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Review Article

Graves' disease Induced by Sars-Cov-2 Vaccination

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Abstract

Background: Several cases of Graves' disease were recently reported in individuals vaccinated against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Objective: To determine characteristics and patterns of Graves' disease occurring following SARS-CoBV-2 vaccination.

Methods: Pubmed search up to March 31st, 2022. Search terms are Graves' disease, SARS-Cov-2, vaccine, COVID-19. Case reports, case series, review articles and pertinent in vitro studies are reviewed.

Results: Review of literature revealed 28 cases (19 women) of new onset and 5 cases (4 women) of relapses of Graves' disease after receiving different types of vaccines against coronavirus disease 2019 (COVID-19). Onset of hyperthyroid symptoms started 2-60 days after vaccination and occurred more frequently after the first vaccine dose (n=13) than after the second dose (n=5). In 70% of cases (23 of 33), the implicated agent was the m-RNA based vaccine of Pfizer-BioNtech. Severity of Graves' disease symptoms was generally moderate and controlled by anti-thyroid medications (mainly methimazole) and beta-adrenergic blockers. The course of Graves' disease is unclear as patients are still receiving therapy. No specific risk factors could be defined that may increase predisposition to the COVID-19 vaccine-induced Graves' disease. Mechanisms of development of Graves' disease after COVID-19 vaccination are unclear but may be related to the phenomena of molecular mimicry or autoimmune/inflammatory syndrome by adjuvants (ASIA).

Conclusions: The timing of onset of symptoms of Graves' disease in relation to the administration of COVID-19 vaccine strongly suggests a causal relationship. Physicians should be aware of the occurrence of this uncommon adverse effect.

Key words: COVID-19; vaccine; Graves' disease; hyperthyroidism; mechanisms; thyrotropin-receptor antibodies; ASIA; TPO

Introduction

Graves' disease, the most common cause of hyperthyroidism, is an autoimmune disease due to activating autoantibodies directed against the thyrotropin receptors [1]. After the widespread use of SARS-CoV-2 vaccination, several cases of new-onset or recurrent Graves' disease were reported throughout the world. The main purpose of this article is to analyze characteristics of these cases. Confirmation of diagnosis of Graves' disease was demonstrated by documentation of hyperthyroid symptoms and signs, elevation of circulating thyroid hormones and high titers of thyrotropin-receptor antibodies. The latter have 99% sensitivity and specificity for Graves' disease [1].

Characteristics of COVID-19 induced Graves' disease

28 cases of newly diagnosed [2-16] and 5 cases [3,9,17] of relapsed Graves' disease were reported after receiving COVID-19 vaccination (tables 1 and 2). 23 of the 33 patients were women reflecting the usual female predominance of Graves' disease. Age range was 28-71 years. 5 patients had history of other thyroid diseases: 2 patients had Hashimoto's (autoimmune) thyroiditis, 2 had nodular goiter, and 1 patient had "hypothyroidism". Family history of autoimmune thyroid disease or autoimmune diseases in general was recorded in 4 patients. However, family history was not documented in approximately half of patients. The onset of hyperthyroid symptoms occurred 2-60 days after vaccination. In

recurrent cases, relapse was diagnosed 2 months to 30 years (median 8 years) after the first episode of Graves' disease (table 2). In 13 patients, hyperthyroidism started after the first vaccine dose, in 5 patients after the second dose, and was not specified in the remaining patients. No clear characteristics or precipitating factors that might predispose patients to develop Graves' disease could be identified. The most common implicated vaccine was the Pfizer-BioNTech vaccine (m-RNA based) reported in 23 of the 33 (70%) patients, followed by Oxford-AstraZeneca (recombinant adenovirus vector-based) in 6 patients, and Moderna (mRNA-based) in 3 patients [18-20]. Overall, the severity of hyperthyroidism was moderate and easily controlled by anti-thyroid medications (mainly methimazole) and beta-adrenergic blockers. However, one 38-year-old woman reported by Weintraub et al [10] presented with thyrotoxic crisis (thyroid storm). No deaths were reported. With respect to the disease outcome, as of the date of writing, all patients are currently under treatment which usually takes 12-18 months [1]. The close timing relationship between vaccine administration and development of Graves' disease provides the strongest evidence that SARS-CoV-2 vaccination may be causally related to Graves' disease. In addition, 3 of the 5 relapsed cases occurred 8-30 years after the initial episode of Graves' disease [3,9,17]. It is very uncommon for relapses of Graves' disease to take place after such long duration [21]. Hence, it is unlikely that relapsed cases are simply a coincidence.

