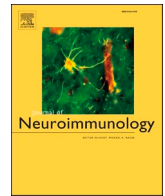




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Review Article

AstraZeneca COVID-19 vaccine and Guillain- Barré Syndrome in Tasmania: A causal link?

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ABSTRACT

The emergence of the coronavirus 2019 (COVID-19) pandemic has presented an unprecedented global challenge. Vaccines against COVID have been developed to date. Covid-19 has been linked with the development of Guillain-Barre Syndrome (GBS), a rare immune-mediated demyelinating neuropathy. We report three cases of Guillain-Barre Syndrome and one case of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), presenting to a Tasmanian hospital, and review 15 other reported cases and discuss likely immunopathology. Nearly all reported cases of post-COVID-19 vaccination inflammatory demyelinating polyneuropathy are linked to AstraZeneca vaccination and a variant with bifacial weakness is the most reported form of GBS globally.

1. Introduction

Guillain-Barré syndrome is an immune-mediated demyelinating polyneuropathy characterised by progressive symmetrical weakness of limbs and decreased or absent deep tendon reflexes (Yuki and Hartung, 2012; van Doorn, 2013). Most cases are self-resolving, but some cases experience life-threatening respiratory muscle paralysis requiring mechanical ventilation (Verboon et al., 2017). It typically occurs in the post-infectious phase following bacterial or viral illness with most cases preceded by respiratory or gastrointestinal symptoms (Willison et al., 2016; van Doorn et al., 2008). *Clostridium jejuni* infection is associated with about one-third of the cases (McCarthy and Giesecke, 2001), but other identified infectious causes include viral infections such as cytomegalovirus, hepatitis E, Epstein Barr virus and influenzae A virus, and bacterial infections such as *Mycoplasma pneumoniae* and *Haemophilus influenzae* (Yuki and Hartung, 2012). Although not completely understood, current studies suggest that pathogenesis is due to autoimmune destruction of the myelin sheath and/or axonal damage caused by autoantibodies leading to functional blockade of nerve conduction (Yuki and Hartung, 2012; Willison et al., 2016; van Doorn et al., 2008; Walling and Dickson, 2013).

Although rare, several studies have explored a possible association of GBS to vaccination, notably the increased risk of GBS with H1N1 influenza (Swine Flu) vaccination in 1976 (Schonberger et al., 1979). The vaccination campaign against 'Swine Flu' was halted after a spike in cases of GBS was noted, with an incidence as high as 1 per 100,000 vaccinations (Lunn et al., 2021). Other studies explored the occurrence of GBS during influenza vaccination campaigns in 1990–2005 but suggested a relatively low risk associated with influenza vaccination (Lehmann et al., 2010; Stowe et al., 2009).

Herein, we report four cases of inflammatory demyelinating polyneuropathy presenting to the same hospital in northern Tasmania 1–3 weeks following ChAdOx1 nCoV-19 vaccination (AstraZeneca vaccine, AZ).

2. Cases

Over the course of six weeks, four individuals presented with Inflammatory Demyelinating Polyneuropathy (IDP), one with Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) and three with GBS, commencing one to three weeks after receiving the AZ vaccine. These included three males (51, 66 and 72 years) and one female (65

Abbreviations: GBS, Guillain- Barré Syndrome; CIDP, Chronic inflammatory demyelinating polyneuropathy; IDP, Inflammatory demyelinating polyneuropathy; CSF, Cerebrospinal Fluid; IVIG, Intravenous immune globulin; ICU, Intensive care unit; AZ, AstraZeneca Vaccine/ ChAdOx1 nCoV-19 vaccine; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ACE2 receptor, Angiotensin-converting enzyme 2 receptor; NCV, nerve conduction velocity.

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years) (Table 1). All of them developed lower back pain followed by progressive ascending paraesthesia, predominantly proximal paraparesis or quadriparesis and areflexia. Two developed facial weakness. Two progressed to respiratory failure requiring mechanical ventilation.

In all patients, investigations revealed albuminocytologic dissociation in the CSF, and no potentially pathogenic organism was isolated. Electrophysiological confirmation of a demyelinating pathology consistent with IDP was obtained in all patients. All four were treated with IVIG (Intravenous immune Globulin). Three are currently inpatients at the hospital, one in ICU, one in rehabilitation, and one in the general medical ward. The patient with CIDP was safely discharged home.

