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LETTER TO EDITOR

Central diabetes insipidus revealing a hypophysitis induced by SARS-CoV-2 vaccine☆

Keywords Hypophysitis; COVID-19; Endocrinopathy; Adjuvants vaccines; ASIA syndrome.

Abbreviations

AID	auto-immune disease
ASIA	autoimmune syndrome induced by adjuvants
COVID-19	coronavirus disease 2019
DI	diabetes insipidus
MRI	magnetic resonance imaging
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
T4	thyroxine hormone
TSH	thyroid-stimulating hormone

Introduction

Coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has inflicted a major blow on public health worldwide accounting for millions of deaths [1]. Vaccination is one of the most effective interventions to substantially reduce severe disease and death due to SARS-CoV-2 infection.

Local and systemic side effects are relatively common, especially after the second vaccination. These mostly include fever, malaise, headache, myalgia and arthralgia, which are only mild or moderate in severity and are limited to the first 2 days after vaccination [2].

The published data on the endocrine complications of SARS-CoV-2 vaccine is sparse, particularly a few cases of isolated pituitary abnormalities such as hypophysitis were reported [3].

Hypophysitis is a rare chronic inflammatory affection of the pituitary gland that leads to structural changes in the hypothalamic-pituitary axis and varying degrees of anterior and/or posterior pituitary hormonal deficiencies. Hypophysitis is described as a highly heterogeneous entity and may be caused by certain medical treatments such as immunotherapies [3]. Recently, Frara et al. published the main pituitary manifestations of COVID-19, reviewed several reported cases of pituitary lesions but no data is yet available on possible occurrence of hypophysitis associated with SARS-CoV-2 vaccine [3]. To our knowledge, this is the fourth case of hypophysitis following SARS-CoV-2 vaccination and only the second one revealed with central diabetes insipidus.

Herein, we present a rare case of hypophysitis with magnetic resonance imaging (MRI) evidence of pituitary stalk thickening three days after administration of SARS-CoV-2 vaccine.

Case presentation

The patient is a fifty-four-year-old female with a personal history of high blood pressure diagnosed four years ago treated with calcium channel blocker. She did not have any personal or family history of autoimmune or endocrine diseases, nor a history of upper respiratory system infection or COVID-19.

She presented with sudden onset polyuria and nycturia of almost 10 liters per day, a polydipsia of 4 liters of water per day, 3 days after she received her first SARS-CoV-2 vaccine dose (Oxford-AstraZeneca ChAdOx1 nCoV-19), a vaccine made from a modified adenovirus.

On presentation, her pulse rate was estimated at 90 beats per minute, her blood pressure was 130/70 mmHg. She weighed 104 kg and was 163 cm tall, resulting in a body-mass index of 36 kg/m^2. She complained of fatigue, though the physical examination was unremarkable.

Laboratory findings showed high levels of serum sodium estimated at 151 mmol/L and high plasma osmolarity equaling 305.8 mosmol/kg. Urinary osmolarity was low at 138 mosmol/kg.

A water deprivation and vasopressin challenge tests were undertaken. The test was stopped at the third hour due to an extreme intolerance to thirst. The 3-h water deprivation test started at 08 am. The urine osmolarity did not increase above 200 mosmol/kg (maximal increase at 170 mosmol/kg), despite a 1 kg weight loss in just 3 hours.

Central diabetes insipidus (DI) was diagnosed based on a decrease in the urine output and an increase in more than 60% in urine osmolality in response to vasopressin.

Pituitary MRI showed thickening of the pituitary stalk of 5.05 mm in transverse dimension suggestive of infundibuloneuro hypophysitis (Fig. 1).

Further endocrine workup showed normal thyroid function. Cortisol under synacthen 1 μg stimulation test reached a peak superior to 18 μg/dL thus eliminating corticotrop insufficiency. Her prolactinemia was normal.

☆ This report was notified in August 2022 to the Ethical board of the University Hospital of Farhat Hached of Sousse (Tunisia) and registered with the file number 60/2022.

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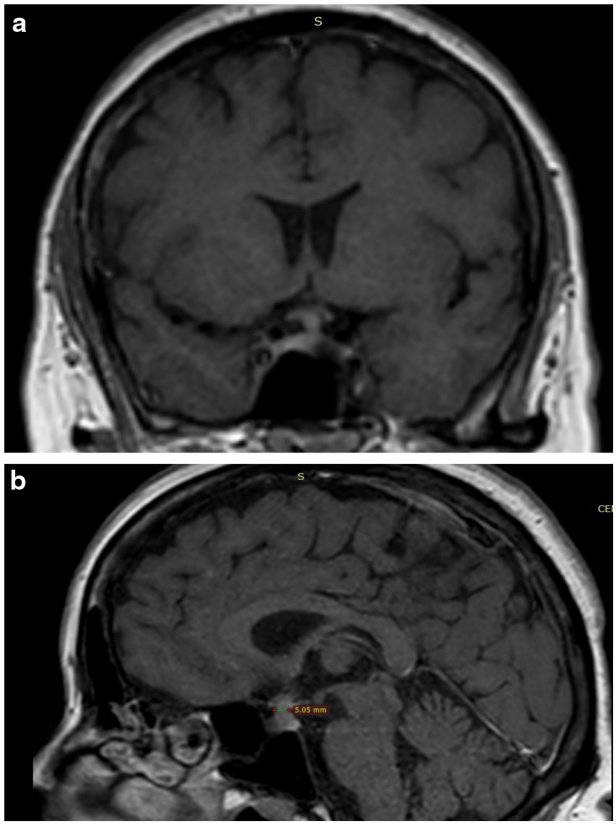

Figure 1. Pituitary MRI with gadolinium contrast, showing a thickened pituitary stalk measured at 5.05 mm in the sagittal T1 W image.

