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Antibody-mediated autoimmune encephalitis evaluated by ^{18}F-DPA714 PET/MRI

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ABSTRACT

SARS-CoV-2 vaccine has considered being the most effective method to prevent SARS-CoV-2 infection. The safety and effectiveness of the SARS-CoV-2 vaccine has been confirmed. However, in very rare cases, autoimmune neurological diseases may occur. In this article, we report three rare cases of autoimmune encephalitis with definite auto-antibody after SARS-CoV-2 vaccination. They all have good prognosis after treatment. In addition, we first use 18F-DPA-714 PET/MRI to evaluate microglia activation in our patients. We found that 18F-DPA-714 PET/MRI may be a powerful tool for quantitative analysis of neuroinflammation in patients of autoimmune encephalitis. Finally, although rare complications may happen after vaccination, we still consider the benefits of vaccination far outweigh the risks. People without contraindications should be vaccinated without delay to prevent infection in current outbreak situation.

1. Introduction

Vaccine against SARS-CoV-2 has become a key countermeasure in the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) global pandemic. The safety of the SARS-CoV-2 vaccine has been confirmed. However, in very rare cases, neurological autoimmune disorders may occur (Chun et al., 2022; Kwon and Kim, 2021; Zuhorn et al., 2021). Herein, we first describe three cases of postvaccination autoimmune encephalitis (AE) with confirmed autoantibody after inactivated SARS-CoV-2 vaccination (Table 1). Moreover, we applied ^{18}F-DPA-714 PET/MRI to evaluate microglia activation in AE patients for the first time.

2. Case presentation

2.1. Case 1: MOG (Myelin oligodendrocyte glycoprotein)-IgG associated disorders (MOGAD)

A 17-year-old male received two doses of SARS-CoV-2 vaccination on August 8th and 29th 2021. On September 10th he developed fatigue, which was followed by fever and headache. On October 19th, he was transferred to our hospital due to status epilepticus. He was somnolent and his modified RANKIN scale (mRS) score was 4. Cerebrospinal fluid (CSF) testing revealed a normal opening pressure (130 mmH_2O), pleocytosis (320.00 $\times$ 10^6/L, 59% multinucleated cells, 41% monocytes), and normal protein (58.2 mg/dL). Electroencephalography (EEG) showed generalized background slowing significantly in left hemisphere, with sharp waves. T2 FLAIR MRI demonstrated a focal hyperintense signal in the grey matter region of left frontal lobe. Registered to T2 FLAIR image, the uptake level of ^{18}F-DPA-714 in left frontal lobe (SUVR = 1.39) was obviously higher than that in contralateral region (SUVR = 1.23) and other grey matter region (Table 1), indicating increased microglial activation accompanied by inflammatory edema. The encephalitis antibody panel revealed positive antibodies against MOG in serum (titer as 1:100) method and CSF (1:10) via cell-based assay (CBA), while other antibodies were negative. Next-generation sequencing (NGS) of the CSF detected no causative pathogen. Unilateral cortical FLAIR-hypertense lesions in MOG-associated encephalitis with seizures (FLAMES) was ultimately diagnosed (Budhram et al., 2019). The patient received levetiracetam and responded well to intravenous immunoglobulin (IVIg) at 0.4 g/kg/day and methylprednisolone 500 mg/day simultaneously for 5 days. After a course of treatment,

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patient was able to perform daily activities. The patient received a tapering dose of prednisone and was maintained on 30 mg daily after discharge. Two and a half months later, post-treatment PET/MRI images (Fig. 1) showed the disappearance of localized T2 hyperintensity in the left frontal lobe, with a reduction in the intensity of ^{18}F-DPA-714 uptake (SUVR = 1.29) which was consistent with improvement in the patient's symptoms. MOG antibody tittered 1:10 in serum and was not detectable in CSF. His cognitive functions returned to normal (MMSE:30) and his mRS was 0. Patient remained asymptomatic 11 months after discharge.

2.2. Case 2: Anti-CASPR2 (contactin-associated protein-2) AE

A 14-year-old boy developed fever and seizure with transient loss of consciousness on December 5th, 81 days after his second dose of SARS-COV-2 vaccination (first dose on August 18th, second dose on September 15th). He also complained of profuse sweating. His mRS was 3. CSF analysis showed 1.00 × 10^6/L nucleated cells and protein 41.1 mg/dL. EEG revealed an increased widespread slow wave, accompanied by sharp waves. Cranial MRI showed no abnormality; the patient refused ^{18}F-DPA-714 PET/MRI. NGS of CSF and blood found no causative pathogen. Antibodies against CASPR2 were positive for serum (titer as 1:32+) via CBA method. The patient was treated with levetiracetam and valproate plus two rounds of IVIg at 0.4 g/kg/day followed by methylprednisolone 500 mg/day for 5 days. A tapering dose of prednisone was used, and his functional outcome was favorable (mRS score 0). The patient was discharged with no seizure or sweating. CASPR2 antibody tittered 1:10 in serum only in his two-month follow-up visit. Patient remained symptomless after ten months' follow-up.

