Aerobic/Anaerobic/Fungal Culture			-
	Flow Cytometry	-	92% T cells with mild elevated CD4:CD8 ratio; 0.2% CD38+/CD19+ cells.	Lymphocytosis [predominantly T-cells]
	Cytology	-	No malignant cells	-
	Encephalopathy-Autoimmune panel[&]		-	Negative
	GFAP, cell-binding assay		-	Positive
	GFAP IFA Titre [<1:2]			Positive; 1:16
Radiology	MRI Brain [contrast]	Refer to Fig. 1		
	MRI Spine [contrast]		Refer to Fig. 1.	
	CT Thorax/Abdomen/Pelvis; Ultrasound Testes	Fatty Liver, left renal calculus		
	ANA / [Negative; Ratio <1]		0.09	
Serum Antibodies	ds-DNA [IU/ml; < 100]		<10	
	Anticardiolipin/ B2 Glycoprotein		Negative	
	IgG/M		Positive	
	Lupus Anticoagulant		Negative	
	Anti-Ro/La		Negative	
	Antibodies to : *NMDA-R, CASPR2, LGI1, AMPAR1/2, DPPX, GABA-B-R, GAD*		Negative	
	Anti-Aquaporin 4 IgG		Negative	
	Anti-Myelin Oligodendrocyte Glycoprotein Ab		Negative	
	Paraneoplastic Anti-neuronal Antibodies[@]			

[#] *Nasopharyngeal Film array- Adenovirus; Coronavirus 229E, HKU1,NL63, OC43; Human metapneumovirus; Influenza A, Influenza A subtypes H1,H3, H1-2009; Influenza B; Parainfluenza 1-4 ; Human rhinovirus ; RSV; B-pertussis; C.pneumoniae; M.Pneumonia.*

[**] *CSF PCR- Escherichia coliK1, Haemophilus influenze, Listeria monocytogenes, Neisseria meningitides, Streptococcus agalactiae, Streptococcus pneumonia, Cytomegalovirus, Enterovirus, Herpes Simplex 1, herpes simplex 2, Human herpesvirus 6, Human parechovirus, Varicella zoster, Cryptococcus neoformans/gattii, Herpes simplex virus DNA; Cytomegalovirus DNA; Varicella-zoster DNA; Toxoplasma gondii.*

[&] *Encephalopathy-Autoimmune panel: Antibody to AMPA-R, ampiphysin, AGNA-1, ANNA-2, ANNA-3, CASPR2IgG,CRMP-5IgG, GABA-B-R, GAD65,IgLON5, LGI1-IgG, mGLUR1, NIF, NMDA-R, PCA-Tr, PCA-1,2.*

[@] *Paraneoplastic Anti-neuronal Antibodies [Hu, Yo, Ri, CV2, amphiphysin, PNMA2/Ta, recoverin, SOX1, titin, zic4, GAD65, Tr(DNER]*

Physical examination revealed nuchal rigidity, without lateralizing focal neurological deficits. Cerebrospinal fluid (CSF) showed a lymphocytic pleocytosis and raised protein [Table 1]. Empirical treatment for meningoencephalitis (intravenous ceftriaxone, vancomycin, acyclovir, oral doxycycline) was instituted, along with levetiracetam for acute symptomatic seizures. Investigations are summarized in Table 1. No infective agent was identified in CSF, serum, and respiratory swabs performed in the first week of illness.

In his second week of illness, he sequentially developed signs of brainstem and cerebellar dysfunction (persistent hiccups, titubation, tremors, ocular flutter), along with dysautonomia. Fundoscopic examination did not reveal any optic disc swelling. Magnetic resonance imaging (MRI) of the brain [Fig. 1A] showed subtle leptomeningeal signal abnormality around the medulla, and serum autoimmune encephalitis panel was negative. Between day 15-18, he developed progressive lower limb weakness and numbness. Physical examination revealed asymmetric lower limb weakness (upper motor neuron pattern), distal areflexia, and thoracic sensory level. Repeat CSF analysis (2-3 weeks) showed persistent lymphocytic pleocytosis [Table 1]. MRI spine showed long segment leptomeningeal enhancement of the brainstem and spinal cord, most prominently involving the cervical segment [Fig. 1B, C].

The constellation of symptoms and signs, together with the lack of an infective aetiology led to the clinical impression of an immune-mediated meningoencephalomyelitis. CSF GFAP antibody (Ab) was tested, which returned positive (Mayo clinic laboratory: indirect immunofluorescence assay titre 1:16; cell binding assay positive). A screen for underlying oncologic diseases was negative [Table 1].