Based on these findings, inflammatory, autoimmune and infiltrative granulomatous disorders were suspected and searched for by clinical and biological explorations. Serum calcium was normal. Complete blood count, liver function tests, antinuclear antibody and chest radiograph were all normal. Serum levels of angiotensin converting enzyme were normal, as was serum β2 microglobulin. She also had normal serum levels of IgG4. Hypophysitis induced by adjuvants of SARS-CoV-2 vaccine was the most probable diagnosis after having eliminated autoimmune and infiltrative granulomatous disorders. The responsibility of the vaccine was assessed as C2S2 according to the updated French method of imputability because of the compatible chronology (3 days after the injection) [4].

The patient was treated with oral desmopressin at 60 mg/day. On the second day of treatment, she experienced a decrease in thirst. The dose of desmopressin was titrated to 120 mg/day. Thereafter, she had almost complete remission of DI symptoms.

Discussion

In this paper, we presented the second case of central DI revealing a hypophysitis that might be induced by adjuvants of SARS-CoV-2 vaccine.

The emergence of a novel coronavirus and global pandemic raised the need for the rapid development of new vaccines to reduce the morbidity and mortality associated with COVID-19.

Vaccination programs are being rolled out globally; however, most of these vaccines have been approved without extensive studies on their side effects [2].

There have been a few reported cases of endocrinopathies post-vaccination, including cases of adrenal hemorrhage, new onset type 1 diabetes mellitus, subacute thyroiditis, Grave's disease and hypophysitis [5].

Hypophysitis is a rare condition characterized by inflammation of the pituitary gland, usually resulting in hypopituitarism and pituitary enlargement. Pituitary inflammation can occur as a primary hypophysitis (most commonly lymphocytic, granulomatous or xanthomatous disease) or as secondary hypophysitis as a result of systemic diseases, immunotherapy or alternative sella-based pathologies [6]. Hypophysitis can potentially manifest with one or more of the following four clinical features: mass effects such as headaches and visual symptoms; symptoms of deficiency of anterior pituitary hormones; central DI; and hyperprolactinemia [6]. The main presentation of a pituitary stalk thickness is more likely with diabetes insipidus as a first symptom [7]. The diagnosis is based mainly on clinical presentation, laboratory tests, and imaging. MRI often shows a pituitary enlargement often mimicking an adenoma, pituitary stalk thickening, with diffuse homogeneous anterior pituitary contrast enhancement, and loss of posterior pituitary bright spot on T1-weighted imaging [8].

Autoimmune/inflammatory syndrome induced by adjuvants (ASIA syndrome) can be seen as a post vaccination phenomenon that occurs after exposure to adjuvants in vaccines that increase the immune responses [9]. Data regarding ASIA syndrome following severe SARS-CoV-2 vaccines are limited, and the entity is still a debating controversial among the scientific community. For example, during the period from May 2021 to December 2021, 36 patients referred to hospitals in Mexico City were diagnosed with ASIA after vaccination with different types of COVID-19 vaccines [9]. ASIA syndrome associates three major criteria such as an exposure to an external stimulus (COVID-19 vaccine). Average number of days-of-onset of symptoms after applying the COVID-19 vaccine is short and ranges from 8 days to 3 weeks as it was in our case [10]. The other criteria was the developing of an acute clinical pictures with manifestations of autoimmune diseases, including vasculitis, arthritis, and neurological syndromes [10]. The third criteria could not be applied to vaccines, but only on medications which removal of the inciting agent induces improvement. To our knowledge, this is the fourth report of hypophysitis after SARS-CoV-2 vaccination, which meets the diagnostic criteria for ASIA [9]. A published review by Bargazzi et al. reported that ASIA is often associated with other endocrine diseases such as Hashimoto's thyroiditis, primary ovarian failure, autoimmune diabetes, and hypophysitis [10].

In addition to the plausible hypothesis of ASIA syndrome, another pathophysiological mechanism arises. Vaccination-mediated adverse effects can be attributed to the unique characteristics of the S protein itself either due to molecular mimicry with human proteins or as an ACE2 ligand [10]. The vaccine-encoded antigen (S protein) is stabilized in its perfusion form in the mRNA vaccines; it is therefore plausible that, if entering the circulation and distributing systemically throughout the human body, it can contribute to enhancing autoimmune disease in susceptible individuals [2,10].

The clear chronological relationship of the onset of hypophysitis to SARS-CoV-2 vaccine along with the exclusion of the most common causes of hypophysitis make us suspect that the DI in our patient was due to SARS-CoV-2 vaccine induced hypophysitis. Clinical aspects and the chronological order concurred with the latest aspects of pharmacovigilance and drug safety information [4]. This may result in a vaccine-induced autoimmunity especially in the presence of a genetic disposition.

Conclusion

We present a rare case of COVID-19 vaccine induced hypophysitis in a middle-aged woman with central DI manifestations 3 days after receiving her first SARS-CoV-2 vaccine dose (Oxford-AstraZeneca ChAdOx1 nCoV-19).

We suspect autoimmune/inflammatory syndrome induced by adjuvants based on the delay between the symptoms and the receipt of the vaccine, in absence of signs suggestive of other potential etiologies.

We recommend that further research should be directed to investigate the long-term endocrine and autoimmune effects of the mRNA COVID-19 vaccine in order to avoid these side effects.

Informed consent

An oral and informed consents were obtained from the patient.

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Disclosure of interest

The authors declare that they have no competing interest.

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