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Acute and Chronic Demyelinating Polyneuropathy post AstraZeneca Covid-19 Vaccine

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Introduction

With the rollout of worldwide Covid-19 vaccination programmes, there have been reports of potential neurological complications which may be attributable to the vaccines. These include cerebral venous sinus thrombosis (CVST)[1], which appears to be a complication of thrombosis with thrombocytopenia syndrome (TTS). This has been documented as a rare complication of the AstraZeneca and Ad26.COV2.S (Janssen) Covid-19 vaccines [3].

Guillain-Barre syndrome (GBS) i
s an acute autoimmune polyneuropathy characterised by areflexia and ascending muscle weakness. Cranial nerves may be affected. In severe cases, there may be respiratory muscle involvement, requiring ventilator support. A number of case series' have highlighted a potential association between GBS and the AstraZeneca Covid-19 vaccine[4-8].

Here we present a small series of two cases of GBS and one case of A-CIDP post AstraZeneca Covid-19 vaccination, highlighting this rare but serious complication of this vaccine. In two small studies on CIDP, preceding vaccinations have been reported in 1.5% to 11% of patients, with the first neurological symptoms appearing within 8 weeks of vaccination[9,10].

Case 1

A 62 year old woman presented to the emergency department with a 3 day history of left facial droop, slurred speech, swallowing difficulties, upper back pain and subsequent ascending symmetrical weakness in her upper and lower extremities, and diffuse numbness of her entire

body including her face. She denied preceding respiratory or diarrhoeal illnesses. She had received the AstraZeneca Covid-19 vaccine 14 days prior to symptom onset. She had a history of secondary progressive multiple sclerosis (MS) with a longstanding mild left-sided hemiparesis but she was ambulant and independent at baseline. She had never tested positive for SARS-CoV-2 and had a negative test on admission. Neurological examination revealed bilateral lower motor neuron facial weakness, flaccid tetraparesis, areflexia and severe impairment in all sensory modalities in her limbs and trunk. She was unable to sit up and was non-ambulatory.

A diagnosis of GBS was suspected on neurology consultation in emergency department and she was started on intravenous immunoglobulin (IVIG) with a total dose of 2g/kg. She then received a 3-day course of intravenous methylprednisolone 1g/day (for a potential MS relapse), whilst her nerve conduction studies and magnetic resonance imaging (MRI) of her brain and spine were pending. A lumbar puncture showed elevated protein of 1.1 g/L (0.15–0.45g/L) without pleocytosis. MRI brain and spine revealed multiple non-enhancing demyelinating lesions in keeping with her known MS. Chest X-ray was normal. Extensive infectious and autoimmune screens were negative as were her anti-ganglioside antibodies. Nerve conduction studies (NCS) revealed features in keeping with an acute generalised demyelinating peripheral neuropathy. In the second week of her admission she started to make a gradual and continuous improvement. She was able to transfer and mobilise with assistance of one person when she was transferred to a rehabilitation facility. She is currently improving.

Case 2

A 62 year old gentleman presented to a separate tertiary hospital with acute onset right-sided facial droop and moderate back pain. He was treated with a five day course of high dose oral corticosteroids and anti-viral medications. He had received his first dose of AstraZeneca Covid-19 vaccine 14 days prior to his first symptoms. He subsequently presented to our centre with a 3-day history of progressive lower limb weakness, severe back pain and falls. He had never previously tested positive for SARS-CoV-2 and had a negative PCR test on admission. He denied symptoms of recent infection or diarrhoeal illness. His past medical history was significant for obstructive sleep apnoea, hypertension, gout and a left total knee replacement. On examination, he had lower limbs predominant weakness (2/5 power in lower extremities and 4/5 power in upper extremities bilaterally) and he was areflexic. Cranial nerves and sensory exam were normal.

MRI brain and spine were normal. A lumbar puncture revealed high protein (2.3g/L) and raised

leucocytes (12). Subsequent anti-ganglioside antibodies were negative. NCS revealed a demyelinating peripheral sensory-motor neuropathy. He was diagnosed with GBS and started on IVIG (2g/kg total). His recovery was protracted and he remained an in-patient for five weeks. He is currently improving and is walking unaided. He received a dose of the Pfizer/BioNTech 'Comirnaty' Covid-19 vaccination without adverse effect.