2.1. Case 1

A 51-year-old male presented to the emergency department with lower back pain two weeks after receiving his first dose of the AZ vaccine, rapidly followed by generalised weakness, diplopia, dysphagia, and impaired balance. He had no previous SARS-CoV-2 exposure. He received seasonal influenza vaccination with quadrivalent inactivated vaccine two months prior to admission. Clinical examination revealed diplopia, bifacial weakness, moderate neck weakness, and flaccid

areflexic quadriparesis with prominent proximal lower limb weakness. Pin-prick sensation was distally reduced on the right lower limb. He later developed respiratory failure, resulting in an ICU admission for ventilatory support. Examination of his CSF showed albuminocytologic dissociation with protein 0.70 g/L and absent pleocytosis; nerve conduction studies were consistent with the demyelinating pathology of GBS. A transient improvement in motor function in response to IVIG, was followed by worsening bulbar function leading to aspiration pneumonia necessitating further ventilatory support and therapeutic plasma exchange with ongoing slow and partial recovery.

2.2. Case 2

A 65-year-old female with no significant past medical history, independent activity of daily living, and no previous COVID exposure developed GBS with generalised ascending weakness, ocular involvement, and respiratory distress.

She developed lower back pain one week after receiving the first dose of the AZ Vaccination, followed by progressive weakness in both her lower limbs ascending towards the arms within a week, distal sensory loss in all limbs and diplopia.

On examination, she had a bilateral symmetrical hypotonic and

Table 1

Description of 4 cases of COVID-19.

Demographics	Co-morbidities	Vaccine	Onset of symptoms in relation to vaccination	Other vaccines	Type of IDP	Clinical presentation	CSF	NCS
Age: 51 Sex: Male Ethnicity: Caucasian	NSTEMI*2020	AZ ^a	2 weeks post 1st dose	Influenza vaccine 8 weeks post influenza vaccination	GBS ^a	Nadir: at 2 weeks -lower back pain -Bifacial weakness -Dysphagia -Diplopia -Respiratory failure - Upper limb motor deficit - Progressive ascending lower limb sensorimotor deficit -Areflexia	Albuminocytologic dissociation Protein: 0.70 WCC: 0 RBC: 0 Viral panel: negative Culture: no growth	Absent ulnar and sural sensory responses with slowed median sensory and motor NCV, prolonged distal motor latencies, absent F-waves.
Age: 65 Sex: Female Ethnicity: Caucasian	None	AZ	Onset: 1 week post 1st dose	Influenza vaccine 4 weeks post influenza vaccination	GBS	Nadir: at 2 weeks -Lower Back Pain -Dysphagia - Diplopia -Respiratory failure -Progressive ascending upper limb and lower limb sensorimotor deficit -Areflexia	Albuminocytologic dissociation Protein 2.51 g/L WCC: 5 RBS: 95 Viral panel - negative Culture – no growth	Absent upper limb sensory responses with sural sparing, prolonged distal latencies, reduced amplitudes with temporal dispersion, slowed motor NCV, absent F-waves
Age: 72 Sex: Male Ethnicity: Caucasian	Idiopathic neuropathy	AZ	Onset: 3 weeks post 1st dose	Influenza vaccine 6 weeks post influenza vaccination	CIDP ^a	Nadir: at 5 weeks -Lower back pain -Progressive ascending lower limb sensorimotor involvement -Upper limb motor deficit - areflexia	Albuminocytologic dissociation Protein: 0.55 WCC: 0 RBC: 0 Viral Panel: not tested Culture: no growth	Absent sensory responses, Prolonged distal motor, and F- minimum latencies, slowed motor NCV.
Age: 66 Sex: Male Ethnicity: Caucasian	Renal Cell Carcinoma Atrial Fibrillation Hypercholesterolemia	AZ	3 weeks post 1st dose	Influenza vaccine 8 weeks post influenza vaccine	GBS	Nadir at 4 weeks: -lower back pain -Progressive ascending sensorimotor involvement -proximal lower limb weakness -areflexia	Albuminocytologic dissociation Protein: 1.5 WCC 0 RBC 0 Culture: No growth Viral Panel: negative	Absent median sensory responses with sural sparing, absent peroneal and tibial motor responses, prolonged median distal motor, and F- minimum latencies with slowed motor NCV.

^a AZ = Oxford/AstraZeneca ChAdOx1 nCoV-19 COVID-19 vaccine, GBS = Guillain Barre Syndrome, CIDP = Chronic inflammatory demyelinating neuropathy, NCV = nerve conduction velocity.

areflexic quadriparesis most severe in the proximal lower limbs. Her sensory deficit was symmetrical and length dependent. Two days following admission, she developed respiratory distress, resulting in ICU admission with intubation.

Her CSF showed albuminocytologic dissociation and a viral panel was negative. Electrophysiology confirmed a demyelinating polyneuropathy consistent with GBS. Antiganglioside antibodies (anti-GM1, anti-GQ1b), HIV, and vasculitis screen were negative. Imaging of the neuraxis was normal aside from a few nonspecific white matter T2-hyperintense lesions. She improved remarkably after a course of IVIg. She was extubated and is currently in a rehabilitation centre.

