Atypical acute disseminated encephalomyelitis with systemic inflammation after a first dose of AztraZaneca COVID-19 vaccine. A case report

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Background: Only a few cases of acute disseminated encephalomyelitis (ADEM) following coronavirus disease 19 (COVID-19) vaccination have been described since the beginning of the vaccination campaign.

Results: Here we report the first case of central nervous system (CNS) demyelination with systemic inflammatory findings on whole body 19-fluorodeoxyglucose positron emission tomography with computed tomography (FDG-PET/CT) following the ChAdOx1 nCoV-19 vaccine. A case report. Front. Neurol. 13:995875. doi: 10.3389/fneur.2022.995875

Conclusions: Clinicians should stay aware of potential new adverse events after immunization.

Keywords: acute disseminated encephalomyelitis (ADEM), COVID-19, vaccination, systemic inflammation, fluorodeoxyglucose positron emission tomography with computed tomography (FDG-PET/CT)

Introduction

Since the beginning of the pandemic, vaccines were produced in record time. Real-world studies indicated an excellent safety profile. Despite these studies, the scientific community must stay aware of rare but severe complications and report them. This allows more accuracy of the real-world safety profile of the vaccine. We can take appropriate measures, as we did with the AztraZaneca vaccine (ChAdOx1 nCoV-19) and its thromboembolic complications (1). The ChAdOx1 nCoV-19 is a vaccine based on a recombinant adenoviral vector encoding the spike protein of SARS-CoV-2 (2). Acute disseminated encephalomyelitis (ADEM) is an immune-mediated inflammatory disorder of the central nervous system (CNS) that occurs after an antigenic challenge. The post-vaccine etiology represents 5% of all ADEM cases and the annual incidence of ADEM ranges from 1 to 10 per million (3). Here we report the first case of central nervous system (CNS) demyelination with systemic inflammatory findings on whole...
body 19-fluorodeoxyglucose positron emission tomography with computed tomography (FDG-PET/CT) following the ChAdOx1 nCoV-19 vaccine.

Case report

A previously healthy 49-year-old female received her first dose of ChAdOx1 nCoV-19 vaccine. She experienced mild flu-like symptoms during the following 48 h. One week later, the patient presented another episode of flu-like symptoms with fever, fatigue, neck pain, followed over the next few days by rapidly progressive sensitive symptoms including paresthesia in both legs, up to the chest, Lhermitte’s phenomenon and sphincter dysfunction. In April, the patient came to the neurological consultation at another hospital. During the examination a hypoesthesia with a thoracic (Th) 8 level was noticed with a sensory ataxia. A full spine magnetic resonance imaging (MRI) was normal but somatosensory evoked potentials (SSEPs) showed abnormal conduction above the sensory decussation in the lower brainstem. Four weeks later, the patient came to our neurological outpatient clinic. Her symptoms had worsened with sensory symptoms now involving her hands, worsening sensory ataxia and of sphincter dysfunction. Her neurological examination showed normal strength, hypoesthesia to all modalities with a Th 8 level, absent plantar response, impaired tandem walking and the presence of a Romberg sign.

An MRI of the brain was obtained and revealed large, ill-defined T2 fluid attenuated inversion recovery (FLAIR) hyperintensities of periventricular and deep white matter, along with smaller lesions infratentorially (Figure 1, part 1). Subcortical U fibers were spared, and so were the cortex and deep gray matter. Lesions showed mildly increased diffusivity and were mostly non-enhancing. They exerted no mass effect. No meningeal enhancement was noted. MRI of the spinal cord revealed the appearance of numerous contiguous short-segment cervical and thoracic lesions, showing variably increased T2 signal intensity and contrast enhancement (Figure 1, part 2). The