2.3. Case 3: Anti-SOX 1 related AE

A 16-year-old girl experienced fatigue on September 20th, one day after her second dose of SARS-COV-2 vaccination (first dose on August 27th, second dose on September 19th). She developed an unsteady gait two weeks later. Upon admission, she had a head titubation while awake, cognitive dysfunction, and was somnolent. Neurological examination revealed prominent cerebellar ataxia and ataxic dysarthria. Her mRS was 5. CSF analysis showed 66.00 × 10^6/L nucleated cells (1% multinucleated cells, 99% monocytes) and protein 84.9 mg/dL. No causative pathogen was detected in NGS of CSF or blood. Antibodies against SOX1 were detected in both serum (1:100) and CSF (1:10) via immuno-blotting. No structural or signal abnormalities in the cerebral and cerebellar cortices was found on the T2 FLAIR MRI. Notably, there was a significant increase of ^{18}F-DPA-714 uptake (SUVR = 1.44, 1.41) in the bilateral cerebellum on the PET images (Fig. 2), indicating inflammation-mediated microglia activation. She was diagnosed with SOX1-related AE. She was treated with IVIg at 0.4 g/kg/day for 5 days followed by methylprednisolone 500 mg/day for 5 days. The patient maintained on 30 mg prednisone and 500 mg mycophenolate mofetil daily. Three months later, she had a good recovery with improved walk and speech. Her mRS improved to 1. Follow-up PET/MRI showed improved ^{18}F-DPA-714 uptake (SUVR = 1.20, 1.22) in the bilateral cerebellum, but still higher than that in the other cerebral regions, suggesting partial attenuation of neuroinflammation. SOX1 antibody was not detectable in either serum or CSF in her 3-month visit. In her 10-month visit, patients still had minor head titubation but was able to return to daily life.

Table 1
Characteristics and clinical manifestation of the three cases.

		Case1	Case2	Case3
Age		17	14	16
Doses taken		2	2	2
Date of 1st dose		8th August	18th August	29th August
Date of 2nd dose		29th August	15th September	19th September
Date of neurological onset		27th September	5th December	3rd October
Interval Time (Days)		29	81	14
Prodromal infectious		None	None	None
Prodromal symptom		Fatigue	None	Weakness
Main symptom		Fever, headache, seizure	Hidrosis, seizure	Ataxia, tremor
CSF	*Opening pressure(mmH2O)*	120	150	135
	Cells(x10^6/L)	320, 59% multinucleated cells, 41% monocytes	1	66, 1% multinucleated cells, 99% monocytes
	Protein(mg/dL)	58.2	41.2	84.9
	Glucose(mmol/L)	3.83	3.44	3.35
	Chloride(mmol/L)	126	132	129
Positive antibody		MOG	CASPR2	SOX1
Titer(s)		1:100(serum) 1:10(CSF)	1:32(serum)	1:100(serum) 1:10(CSF)
mRS before treatment		4	3	5
Structural Imaging		MRI T2 FLAIR shown hyperintense lesion in left frontal lobe.	Normal structural MRI.	Normal structural MRI.
^{18}F-DPA-714 PET (SUVR)	Frontal L.	1.39(L)1.23(R)	N.A.	1.17(L)1.16(R)
	Parietal L.	1.23(L)1.04(R)		1.17(L)1.19(R)
	Temporal L.	1.00(L)0.93(R)		1.16(L)1.10(R)
	Occipital L.	1.14(L)1.02(R)		1.27(L)1.22(R)
	Cerebellum	1.04(L)1.07(R)		1.44(L)1.41(R)
Treatment		IVIg and methylprednisolone. Levetiracetam.	IVIg and methylprednisolone. Levetiracetam and Valproate.	IVIg, methylprednisolone, and mycophenolate mofetil
mRS after treatment		0	0	1
^{18}F-DPA-714 PET (SUVR)	Frontal L.	1.29(L)1.21(R)	N.A.	1.14(L)1.14(R)
	Parietal L	1.13(L)1.06(R)		1.09(L)1.08(R)
	Temporal. L	0.96(L)0.88(R)		1.01(L)1.00(R)
	Occipital L	1.17(L)1.06(R)		1.19(L)1.14(R)
	Cerebellum	1.04(L)1.10(R).		1.20(L)1.22(R)

SUVR：Standard uptake value ratio; L: left; R: right.
The modified Rankin Scale (mRS) is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered neurological disability.