Reference/country	Age/gender	Type of vaccine (written as in original article)	Timing of onset of hyperthyroid symptoms	Comment
1.Vera-Lastra et al (Mexico) [2]	40/F	Pfizer-BioNTech	2 days after first dose	Had COVID-19, 8 months before vaccination
2.Vera-Lastra et al [2]	28/F	Pfizer-BioNTech	3 days after first dose	
3.Zettinig & Krebs (Austria) [3]	46/M	Pfizer-BioNTech (Tozinameran)	15 days after first dose	
3.diFilippo et al (Italy) [4]	32/M	Oxford-AstraZeneca (Vaxzevria)	10 days after second dose	Ex-smoker*
5.diFilippo et al [4]	35/M	Oxford-AstraZeneca (Vaxzevria)	5 days after the first dose	Ex-smoker*
6.Lui et al (China) [5]	40/F	BNT162b2 mRNA Pfizer BioNtech	5 weeks after second dose	8-year history of hypothyroidism
7.Sriphapradang and Shantavasinkul (Thailand) [6]	70 y/M	ChAdOx1 nCoV-19	2 days after second dose	
8.Peris et al (Spain) [7]	71/F	Pfizer	60 days	
9.Peris et al [7]	42/F	Pfizer	10-14 days	
10.Peris et al [7]	54/F	Moderna	10-14 days	
11.Peris et al [7]	46 y/F	Pfizer	50 days	
12.Shih et al (Taiwan) [8]	39/F	Moderna (Spikevax)	2 weeks	History of euthyroid autoimmune thyroid disease
13.Shih et al [8]	59 y/F	Vaxzevria (AstraZeneca)	2 weeks	Sister has hyperthyroidism
14.Shih et al [8]	44/F	Vaxzevria (AstraZeneca)	4 days	
15.Bostan et al (Turkey) [9]	54/F	Pfizer BioNtech	1 week after first dose (received 2 doses 1 month apart)	2-year history of Hashimoto's thyroiditis
16.Bostan et al [9]	51/F	Pfizer BioNtech	4 days after the second dose	Rapidly progressive ophthalmopathy
17.Bostan et al [9]	47/F	Pfizer BioNtech	5 days after first dose	Hyperthyroid symptoms did not worsen after second dose
18.Bostan et al [9]	46/M	Pfizer BioNtech	3 weeks after second dose	
19.Weintraub et al (USA) [10]	38/F	Pfizer BioNtech	5 days after first dose. She decided to postpone second dose.	Presented with thyroid storm. Had enlarged thyroid gland shown 1 year earlier by computed tomography
20.Weintraub et al [10]	63/F	Moderna	1 week after first dose. Received 2 doses	Has sister and aunt with lupus

21.Weintraub et al [10]	30/M	Pfizer BioNtech	4 weeks after first dose	Mother has Grave' s disease
22.Goblirsch et al (USA) [11]	71/F	Pfizer BioNtech	14 days after second dose	Patient had multinodular goiter
23.Hamouche et al (USA) [12]	32/M	Pfizer BioNtech	22 days after first dose	Patient was diagnosed with COVID-19 10 days after vaccination
24.Patrizio et al (Italy) [13]	52 /M	Pfizer BioNtech	4 weeks after second dose	Patient has vitiligo and develops type 1 diabetes at the same time of Grave's disease
25.Pujol et al (Spain) [14]	38/F	Pfizer BioNtech	12 days after first dose	
26.Raven et al (Australia) [15]	35/F	Adenovirus-vectored (AZD1222)	5 days after vaccine	Both grandmothers have history of thyroid disease
27. Oğuz et al (Turkey) [16]	40/F	CoronaVac 2 doses followed by BNT162b2 (Pfizer)	2 days after BNT162b2 (Pfizer)	
28. Oğuz et al [16]	29/M	CoronaVac 2 doses followed by BNT162b2 (Pfizer)	9 days after BNT162b2 (Pfizer)	History of nodular goiter and ankolysing spondylitis

*Smoking is one risk factor for Graves' disease [1].

Table 1: *Cases of new onset Grave's disease after COVID-19 vaccination*

Reference/Country	Age/gender	Time since remission of Graves	Type of vaccine	Timing of onset of hyperthyroid symptoms	Comment
1.Zettinig & Krebs (Austria) [3]	71/F	Since 2004 (17 years)	Pfizer BioNtech (Tozinameran)	34 days after second dose	
2.Pierman et al (Belgium) [17]	34/F	Since 2014 (8 years)	Pfizer BioNtech	10 days after first dose	Symptoms worsened after receiving second vaccine dose 34 days after first dose
3.Bostan et al (Turkey) [9]	44/F	30 years	Inactivated vaccine (CoronaVac)	1 week after first dose	
4.Bostan et al [9]	49/M	1 year	Pfizer BioNtech	1 month after second dose	
5.Bostan et al [9]	31/F	2 months	Pfizer BioNtech	3 weeks after first dose	

Table 2. *Cases of relapses of Grave's disease after COVID-19 vaccination*

Mechanisms of COVID-19 vaccine induced Graves' disease

The mechanisms underlying vaccine-induced Graves' disease are not fully understood. In this regard, there are 2 main theories: the molecular mimicry or cross-reactivity theory and the autoimmune/Inflammatory syndrome induced by adjuvants (ASIA).