Abbreviations: ADEM, acute disseminated encephalomyelitis; Coronavirus disease 19, COVID-19; CNS, central nervous system; FDG-PET/CT, whole body 19-fluorodeoxyglucose positron emission tomography with computed tomography; Th, thoracic; MRI, magnetic resonance imaging; SSEPs, somatosensory evoked potentials; FLAIR, fluid attenuated inversion recovery; ADC, apparent diffusion coefficient; PMR-GCA, polymyalgia rheumatic associated with a giant cell arteritis.
## Clinical evolution and complementary assessments done during patient follow-up.

| Temporality | Neurological examination | Laboratory investigations | Cerebrospinal fluid investigations | MRIs | Others | Treatment |
|-------------|--------------------------|---------------------------|-----------------------------------|------|--------|-----------|
| April 2021  | Hypoesthesia with a Th8 level Lhermitte phenomenon Sensitive ataxia Sphincter dysfunction. | Thyroid, hepatic, hematologic and renal functions normal. | None. | Normal spinal MRI. | SSEPs: asymmetric conduction of the somesthetic influx with a subcortical but supramarginal level. | |
| May and June 2021 | As above but with decreased pallesthesia and absent plantar response. | Serum protein electrophoresis, vitamins, angiotensin converted enzyme, erythrocyte sedimentation speed, microbiological studies (including Tuberculosis - QuantIFERON blood test, HAV, HBV, EBV, CMV, HIV, HSV, Syphilis, Borrelia, Toxoplasma, JC virus, SARS-CoV-2), screening for antibodies targeting antigens associated with demyelinating disorders of the CNS (MOG, AQP4) and other auto-immune disorders (ANA, ANCA) remained negative. | 8 WBC, protein level at 101 mg/dl, normal IgG/Albumin Index, OCBs identical in CSF and serum. Negative infectious panel. | Extensive, asymmetric involvement of periventricular and deep white matter. Smaller lesions were observed in the ponto-mesencephalic tegmentum, superior and middle cerebellar peduncles. Lesions were mildly hyperintense on ADC cartography; revealing increased diffusivity. A small focus of contrast enhancement was demonstrated in the left superior cerebellar peduncle. | Normal nerve conductive studies. | IV MP 1 gr/day, for 5 days. |
| July 2021   | Paraparesis 2/5 in the right leg and 3/5 in the left leg. Apallesthesia up to iliac crests. Sensory level at Th5 level. Need walking aids. | Negative MOG and AQP4 antibodies. Negative ANA and ANCA. | Normal nerve conductive studies. | Numerous contiguous short-segment cervical and thoracic lesions, showing variably increased T2 signal intensity and contrast enhancement. | 5 sessions of Therapeutic Plasma Exchange. |
| August 2021 | Weakness worsened after an improvement. | Normal thyroid hormone level and autoantibodies. Negative ANA and ANCA Negative MOG antibody. | 2 WBC, protein level at 95mg/dl, normal IgG/Albumin Index, OCBs identical in CSF and serum. Negative infectious panel. | Increase in the number and size of spinal cord lesions and the appearance of new foci of contrast enhancement. Brain findings were unchanged. | FDG PET-CT: increased glucose uptake in the thyroid, the pulmonary nodules, the thoracic aorta walls, the lumbar spinous processes and the whole spinal cord. Normal thyroid echography. | Rituximab 1 gr IV in 2 times at 15 days and another course of IV MP. |
| November 2021 | Paraparesis 3+/5 in the right leg and 4+/5 in the left leg. Sensory level at Th12. Few steps without help. | Normal thyroid hormone level and autoantibodies. Negative ANA and ANCA | Brain and spinal MRIs stable or regression of the most enhanced lesions. | Brain and spinal MRIs stable or regression of the most enhanced lesions. | FDG PET-CT: thyroid and pulmonary uptake disappeared or decreased, new uptake in scapular and pelvic belts, ischiatic, and great trochanters. | |