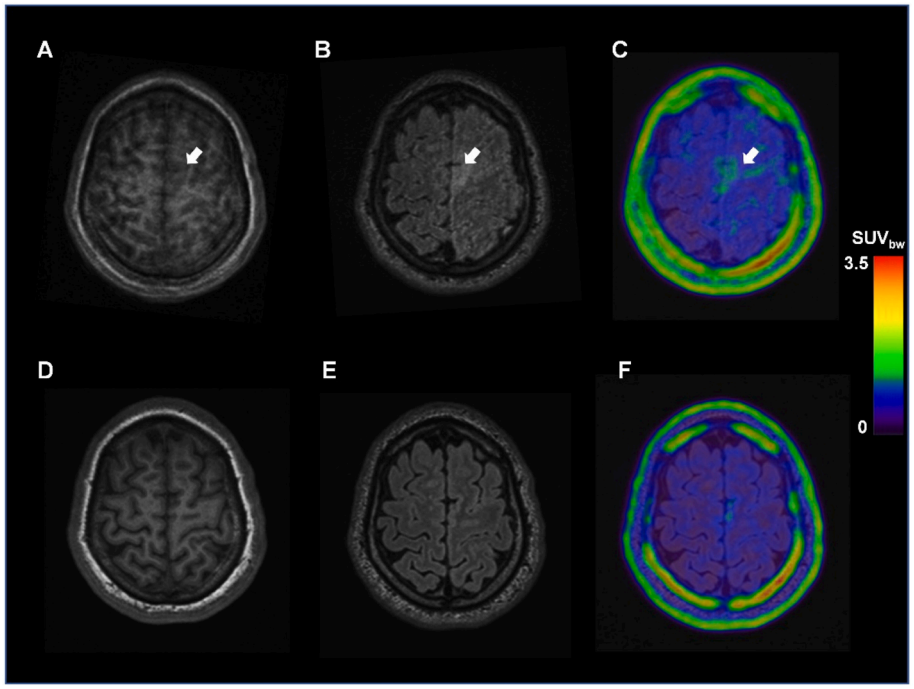

Fig. 1. Pre-treatment A) axial T1W, B) T2 FLAIR and C) hybrid ^{18}F-DPA-714 PET/T2 FLAIR images indicated an inflammatory lesion (white arrow) in the left frontal lobe. The disappearance of the lesion with a reduction of ^{18}F-DPA-714 uptake was observed on post-treatment D) axial T1W, C) T2 FLAIR MRI and E) hybrid ^{18}F-DPA-714 PET/T2 FLAIR images.