1. Molecular mimicry theory

Molecular mimicry refers to a close similarity between certain pathogenic elements contained in the vaccine and specific human proteins [22]. It follows that cross-reactivity may occur when amino acid homology exists between the pathogen and a given self-tissue protein. Thus, antibodies developed against the spike protein of SARS-CoV-2 following COVID-19 vaccination might cross react with human thyroid tissues to trigger an autoimmune disorder such as Graves' disease in susceptible individuals. In fact, Vojdani et al [23] have shown that anti-spike antibodies of SARS-CoV-2 react in vitro with human thyroid peroxidase (TPO). Furthermore, they found that SARS-CoV-2 protein shared a 50-70% of peptide sequences with TPO [23]. Unfortunately, Vojdani et al [23] did not evaluate cross-reactivity between the anti-SARS-CoV-2 spike protein and thyrotropin receptors which are more relevant to Graves' disease compared with TPO [1].

2. The ASIA theory

The ASIA theory entails development of an autoimmune disease due to the use of adjuvants in the vaccine. Adjuvants are immunological molecules that potentiate antigen specific immune response. These molecules are frequently employed in vaccination production to increase immunogenicity repose of a vaccine. This results in a reduced frequency and amount of vaccination required to achieve adequate immunity [24]. However, in predisposed subjects, adjuvants may trigger autoimmune diseases [25].

Clinical implications

This review raises 3 important practical questions. First, is there any risk for patients with actual Graves' disease if they receive COVID-19 vaccine? Unfortunately, very limited data exist with respect to the effects of COVID-19 vaccine on patients who already have Graves' disease. In a report from Thailand, Sriphapradang [26] described a 30-year-old woman with Graves' disease whose hyperthyroid symptoms worsened 4 days after receiving a booster dose of the Oxford-AstraZeca (Vaxzevria) vaccine [19]. Meanwhile, in our busy thyroid disease clinics, we did not observe any evidence of exacerbation of Graves' disease following COVID-19 vaccination. Nevertheless, Graves' patients should be counselled about possible worsening of hyperthyroid symptoms after vaccination. Second, should patients with past-history of Graves' disease receive COVID-19 vaccine? As shown in table 2, 5 cases had relapses of Graves' disease after receiving COVID-19 vaccine. Therefore, patients should be counselled about possible relapse after vaccination. Finally, should patients with COVID-19 vaccine induced Graves' disease receive a booster vaccine dose? In this respect, 2 such cases were reported by Bostan et al [9] (table 1) and Pierman et al [17] (table 2). The first patient was a 47-year-old woman who was diagnosed with Graves' disease after onset of hyperthyroidism 5 days after the first dose of Pfizer-BioNtech vaccine. No worsening of symptoms occurred after she received the second dose of the same vaccine (exact timing not reported) [9]. Conversely, the second patient who was 34-year-old woman had aggravation of hyperthyroid symptoms shortly after receiving the booster Pfizer-BioNtech vaccine [17]. Given the devastating consequences of COVID-19 infection, it may be still reasonable to give a booster vaccine dose. Yet, we suggest monitoring thyroid function very closely for approximately 2 months after receiving the booster vaccine dose for optimum control of hyperthyroid symptoms. Clearly, more data are needed to determine the ideal approach for the above 3 situations.

Conclusions and current needs

28 cases of new-onset and 5 cases of relapsed Graves' disease were reported 2-60 days following the administration of different types of SAR-CoV-2 vaccines. This number of cases is most likely underreported, but the true incidence may be still considered rare given the millions of people who received the vaccine worldwide. Most cases were related to the Pfizer-BioNtech vaccine. It is unclear whether this observation is real or a result of reporting bias. Physicians should be aware of the possible occurrence of new-onset or relapsed Graves' disease following the administration of COVID-19 vaccines. Thus, if patients complain of hyperthyroid symptoms, laboratory investigations should be performed to clarify the etiology. Interestingly, in the latest prescribing information of the 2 mRNA COVID-19 vaccines produced by Pfizer-BioNtech and Moderna, there was no mention of Graves' disease among the rare adverse effects of the vaccines occurring during clinical trials or in the post-marketing period [18, 20]. All cases of COVID-19 vaccine induced Graves' disease should be reported to the Federal Drug Administration (FDA) and the vaccine manufacturer to clarify the exact link between COVID-19 vaccines and Graves' disease.

Conflict of interest

The authors do not conflict of interest to declare

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