2.3. Case 3

A 72-year-old male developed ascending lower limb weakness and sensory changes, on the background of pre-existing peripheral neuropathy with stable distal sensory loss in the legs and feet for over three years.

Three weeks after his first dose of AZ vaccination, he observed weakness in his left foot which eventually evolved into symmetric proximal lower limb weakness. These symptoms antedated a subsequent influenza vaccination. He then presented to the emergency department six weeks after onset with worsening lower limb weakness impairing ambulation. His pre-existing sensory symptoms also progressed proximally to involve his thighs.

On examination, he had a predominantly proximal quadriparesis with loss of vibration, proprioception, and pinprick sensation in both hands and up to mid-thigh in lower limbs.

His CSF showed albuminocytologic dissociation. A Nerve conduction study revealed a prolonged distal motor latency with reduced nerve conduction velocity in keeping with demyelinating disease.

The temporal course of the illness was consistent with CIDP. He improved clinically after a course of IVIg and is currently ambulant without aid, showing continuing improvement with rehabilitation.

2.4. Case 4

A 66-year-old male developed lower back pain and bilateral symmetrical distal paraesthesia in hands and feet, three weeks post-AZ vaccination and eight weeks after an influenza vaccine. He developed predominantly proximal paraparesis one week after ascending paraesthesia, with a subsequent right infranuclear facial palsy over the course of 3 weeks from the onset of symptoms.

On examination, he had proximal paraparesis, prominent right facial lower motor neuron weakness, and areflexia.

His CSF showed albuminocytologic dissociation and nerve conduction study was in keeping with the demyelinating nature of GBS. A CSF viral panel was negative. IVIg effectively halted the progression of the disease. He is currently an inpatient for rehabilitation and other medical issues.

3. Discussion

Since late 2019, the emergence of the coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has presented an unprecedented global challenge (Rothan and Byrareddy, 2020; Lu et al., 2021). Multiple vaccines have been developed against SARS-CoV-2 and at the time of writing, 20 vaccines are approved and being used globally with over 4 billion doses administered to date (COVID-19 Map, 2021). All vaccines against COVID-19 were developed rapidly and rare adverse outcomes related to these vaccines are still being documented as the global rollout continues (Mullard, 2020; Kaur et al., 2021). Multiple case reports describe a likely causal association between COVID-19 and GBS (Ray et al., 2021; Montalvan et al., 2020). This raises the possibility that COVID-19 vaccination may also cause GBS. Indeed, 18 cases of

ChAdOx1 nCoV-19 vaccine-related GBS have been reported across 6 published studies from UK, Qatar, and India (Hasan et al., 2021; Patel et al., 2021; Azam et al., 2021; Razok et al., 2021; Maramattom et al., 2021; Allen et al., 2021) (Table 2). Our four cases lend further weight to the likely causal link between COVID-19 vaccine AZ and GBS.

GBS is characterised by varying combination of limb weakness, autonomic dysfunction, and cranial nerve involvement (Yuki and Hartung, 2012), usually within one or two weeks of immune activation with peak severity at about four weeks (Fokke et al., 2014). The temporal relationship of receipt of COVID-19 vaccination in our cases fits this timeframe. All our cases demonstrated the characteristic CSF features of albuminocytological dissociation and demyelination on electrophysiological studies (van Doorn, 2013; Fokke et al., 2014).

The annual incidence of GBS varies between 1.1 and 2.66 cases per 100,000 (McGrogan et al., 2009). In a binational study conducted in Australia and New Zealand, the incidence of GBS was 5.4 cases per million population every year (Ancona et al., 2018). Tasmania has a population of 541,071 and the hospital serves a population of 110,472. Therefore 6 cases over the short timeframe, 4 cases reported above and 2 other cases unrelated to vaccine, equates to a rate of 5.4 per 100,000 and is highly unlikely to have occurred as a cluster by coincidence.

CIDP is a common chronic neuropathy characterised by relapsing and progressive weakness (Mathey et al., 2015). Clinical features include peripheral and distal neuropathy involving motor and sensory deficits that usually develop within eight weeks (Dalakas, 2011). Usually responding to immunotherapies, the demyelinating process in CIDP involves spinal nerve roots and proximal nerves. Although the immunopathological mechanisms of the disease process are similar to GBS, the symptoms in CIDP usually peak within six to eight weeks with a fluctuating course depending on the response to treatment (Dalakas, 2011).