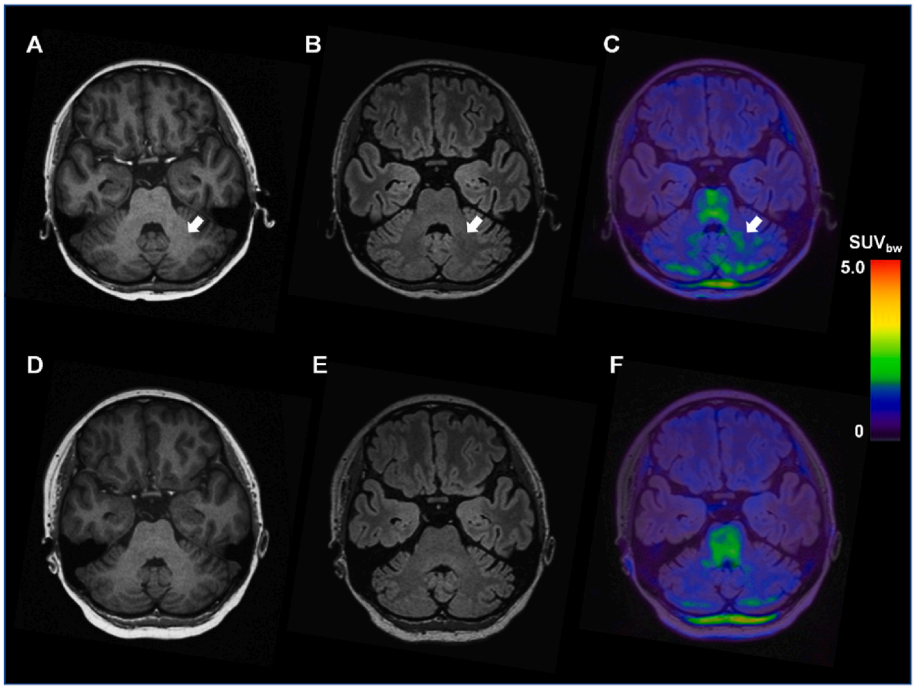

Fig. 2. A significant increase of ^{18}F-DPA714 uptake (white arrow) in the cerebellum was found without any structural or signal abnormalities on A) T1W, B) T2 FLAIR images and C) hybrid ^{18}F-DPA-714 PET/T2 FLAIR images. Post-treatment PET/MRI showed reduced ^{18}F-DPA714 uptake in the bilateral cerebellum on D) T1W, E) T2 FLAIR images and F) hybrid ^{18}F-DPA-714 PET/T2 FLAIR images.

3. Discussion

Our study has two important findings.

First, we report three cases of antibody related AE after vaccination. Very limited cases of postimmunization autoimmune encephalitis following SARS-CoV-2 mRNA vaccination have been reported (Kwon and Kim, 2021; Zuhorn et al., 2021; Kaulen et al., 2022; Koh et al., 2022). Here, we first report three cases of antibody-mediated autoimmune encephalitis following immunization with inactivated SARS-CoV-2 vaccine. Autoimmune reactions are reported to occur after a median of 11 days following SARS-Cov-2 vaccination (range 3–23 days) (Kaulen et al., 2022). Besides, vaccination is associated with a

significantly increased risk of acute disseminated encephalomyelitis in the 31–60 days exposure interval (Chen et al., 2018). Thus, disease onset in Cases 1 and 3 have a clear temporal association with the second dose of vaccination. In Case 2, the interval between immunization and AE onset was relatively longer, indicating that antibody-mediated autoimmune encephalitis may exhibit a variable incubation period. It may also be a coincidence between vaccination and encephalitis. Since all patients exhibit no signs of infection, we consider that vaccine is the possible trigger. Intriguingly, each of the three cases exhibited a different confirmed antibody after the second dose of vaccination, suggesting possible dysfunction of B cells induced by the vaccine (Dhenni and Phan, 2020). It should be noted that all three patients responded well to immunotherapy. We consider that AE after SARS-CoV-2 vaccine may have good short-term prognosis.

Second, we use ^{18}F-DPA-714 PET/MRI to evaluate AE patients for the first time. The 18 kDa translocator protein (TSPO) expression in the central nervous system is upregulated in response to microglia activation. ^{18}F-DPA-714 PET/MRI which can specifically trace unregulated TSPO in vivo becomes a promising tool to unveil neuroinflammation in neurologic diseases (Zhang et al., 2021). Thus, ^{18}F-DPA-714 is a good tracer to demonstrate neuroinflammation related disease (Golla et al., 2016). Although increased TSPO expression via ^{18}F-DPA-714 uptake in patients with progressive multiple sclerosis can reliably identify increased focal and diffuse neuroinflammation (Hagens et al., 2018), no longitudinal studies have demonstrated the increased TSPO expression in the brain of AE patients to our knowledge. Since pathology of AE is autoimmune induced neuroinflammation in which microglia activation is participated, ^{18}F-DPA-714 PET/MRI should be a promising tool in AE evaluation. In this case series, we found that (Chun et al., 2022): patient in case 3 exhibited normal structural MRI imaging but abnormally higher ^{18}F-DPA-714 uptake in bilateral cerebellum, which could explain her instability and ataxia. This indicates that compared with traditional structural MRI, ^{18}F-DPA-714 PET had a higher sensitivity to identify insidious lesions. This may remedy the deficiency of structural MRI when making a diagnosis of AE (Kwon and Kim, 2021). Patients showed higher ^{18}F-DPA-714 uptake in their acute phase, but decreased to lower level after recovery, suggesting that TSPO traced by ^{18}F-DPA-714 may be correlated with disease severity and could be a good biomarker to track the disease process. It may provide clinicians a quantitative analysis to evaluate neuroinflammation in AE patients.

In summary, SARS-CoV-2 vaccination remains a safe and the most effective macroscopical anti-epidemic strategy worldwide. The benefits of vaccination far outweigh the risks. People without contraindications should be vaccinated in time. However, AE after vaccination needs our attention. It may have good prognosis when diagnosed and treated properly and timely. We suggest clinicians screen for autoantibodies in patients who exhibit postvaccine AE like symptoms. In addition, ^{18}F-DPA-714 PET/MRI may be a powerful tool for not only assisting the diagnosis of AE, but also predicting its prognosis. We certainly need to carry out proper clinical research to verify all these speculations.

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Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.bbih.2022.100535.

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