Subsequent to clinical diagnosis, methylprednisolone (intravenous, 1g/day) was given for 5 days, whereupon rapid resolution of fever, confusion and brainstem/cerebellar signs was noted. A tailing dose of oral prednisolone (initial dose of 1mg/kg/day) was continued. Lower limb weakness reached a nadir (power- medical research council grade 1-2) between the third and fourth week of his illness. Intravenous immunoglobulin (2 g/kg body weight, over 5 days) was initiated. Further gradual improvement was noted in lower limb function. Clinical course was complicated by femoral vein thrombosis, secondary to a venous

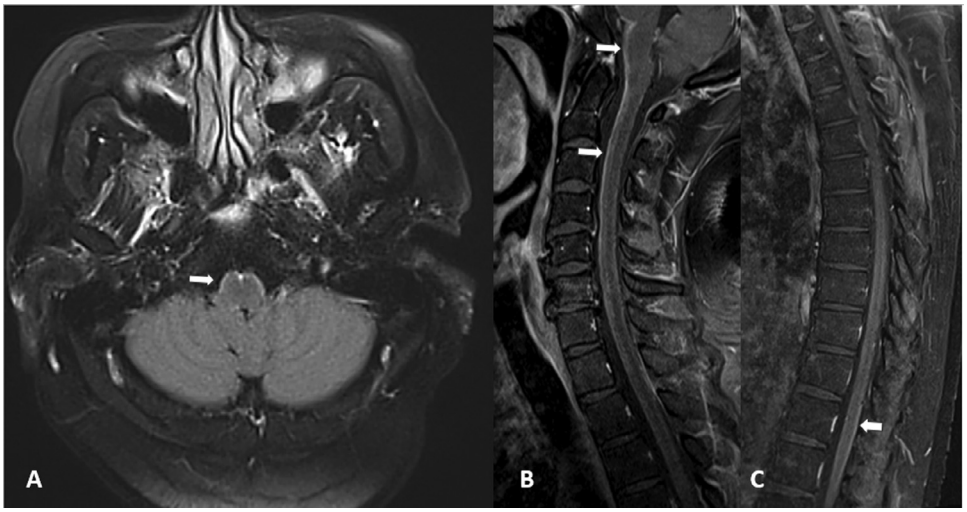

Fig. 1. Magnetic resonance imaging [MRI] of the brain [A; week 1] showed mild leptomeningeal enhancement around the medulla. MRI of the spine [Week 3] showed long segment meningeal enhancement involving the ventral brainstem and cervical spinal cord [B] and less prominently around the conus [C].

line, and cholecystitis. At the time of this report, he remains paraparetic (power- medical research council grade 3-5) and requires an indwelling urinary catheter.

4. Discussion

GFAP is an intracellular filament protein expressed predominantly in astrocytes, but not limited to the central nervous system (CNS). (Günther et al., 2021 Jun 25) As GFAP is not accessible to circulating immunoglobulin G (IgG), GFAP-specific cytotoxic T cells are believed to be the key players in pathogenesis of GFAP-A. Pathological evidence from these patients shows perivascular lymphocytic infiltrate composed predominantly of CD8+ T lymphocytes. (Yuan et al., 2021) In addition, other immune system components, including microglia, macrophages, and cytokines, may play a role in disease pathogenesis.

Reported associations for GFAP-A include viral infections, neoplasia, and dysregulation of T-cell function. (Fang et al., 2016, Iorio et al., 2018, Dubey et al., 2018) To date, there are no published reports of GFAP-A associated with vaccination. Vaccines may trigger autoimmune conditions via bystander activation of dormant autoreactive T-cells, epitope spread, molecular/epitope mimicry, or may intensify pre-existing immune dysregulation via pro-inflammatory responses. (Akinosoglou et al., 2021) Reports of myelitis and encephalitis following adenoviral vector ChAdOx1 SARS-CoV-2 vaccine have emerged recently. (Vegezzi et al., 2021, Zuhorn et al., 2021)

The novel nature of mRNA vaccines has raised concerns over immune-mediated adverse events (AE). The mechanism of action of mRNA vaccines involves introducing the gene of the spike protein inside the host cell, and translation of mRNA within the cytoplasm. (Qian et al., 2021) Though SARS-CoV-2 mRNA vaccines utilize modified mRNA (encoding stabilised pre-fusion S-protein) that may not trigger pathogen-associated molecular pattern sensing mechanisms, (Bettini and Locci, 2021) potent adaptive B-and T-cell mediated immune response is documented following mRNA vaccination; thus bystander activation of autoreactive T-cells may occur. (Bettini and Locci, 2021) Cross-reactivity of spike protein antibody with human tissue proteins (including myelin basic protein and S100B), has been demonstrated, surfacing the possibility of mimotope-related immune injury. (Vojdani and Kharrazian, 2020)