The exact mechanism of the immune response linked to the pathogenesis of GBS is still not clear (Yuki and Hartung, 2012; van Doorn et al., 2008). Immune-mediated damage of myelin sheath and Schwann-cell have been noted in acute inflammatory demyelinating polyneuropathy and the axolemma is directly involved in motor axonal neuropathy (Willison et al., 2016). In GBS, over 50% of patients develop antiganglioside antibodies (van Doorn et al., 2008). Molecular mimicry between microbial proteins and nerve cell surface has been one of the suggested mechanisms of autoreactivity of the immune system leading to axonal damage (Iadecola et al., 2020). Other studies postulate mechanisms including humoral or T-cell mediated antibodies specifically targeting peripheral nerve gangliosides leading to neurological deficits and specific types of GBS subtypes (Yuki and Hartung, 2012; Willison et al., 2016; van Doorn et al., 2008; Walling and Dickson, 2013).

Although COVID-19 is predominantly a respiratory illness, it can affect multiple organs including the nervous system (Montalvan et al., 2020; Song et al., 2020). In-vivo studies in mice and using human pluripotent stem cells have shown that SARS-CoV-2 can cause direct neuronal damage through the ACE2 dependent pathway (Song et al., 2020). Some studies have suggested a possible association between COVID-19 and GBS (Caress et al., 2020) whereby binding of SARS-CoV-2 spike proteins to ACE2 receptors and gangliosides leads to the formation of antiganglioside antibodies and GBS during COVID-19 (van der Meché et al., 2001). This mechanism has also been described for *C. jejuni* and Zika associated GBS (28).

Vaccines to prevent COVID-19 have been developed at a rapid pace (Mullard, 2020). More than 280 vaccines are in different phases of development including >100 in various stages of clinical trials (Mao et al., 2021). AZ vaccine consists of a chimpanzee adenovirus vector encoding the spike protein of SARS-CoV-2 (Madhi et al., 2021). Tens of millions of doses have been administered worldwide across more than 170 countries. The most likely mechanism of GBS induction is that antibodies to the S protein cross-react with gangliosides, forming autoantibodies leading to myelin damage.

Similar to earlier reports from Asia and Europe, our patients

Table 2
Summary of international case reports, from January 2021 to July 2021

Author	Reported month/year	Country	No. of Cases	Vaccine, Symptom onset	Type of IDP	Salient features	CSF, EMG
Patel et al. (2021)	April 2021	UK	1	AZ Onset: 14 days after 1st dose	GBS	-lower back pain -symmetrical progressive ascending upper limb and lower limb sensorimotor deficit -Areflexia	CSF Protein: 1.77 g/L WCC:<0.001 EMG: patchy attenuation of the upper limb motor responses
Azam et al. (2021)	April 2021	UK	1	AZ Onset: 15 days post 1st dose	GBS	-Bifacial weakness - Progressive bilateral lower limb motor deficit - Areflexia	NCS: Demyelinating neuropathy CSF Protein:3.9 g/L WCC:0 EMG: No abnormality detected
Hasan et al. (2021)	June 2021	UK	1	AZ Onset: 11 days post 1st dose	GBS	Ascending Bilateral lower limb weakness preceded by paraesthesia and numbness	CSF Protein:0.9 g/L WCC:1 EMG: demyelinating, sensorimotor polyneuropathy
Razok et al. (2021)	2021	Qatar	1	Pfizer Onset: 20 days post 2nd dose	GBS	Progressive bilateral lower limb weakness	CSF Protein: 0.8 WCC normal. NCS: bilateral Absent H reflexes
Maramattom et al. (2021)	April 2021	India	7	AZ Onset: 10–14 days post first dose	GBS	Bifacial weakness, Respiratory failure, Sensorimotor impairment	CSF: albuminocytologic dissociation EMG: demyelinating neuropathy and axonal motor-sensory neuropathy
Allen et al. (2021)	June 2021	UK	4	AZ Onset: 14–29 days post 1st dose	GBS	-bifacial weakness	CSF: Albuminocytologic dissociation NCS: demyelinating neuropathy?

developed symptoms within three weeks after the first dose of AstraZeneca vaccine. One of our patients had bifacial weakness, which was also reported in twelve of the internationally reported cases. Two of our cases developed respiratory failure requiring ICU admission for ventilatory support, while one had an acute exacerbation of CIDP. Our diagnosis of GBS and CIDP was based on clinical features, CSF results and NCS results with Level 1 diagnostic certainty according to the Brighton criteria (van der Meché et al., 2001; Poser, 1981; Asbury and Cornblath, 1990).

In conclusion, an increasing number of case reports highlight the occurrence of inflammatory demyelinating polyneuropathy following administration of the AstraZeneca COVID-19 viral vector vaccine, emphasizing the need for vigilance regarding this specific adverse effect. Most reported cases involve a variant of GBS with bifacial weakness and respiratory failure. A potential link between GBS and AstraZeneca vaccine cannot be excluded at this time and indeed seems highly likely. Healthcare professionals are urged to report GBS post COVID-19 vaccination since accurate numbers will help us further confirm the potential causal link.

Consent

Informed verbal consent was obtained from all the subjects.

Declaration of Competing Interest

There is no conflict of interest to report.

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