Case 3

A 61 year old gentleman presented to the emergency department with a five day history of worsening thoracic back pain followed by bilateral lower limb weakness. His background history included hypertension, type 2 diabetes, previous stroke and chronic lower back pain. He denied any prodromal illnesses. He had his first dose of the AstraZeneca Covid-19 vaccine 12 days prior to symptom onset.

An MRI brain showed an old caudate infarct but no acute abnormality. MRI spine revealed non-compressive multi-level degenerative changes. His condition deteriorated 4 days into his admission: he developed proximal more than distal upper and lower extremities weakness and he became areflexic. There were no cranial nerve deficits or weakness in his neck muscles.

A lumbar puncture showed elevated protein of 191mg/dl (15-45mg/dl) without lymphocytic pleocytosis. NCS revealed demyelinating features, more pronounced in the lower limbs (Figure 1). Given the findings on NCS and raised CSF protein, on a background of progressive limb weakness and areflexia, he was diagnosed with GBS and commenced on IVIG (2g/kg). His respiratory function deteriorated and he was taken to ICU as a precaution but did not require intubation.

He had a modest non-sustained initial response to IVIG and no response to subsequent plasma exchange. His condition deteriorated and he was given a 3-day course of intravenous methylprednisolone (1g per day) followed by oral steroids and IVIG which resulted in clinical improvement. Neuronal, ganglioside and nodal/paranodal antibodies were negative. A sural nerve biopsy demonstrated patchy depletion of myelinated axons with a mild increase in endoneural macrophages with subtle myelin abnormalities: disruption & ill-definition of the myelin sheath in one or two nerve fibres. Additionally on semi-thin sections occasional myelin ovoids and axonal sprouting was seen. No onion skinning, inflammation or amyloid was seen. Given the relapsing-remitting course, response to steroids and IVIG, NCS findings and supported by sural biopsy findings the diagnosis was revised to A-CIDP.

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Currently. he is making a good progress on combination of three weekly IVIG (6 courses in total so far) and oral steroids. He regained full strength in upper limbs and started to mobilise. He has refused a second dose of a SARS-CoV-2 vaccine.