Th, thoracic; SSEPs, somatosensory evoked potentials; WBC, white blood cells; OCBs, oligoclonal bands; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; IV, intravenous; MP, methylprednisolone; FDG PET-CT, fluorodeoxyglucose positron emission tomography with computed tomography (FDG-PET/CT).
spinal cord was moderately swollen. Nerve conductive studies were normal. A lumbar puncture showed a mild pleocytosis with 8 white blood cells, elevated protein levels (101 mg/dL), normal IgG/albumin index and identical oligoclonal bands in the cerebrospinal fluid (CSF) and serum (type 4 pattern). Based on the clinical history and the radiological aspects an inflammatory origin was retained. Our differential diagnosis workup was mainly focused on an infectious or an auto-immune causes. An infectious panel was negative. An exhaustive blood investigation was done with the intention to exclude auto-immune systemic diseases, no relevant findings were found. A screening for antibodies targeting antigens associated with demyelinating disorders of the CNS (MOG antibody disease and NMO spectrum) remained negative (Table 1).

Based on the exclusion of CNS infection or other autoimmune disorders, the diagnosis of atypical ADEM was made. The patient was treated with an intravenous course of methylprednisolone (1 g/day for 5 days). Her condition stabilized and she was transferred to a rehabilitation center.

Three weeks after discharge, she was readmitted because of a clinical deterioration. Neurological evaluation showed a new paraparesis, evaluated at 2/5 in the right leg and 3/5 in the left leg, complete loss of pallesthesia up to the iliac crests, a sensory Th 5 level, and a severe sensory ataxia requiring walking aids.

Six weeks afterwards, on July 14, an MRI showed an increase in the number and size of spinal cord lesions and the appearance of new foci of contrast enhancement (Figure 1, part 3). Brain findings were unchanged. She was treated with 5 sessions of plasma exchange. She improved and was discharged again to a rehabilitation center. Three weeks later, her weakness worsened. A new MRI showed there were new enhancing lesions in the brain stem and cervical spinal cord.

Because of the atypical course of the disease, the diagnosis of ADEM was reconsidered. Whole body fluorodeoxyglucose positron emission tomography with computed tomography (FDG-PET/CT) was obtained with the aim of excluding systemic inflammation, namely sarcoidosis despite negative biological markers. Results revealed increased glucose uptake not only in the spinal cord but also in the thyroid, the thoracic aorta walls and the lumbar spinous processes (Figure 2).

She did not have any complaints about osteo-articular or vascular systems. Further thyroid testing with echography, hormone levels and autoantibodies were normal. She received IV rituximab (1 g and another after 15 days) and another course of IV methylprednisolone (1 g/day for 5 days). Over the next 2 months, she progressively improved. At last follow-up, strength in her right and left lower limbs was evaluated at 3+/5 and 4+/5, respectively, the sensory level had dropped to the level of Th12 and she could take a few steps without aid. Another MRI showed stability or regression of most lesions.

On repeat whole body FDG-PET/CT (13 weeks after the first one), thyroid uptake had disappeared but other regions’ abnormal uptake had decreased and new areas of increased uptake had appeared at the level of the scapular and pelvic girdles, ischiatic and great troCHANTERS.

**Discussion**

This case report raises two important points: the association between ChAdOx1 nCoV-19 and ADEM and the meaning of incidental findings in the FDG PET-CT.

A review of the SARS-CoV-2 vaccine and ADEM literature showed 13 reported cases of ADEM following the administration of a COVID-19 vaccine, which are summarized in Table 2 (4–14).

In comparison to prior cases except maybe one who had a pseudo relapse (14), our patient had a more protracted course, which evolved in two subsequent worsening phases until improvement 8 months later. These phases occurred each time after treatment cessation and there was no relapse after the symptomatic nadir which occurred in August (Table 1). Therefore, we conclude that these recurrences are part of the same monophasic course.