The latency period between mRNA vaccine administration and immune system activation is unclear but may be extrapolated from existing data. Rare cases of myocarditis (latency ≥24 hours), and a patient with multisystem inflammatory syndrome (latency 2 days) have been reported following mRNA SARS-CoV-2 vaccines. (Lazaros et al., 2021, Nune et al., 2021) Recent reports of neurological AE in relation to mRNA vaccines include encephalopathy/encephalitis following the first dose (latency 7-21 days), though lack of CSF abnormalities in one reported patient limits interpretation. (Torrealba-Acosta et al., 2021, Vogrig et al., 2021) Reports of encephalitis in publicly available databases recording vaccine related AE, are rare. (2021) Lack of clinical and investigative details significantly limit interpretation in terms of causality.

In a recent case series of neurological autoimmune diseases following vaccinations against SARS-CoV-2, 8 cases were noted following the first mRNA vaccine dose, whereas 5 cases occurred after the second dose. (Leon et al., 2021) Studies on vaccine efficacy have shown that after the first dose of mRNA vaccine, the levels of neutralising antibodies are only <5% of the post-second dose peak (Manish et al., 2021). It is postulated that the first dose of mRNA vaccination primes memory B and T cell and the second dose boosts the immune response. Therefore, mechanisms of protection may differ after two doses versus one dose, where neutralising antibodies mediate the predominant protective mechanism following subsequent doses of vaccine, whereas protection after one dose may be a result of non-neutralising antibodies leading to other effector mechanisms and/or is mediated by a relatively low frequency of antigen-specific T cells. (Manish et al., 2021) GFAP IgG autoantibodies lack pathogenicity for live target cells in vivo. Their detection in GFAP-A provides a surrogate marker of activated CD8+ cytotoxic T cells activity against GFAP derived peptides in surface major histocompatibility complex class 1 molecules upregulated on inflamed meningeal astrocytes. Our patient presented with neurologic manifestations 4 days following the second dose of mRNA-1273 vaccine, with a latent period of 31 days from the first dose. The temporal relationship suggests the possibility that the second dose of mRNA vaccine resulted in an enhanced immunogenic response, triggering downstream autoimmunity through bystander activation or molecular mimicry. The serum antibody to the SARS-CoV-2 spike (S) protein was positive in our patient, indicating immune response to mRNA-1273 vaccine, while antibody to nucleocapsid (N) protein was negative, indicating lack of recent SARS-CoV-2 infection. (Wang et al., 2021)

The World Health Organization (WHO) tool for causality assessment of adverse effects following immunization is hinged upon the presence of “known causal association with vaccine or vaccination”. (Tozzi et al., 2013) This limits assessment for rare conditions such as GFAP-A. Pooled data for immune-mediated conditions occurring in close temporal relation to mRNA vaccines, exclusion of alternative aetiologies, and demonstration of a higher incidence following vaccination is essential for determining causality. Similar neurological autoimmune conditions have also been described following adenoviral vectored (Leon et al., 2021) and inactivated (Gulay et al., 2021) SARS-CoV-2 vaccines and while we

are unable to establish causality in our patient, the temporal association and biological plausibility of a vaccine-triggered autoimmunity are notable. However, we must emphasise that the safety profile of mRNA vaccines is extremely reassuring, and cases such as our patient would be exceedingly rare.

In conclusion, we describe a case of GFAP-A following mRNA SARS-CoV-2 vaccination, and propose vaccination as a possible trigger. In light of the ongoing COVID-19 pandemic, the rarity of this association needs to be emphasised, and the underlying mechanism of vaccine-triggered autoimmunity remains a hypothesis.

Author contributions

Conception and design of the study: Pei Xuan Koh, Umapathi N Thirugnanam, Monica Saini

Acquisition and analysis of data: Pei Xuan Koh, Dinesh Rambachan Singh, Monica Saini

Drafting a significant portion of the manuscript or figures : Pei Xuan Koh, Kay Yaw Tay, Tianrong Yeo, Jasmine Shimin Koh, Umapathi N Thirugnanam, Monica Saini

Conflict of Interest

None of the authors declare any conflict of interest.

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