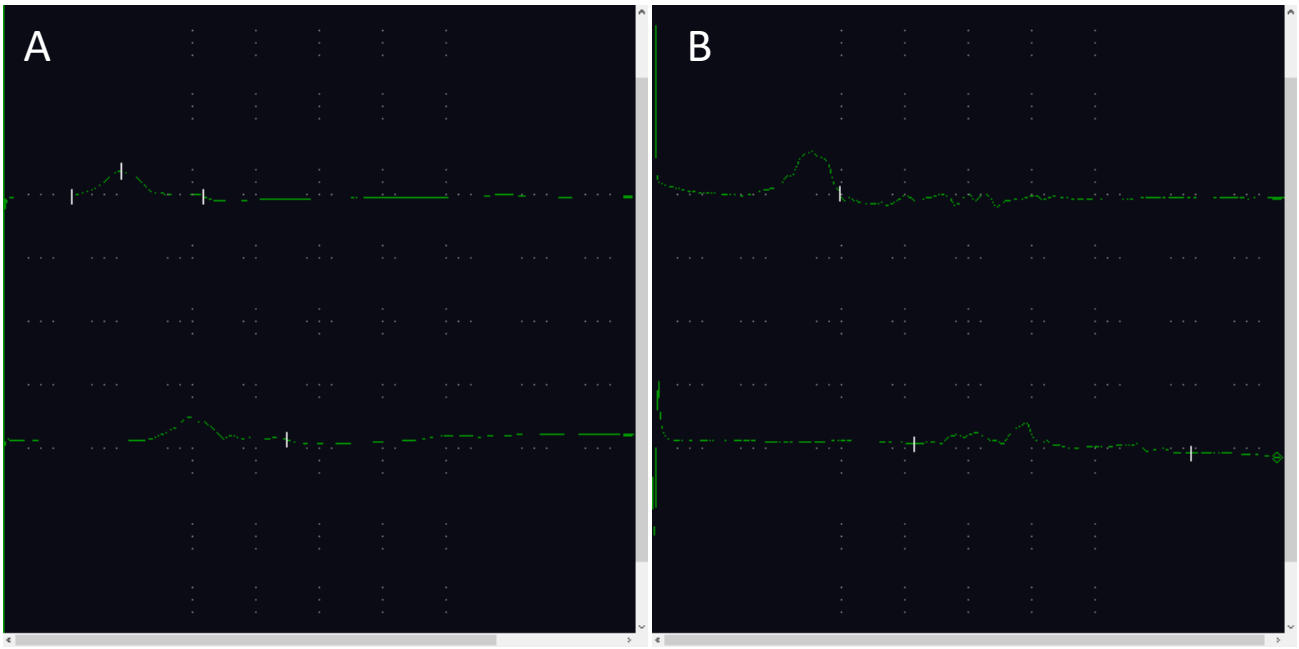

Figure 1: A representative image of the neurophysiological studies performed in Case 3. (A) Demonstrates the right median compound motor action potential (B) Demonstrates the left peroneal compound motor action potential.

Table 1: A summary of the characteristics, investigations, management and outcome of each case

	Case 1: AIDP	**Case 2: AIDP**	**Case 3: A-CIDP**
Age (years)	62	62	61
Gender	Female	Male	Male
Past Medical History	Secondary progressive MS	Obstructive sleep apnoea, hypertension, gout, left total knee replacement.	Hypertension, type 2 diabetes, stroke, chronic lower back pain.
Symptom	14 days post vaxzevria	14 days post vaxzevria	12 days post vaxzevria

onset			
Presenting symptoms	3/7 left facial droop, dysarthria, dysphagia followed by ascending symmetrical weakness in arms, legs & face	Right facial droop, back pain followed by progressive lower limb weakness and falls.	Thoracic back pain, bilateral lower limb weakness
Initial clinical examination findings	Bilateral lower motor neuron facial weakness, flaccid tetraparesis, areflexia, severe impairment in all sensory modalities in limbs & trunk.	2/5 power bilateral lower limbs, 4/5 power bilateral upper limbs, areflexia. Normal cranial nerve & sensory examination.	Proximal > distal bilateral upper and lower limb weakness with areflexia.
Investigations	**CSF:** protein 1.1g/L, cells normal **MRI Brain & Spine:** stable burden of MS lesions **NCS/EMG:** acute generalised demyelinating sensorimotor peripheral neuropathy **Anti-ganglioside antibodies**: negative	**CSF:** protein 2.3g/L, cells normal **MRI Brain & Spine:** no abnormality **NCS/EMG:** demyelinating peripheral sensorimotor neuropathy. **Anti-ganglioside antibodies:** negative	**CSF:** protein 1.9g/L, cells normal **MRI Brain & Spine:** no causative lesion **NCS:** demyelinating peripheral sensorimotor neuropathy **Anti-ganglioside antibodies:** negative **Sural nerve Bx:** patchy depletion of myelinated axons.
Initial Management	IVIG 2g/kg with methylpredisolone 1g/day for 3 days	IVIG 2g/kg	IVIG 2g/kg
Clinical course	Monophasic course with improvement with initial treatment.	Monophasic course with improvement with initial treatment.	Initial non-sustained response to IVIG. Commenced on high-dose steroids & regular IVIG
Outcome	Significant	Discharged	Significant

	improvement with transfer to rehabilitation at assistance of 1 to mobilise & transfer.	independently mobile.	improvement on combination therapy, now independently mobile, tapering steroids, to be commenced on azathioprine.

Results and Discussion

Two small case series from the UK[6] and India[7] reported GBS, or a GBS-variant, between 10-22 days post-first dose vaccination with the AstraZeneca Covid-19 vaccine. A more recent study highlighted 14 cases of GBS in the State of Victoria after AstraZeneca Covid-19 vaccination, with symptom onset, on average, 14.1 days post-vaccination.[8] Our small case series findings is broadly consistent with the Australian study. The onset of GBS symptoms between 12-14 days post-vaccination in our two patients, both aged 61, and the onset of an acute presentation of CIDP in a 62 year old gentleman, is in keeping with the time-frame reported previously.

Much of the focus on GBS post-vaccination has focused on the non-mRNA vaccines (AstraZeneca and Ad26.COV2-S (Janssen)), prompting the EMA to issue a warning that GBS is a rare side effect of both. This might suggest that GBS is confined to recombinant vaccines rather than their mRNA counterparts, however there have been isolated case reports of a potential causal link between GBS and the Pfizer vaccine[11]. Overall, the more compelling evidence has come from small case studies, like our own, that there is a greater likelihood of GBS as a complication of the AstraZeneca Covid-19 vaccine.