Also, the MRI evolution of the lesions is atypical for several reasons: the sub-acute evolution (longer than 3 months),
TABLE 2 Clinical and demographic characteristics of the 6 cases reporting with an ADEM post COVID vaccine.

| Authors                | Age/gender | Vaccine                  | Time of onset | Clinical picture                                                                 | CSF/laboratory investigations                                                                 | MRI                              | Treatment                                                                 | Outcome/follow-up |
|------------------------|------------|--------------------------|---------------|----------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|-----------------------------|--------------------------------------------------------------------------|-------------------|
| Cao et al. (4)         | 24y/F      | Sinovac, inactivated vaccine | 1st dose, 14 d after | Memory decline, headache, low-grade fever, muscle stiffness, extremity weakness, and reduced appetite. GTCs after one week. | Negative anti-AQP4, anti-MOG antibodies, vasculitis, OCBs.                                    | Brain lesions, no enhancement. | IVIG 20 g/d for 5 d.                                                      | No recurrences. Marked improvement. Complete resolution of MRI lesions. No seizures, 30d. |
| Orgen Kenangil et al. (5) | 46y/F      | Sinovac, inactivated vaccine | 2nd dose, 30 d after | GTCs.                                                                            | Negative OCBs.                                                                              | Brain lesions, no enhancement. | IV MP 1 g/d for 7 d.                                                      | Stable. No seizure recurrence. |
| Raknuzzaman et al. (6) | 55y/M      | mRNA-based vaccine        | 1st dose, 21 d after | Headache, somnolence, delirium and GTCs.                                         | Normal ESR.                                                                                 | Brain lesions.                | IV MP 1 g/d for 5d followed by oral tapering steroids.                   | No recurrences. Improvement of MRI lesions and fully recovered, 30d. |
| Vogrig et al. (7)      | 56y/F      | Pfizer-BioNTech COVID-19, mRNA-based vaccine | 1st dose, 14 d after | Malaise, chills, without fever, followed by unsteady gait, clumsiness of left arm. | Negative: anti-AQP4, anti-MOG antibodies, vasculitis, OCBs.                                  | Brain lesions, no enhancement. | Prednisone 75mg q.d. with gradual tapering.                               | Partial improvement, 50d. |
| Kania et al. (8)       | 19y/F      | Moderna, mRNA-based vaccine | 1st dose, 14 d after | Severe headache, fever, back and neck pain, nausea, vomiting, urinary retention. | Negative: anti-AQP4, anti-MOG antibodies, OCBs.                                             | Brain and medullar lesions with enhancement.        | IV MP and TPE (stopped because of allergic reaction)                    | No recurrences. Mild headache, 40d. |
| Rinaldi et al. (9)     | 45y/M      | ChAdOx1 nCoV-19, viral vector | 1st dose, 12 d after | Numbness of all the upper limbs, trunk, and legs and progressive reduced visual acuity, dysarthria, dysphagia, clumsy right-hand movements and urge incontinence. | Negative: anti-AQP4, anti-MOG antibodies, ANA, ESR, OCBs.                                  | Brain and medullar lesions with enhancement. | IV MP 1 g/d followed by oral prednisolone.                               | No recurrences. Complete recovery, 4months. |
| Permezel et al. (10)   | 63y/M      | ChAdOx1 nCoV-19, viral vector | 1st dose, 12 d after | Vertigo, fatigue, declining cognition, disorientation and impaired attention.     | Negative: anti-AQP4, anti-MOG, anti-neuronal, anti-NMDAR, anti-LGI-1 and anti-forantivoltage gated K+ channel antibodies. OCBs positive. | Brain and medullar lesions without enhancement.      | IV MP 1 g/d followed by TPE.                                          | Death 28d after hospitalization. |

(Continued)
| Authors            | Age/gender | Vaccine                  | Time of onset | Clinical picture                                           | CSF/laboratory investigations                                                                 | MRI                                                                 | Treatment                                                                 | Outcome/follow-up                                                                 |
|--------------------|------------|--------------------------|---------------|-----------------------------------------------------------|---------------------------------------------------------------------------------------------|----------------------------------------------------------------------|----------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Shimizu et al.     | 88y/F      | Pfizer-BioNTech          | 2nd dose, 29d | Impaired consciousness and gaze-evoked nystagmus.        | Negative: anti-onconeuronal, anti-ganglioside antinuclear, autoimmune vasculitis and MBP antibodies, OCBs. | Brain lesions without enhancement.                                     | IV MP 1 g/d 3d.                                                           | Clinical and MRI improvement after 66d.                                         |
| Al-Quliti et al.   | 56y/F      | ChAdOx1 nCoV-19, viral vector | 1st dose, 10d | Paraparesis and slurred speech.                          | /                                                                                           | Brain lesions                                                        | IV steroids.                                                              | Clinical improvement.                                                        |
| Nagaratnam et al.  | 36y/F      | ChAdOx1 nCoV-19, viral vector | 1st dose, 14d | Bilateral visual impairment and headache.                | Negative: anti-AQP4, anti-MOG, ANCA, ANA, OCBs positive.                                    | Brain lesions with enhancement and no spinal lesion.                      | Two courses of IV MP 1 g/d 3d with a prednisolone tapering plan.         | Clinical resolution and MRI improvement at 42d.                                  |
| Ancau et al.       | 61y/M      | ChAdOx1 nCoV-19, viral vector | 1st dose, 2d | Fever, headache, apathy and then unconsciousness and GS. | Negative: anti-AQP4, anti-MOG, ANA, ANCA, anti-neuronal and paraneoplastic antibodies, OCBs. | Brain lesions with hemorrhages.                                        | IV MP 1 g/d 5d followed by TPE with concomitant oral MP.                 | MRI improvement at 5d and vegetative state after 98d.                          |
| Ancau et al.       | 25y/F      | ChAdOx1 nCoV-19, viral vector | 1st dose, 9d | Cephalalgia, thoracic back pain, paraplegic syndrome with Anesthesia below dermatome Th6, sphincter dysfunction. | Negative: anti-AQP4, anti-MOG, ANA, ANCA, anti-neuronal and paraneoplastic antibodies, OCBs. | Brain and spinal lesions with enhancement and hemorrhages.              | IV MP 1 g/d 5d followed by TPE with concomitant oral MP.                 | Clinical improvement of sensory symptoms at 42d.                                |
| Ancau et al.       | 55y/F      | ChAdOx1 nCoV-19, viral vector | 1st dose, 9d | Nausea, dizziness and meningism, worsened to severe spastic tetraparesis and coma. | Negative: anti-AQP4, anti-MOG, ANA, ANCA, anti-neuronal and paraneoplastic antibodies, OCBs. | Brain lesions with hemorrhages.                                        | IV MP 1 g/d 5d.                                                           | Death                                                                         |
| Our case report    | 49y/F      | ChAdOx1 nCoV-19, viral vector | 1st dose, 7d | Neck pain, fatigue, fever, partial transverse myelitis and sphincter dysfunction Two recurrences. | Negative: AQP4, MOG antibodies, ANA, ANCA, ESR, OCBs.                                       | Brain and medullar lesions with enhancement.                            | IV MP 1 g/d during 5d, TPE 5 sessions, Rituximab 2gr and IV MP 1 g/d during 5d. | Mild improvement, 9 months.                                                |

CSF, Cerebrospinal fluid; MRI, magnetic resonance imaging; FDG PET-CT, F-fluoro-2-deoxy-D-glucose positron emission tomography with computed tomography; Y, years; F,Female; M, Male; d, days; GTCs, Generalized Tonic-Clonic seizures; OCBs, Oligoclonal Bands; ESR, Erythrocyte Sedimentation Rate; IV, Intravenous; IG, Immunoglobulins; MP, Methylprednisolone; TPE, Therapeutic Plasma Exchange; Th, Thoracic.
the discordance between brain and spinal cord lesions in terms of how they evolved and their aspects, and the limited resolution on the last MRI after 7 months of follow-up. As some studies have described, some lesions could take up to 18 months to disappear (15) or persisted on follow-up imaging (16). We did have the information of the MRI evolution from only 3 previously reported cases as shown in Table 2: one with a complete resolution in 1 month (4) and the other two with a partial resolution at follow-up of 30 and 66d (6, 11). We retained the diagnosis of ADEM according to Sejvar et al. (17) but determined it atypical because of these particular findings.