Our case series was more in keeping with that of Allen et al. and Osowicki et al. in that the GBS reported was more of a typical GBS with limb weakness, with or without cranial nerve involvement when compared to the more prominent cranial nerve involvement reported by Maramattom et al. (2021). Nonetheless, our series highlights a likely causal link between AstraZeneca Covid-19 and GBS.

In addition, we report evidence of a link between AstraZeneca Covid-19 and A-CIDP. A recent report detailed a case of A-CIDP in a patient that had received steroids and Remdesevir for COVID-Infection, 7 months prior to developing neurological symptoms and 17 days post-vaccination with AstraZeneca Covid-19[12]. A-CIDP presentations have been reported previously

following tetanus, flu and hepatitis vaccinations[9].

In conclusion, our case series, along with previous similar reports[3-8,11], may have implications for countries less advanced in their vaccination programs which will rely heavily on the AstraZeneca Covid-19 vaccine. Increased awareness, timely recognition of these rare associations and early targeted immunomodulatory treatments is required to prevent neurological sequelae and disability. Furthermore, while these cases were noted after the first dose of AstraZeneca Covid-19 vaccine, there may be similar complications observed with booster vaccinations. As it stands, local guidelines have recommended that an mRNA vaccine be given as a second dose in those patients who have experienced significant complications following AstraZeneca Covid-19 vaccination.

Declarations of Conflicts of Interest:

None declared.

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References:

1. Ikenberg B, Demleitner AF, Thiele T, et al. Cerebral venous sinus thrombosis after ChAdOx1 Cov-19 vaccination with a misleading first cerebral MRI scan. Stroke Vasc Neurol 2021.

2. Wang YH, Huang LY, Chen YL, et al. ChAdOx1 COVID-19 vaccine-induced thrombocytopenia

syndrome. QJM. 2021 Aug 25. Online ahead of print.

3. Chih-Cheng L, Wen-Chien K, Chih-Jung C, Po-Yen C, et al. COVID-19 vaccines and thrombosis with thrombocytopenia syndrome. Expert Rev Vaccines 2021;20:1027-1035.

4. McKean N, Chircop C. Guillain-Barré syndrome after COVID-19 vaccination. BMJ Case Rep. 2021;14(7).

5. Hasan T, Khan M, Khan F, et al. Case of Guillain-Barré syndrome following COVID-19 vaccine. BMJ Case Rep. 2021;14(6).

6. Allen CM, Ramsamy S, Tarr AW, Tighe PJ, Irving WL, Tanasescu R, Evans JR. Guillain-Barre Syndrome Variant Occurring after SARS-CoV-2 Vaccination. Ann Neurol 2021;90(2):315-318

7. Maramattom BV, Krishnan P, Paul R, et al. Guillain-Barré Syndrome following ChAdOx1-S/nCoV-19 Vaccine. Ann Neurol 2021;90:312-314

8. Osowicki J, Morgan H, Harris A, et al... Guillain-Barré Syndrome in an Australian state using both mRNA and adenovirus-vector SARS-CoV-2 vaccines. Annals of Neurol 2021. **doi.org/10.1002/ana.26218**

9. Kuitwaard K, Bos-Eyssen ME, Blomkwist-Markens PH, et al. Recurrences, vaccinations and long-term symptoms in GBS and CIDP. J Peripher Nerv Syst. 2009;14: 310- 315.

10. Doneddu PE, Bianchi E, Cocito D, et al. Risk factors for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP): antecedent events, lifestyle and dietary habits. Data from the Italian CIDP database. Eur J Neurol. 2020;27:136- 143.

11. Waheed S, Bayas A, Hindi F, Rizvi Z, Espinosa PS. Neurological Complications of COVID-19: Guillain-Barre Syndrome Following Pfizer COVID-19 Vaccine. Cureus 2021;13.

12. Suri V, Pandey S, Singh J, et al. Acute-onset chronic inflammatory demyelinating polyneuropathy after COVID-19 infection and subsequent ChAdOx1 nCoV-19 vaccination. BMJ Case Reports CP 2021;14:e245816.