It is the first reported case of post-ChAdOx1 nCoV-19 vaccination ADEM in which FDG-PET/CT was performed. The observed pulmonary nodules’ hypermetabolism were very small (<5 mm) with a reduction of the glucose uptake at the FDG-PET/CT control. A basic control will be performed at one year with a CT.

The increased glucose uptake observed in the thyroid on the first FDG-PET/CT is difficult to interpret in our clinical setting. Mild FDG uptake by the thyroid is likely physiological and a normal variant but moderate-to-intense diffuse uptake is usually associated with elevated TSH, thyroiditis, hyperthyroidism or Graves’ disease (18). One interesting study reported aortic and thyroid unexpected hypermetabolism without clinical relevance in a cohort of patients with anti-neutrophil cytoplasmic antibodies-associated vasculitis (19). In our case the complementary analysis and also the control FDG-PET/CT were normal, leading to the conclusion that the initial thyroid finding had no clinical relevance.

The increased uptake of the thoracic aorta and the lumbar spinous processes interspaces associated with the increased uptake of the scapular and pelvic girdles, ischiatic and great trochanters in the second FDG-PET/CT raised the question of polymyalgia rheumatica associated with a giant cell arteritis (PMR-GCA) diagnosis. Again, in our case we did not have any clinical correlation and our patient is substantially younger (40 years old) than the median age (70 years old) of diagnosis for this PMR-GCA entity (20). We did not find any description in the literature of the association of ADEM with vasculitis, in particular giant-cell arteritis. Large-vessel vasculitis is not classically associated with extensive myelitis. We only found a case report of NMO spectrum disorder which is a demyelinating auto-immune disease of the CNS, associated with Takayasu arteritis (21). The possibility of CNS and systemic vasculitis, triggered by the vaccination in our case, should be raised. Recent literature reports cases of vasculitis as cutaneous vasculitis (22), hypersensitivity angitis, IgA vasculitis (23) and ANCA-associated vasculitis (24) following ChAdOx1 nCoV-19 vaccine and one case of eosinophilic granulomatosis with polyangiitis after the Moderna vaccine (25). We also found one reported case of CNS vasculitis following BNT162b2, Pfizer/BioNTech vaccine (26) but without FDG-PET/CT done. Vasculitis was described as a complication during COVID-19 because of direct endothelial damage (27) and ChAdOx1 nCoV-19 vaccine is associated with immune thrombosis and thrombocytopenia. To date, current data do not strongly support a causative link between vaccination and most of vasculitis (28). The hypothesis of two autoimmune disorders coexistence rather than a large-vessel vasculitis with CNS involvement could also be raised and it is a situation already described in the literature (29, 30). In our case, the lack of clinical corresponding symptoms to the FDG-PET/CT findings does not allow to confirm a specific diagnosis. For all these reasons we will remain for now with the diagnosis of atypical ADEM with systemic inflammation without a clear diagnosis.

Conclusions

We report the first case of post-ChAdOx1 nCoV-19 vaccination atypical ADEM with incidental findings on the FDG-PET/CT consistent with a large-vessel vasculitis, in particular GCA given the hypermetabolism of scapular and pelvic girdles and typical of polymyalgia rheumatica. Their relevance remains debatable at this stage given the lack of corresponding symptoms. Clinicians should stay aware of potential new adverse events after immunization.

Data availability statement

The original contributions presented in the study are included in the article.Supplementary material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by Comité d’Ethique de l’Hôpital Erasme—CUB. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

LB wrote the first draft of the manuscript. VL, SG, MC, and VO-I wrote sections of the manuscript. All authors
contributed to manuscript revision, read, and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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