Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

La numération formule sanguine n'a pas mis en évidence d'hyperéosinophilie, le bilan hépatique et rénal était normal, les immunoglobulines E (IgE) étaient augmentées à 287 UI/mL pour une normale inférieure à 100 UI/mL. Une biopsie au punch retrouvait une minime spongiose, une hyper-orthokératose focalement parakératosique. Le derme sous-jacent renfermait un infiltrat lymphocytaire périvasculaire et de rares polynucléaires éosinophiles. L'histologie était compatible avec un eczéma. Le patient a été traité par dermocorticoïdes pendant 15 jours (avec une évolution favorable).

Le patient a présenté une récidive des lésions 4 jours après l'administration de la seconde dose de vaccin qui ont régressé après 2 semaines de traitement par dermocorticoïdes. Une déclaration au centre régional de pharmacovigilance et de pharmaco épidémiologie Centre Val-de Loire a été faite le 22 février 2021 et a été enregistrée sous le numéro 210767.

Les autres diagnostics évoqués chez ce patient étaient une dermatite atopique ou un eczéma de contact déclenchés ou aggravés par le vaccin devant le taux élevé des IgE mais le patient n'avait aucun antécédant personnel ou familial d'atopie, et il n'y a pas eu de modifications dans les habitudes d'hygiène ni de topiques appliqués sur la peau. Une toxidermie à un traitement systémique était éliminée devant l'absence de d'introduction de nouveau médicament. Le caractère aigu de l'éruption permet d'éliminer une pemphigoïde pré-bulleuse et une dermatite eczématiforme chronique du sujet âgé.

La relation de causalité entre l'éruption cutanée présentée par ce patient et le vaccin Pfizer-BioNtech a été évaluée « vraisemblable » (C3S1I3) en appliquant la méthode française d'imputabilité [8].

À notre connaissance une telle réaction n'a pas été rapportée auparavant. Compte tenu de l'intensification de la vaccination de masse, ces réactions sont susceptibles de susciter des inquiétudes chez les patients et le personnel soignant d'où l'intérêt de mieux préciser le cadre nosologique de ces effets indésirables.

Déclaration de liens d'intérêts

Les auteurs déclarent ne pas avoir de liens d'intérêts.

Références

[1] Jiang S, Hillyer C, Du L. Neutralizing antibodies against SARS-CoV-2 and other human coronaviruses. Trends Immunol 2020;41:355—9.

[2] Padron-Regalado E. Vaccines for SARS-CoV-2: lessons from other coronavirus strains. Infect Dis Ther 2020;9:1—20.

[3] Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-Covid-19 Vaccine. N Engl J Med 2020;383(27):2603—15.

[4] CDC COVID-19 Response Team; Food and Drug Administration. Allergic reactions including anaphylaxis after receipt of the first dose of Pfizer-BioNTech COVID-19 vaccine - United States, December 14-23, 2020. MMWR Morb Mortal Wkly Rep 2021;70(2):46—51.

[5] Blumenthal KG, Freeman EE, Saff RR, Robinson LB, Wolfson AR, Foreman RK, et al. Delayed large local reactions to mRNA-1273 vaccine against SARS-CoV-2. N Engl J Med 2021;384(13):1273—7.

[6] Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novack R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med 2021;384:403—16.

[7] Jedlowski PM, Jedlowski MF. Morbiliform rash after administration of Pfizer-BioNtech COVID-19 mRNA vaccine. Dermatol Online J 2021;27(1) [13030/qt4xs486zg].

[8] Moore N, Berdaï D, Blin P, Droz C. Pharmacovigilance - The next chapter. Therapie 2019;74(6):557—67.

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Type I interferons as the potential mechanism linking mRNA COVID-19 vaccines to Bell's palsy

Keywords Type I interferons; COVID-19 vaccines; Bell's palsy; Phase 3 clinical trials; Pharmacovigilance

Abbreviations

COVID-19 coronavirus disease 2019
mRNA messenger RNA

Safe and effective coronavirus disease 2019 (COVID-19) vaccines are well recognized as a first-line tool for curtailing the ongoing pandemic. As the first vaccines are being approved in several countries, their safety is a topic of major interest. Based on adverse events from phase 3 clinical trials [1,2], Bell's palsy appears as an atypical and rare adverse reaction of messenger RNA (mRNA) COVID-19 vaccines, leading to its mention in their summary of product characteristics. Although the frequency of Bell's palsy in the vaccine group was considered consistent with the expected rate in the general population, its imbalance between groups is puzzling. Out of the 8 cases of Bell's palsy, 7 occurred in the vaccine group, whereas only 1 occurred in the placebo group (Table 1). One case in a participant who received the vaccine was considered as serious. All cases occurred shortly after injection (i.e. from 3 to 48 days after the second dose). Bell's palsy was resolved in 2 cases, and was continuing or being resolved in 6 cases at data cutoff.

One explanation for this imbalance may be a link between mRNA COVID-19 vaccines and Bell's palsy. Early transversal

Table 1 Description of the 8 cases of Bell's palsy in clinical trials of mRNA vaccines against COVID-19 [1,2]. The participant did not receive the second dose.

Sponsor	Seriousness	Group	Sex	Age, years	Time of onset of Bell's palsy, days (after dose #n)	Duration of Bell's palsy, days	Outcome of Bell's palsy at data cutoff
Pfizer-BioNTech	Non-serious	Vaccine	Not available	Not available	3 (2)	3	Resolved with sequelae
Pfizer-BioNTech	Non-serious	Vaccine	Not available	Not available	9 (2)	> 10	Continuing or resolving
Pfizer-BioNTech	Non-serious	Vaccine	Not available	Not available	37 (1)*	> 15	Continuing or resolving
Pfizer-BioNTech	Non-serious	Vaccine	Not available	Not available	48 (2)	> 21	Continuing or resolving
Moderna	Non-serious	Vaccine	Female	72	22 (2)	Not available	Continuing
Moderna	Non-serious	Vaccine	Female	30	28 (2)	Not available	Resolved
Moderna	Serious	Vaccine	Female	67	32 (2)	Not available	Resolving
Moderna	Non-serious	Placebo	Male	52	17 (not available)	Not available	Resolving

pharmacological analysis enabled to propose type I interferons as the potential mechanism. In addition to the temporal association already suggesting a contribution of the vaccine, the following three biological arguments further strengthen this hypothesis.

First, mRNA vaccines are known to elicit a profound response of type I interferons [3], which regulate lymphocyte recirculation and cause transient lymphopenia [4]. On the one hand, transient lymphopenia was precisely the most commonly hematology changes observed in phase 1 clinical trials of mRNA COVID-19 vaccines (i.e. $< 0.8 \times$ lower limit of normal from 1 to 3 days after the first dose). On the other hand, previous studies also described a decrease in CD3 and CD4 cells during the acute stage of Bell's palsy [5].

Second, Bell's palsy is a rare adverse reaction also reported with interferon-α (i.e. a type I interferon) therapy in hepatitis C virus infection. Some authors postulated that interferon-α therapy can cause a breakdown of tolerance to myelin sheath antigens and lead to neuropathy [6]. It is worth noting that autoimmunity against the myelin sheath is suggested to play a role in the pathogenesis of Bell's palsy [5].

Third, in a phase 1 clinical trial of an mRNA rabies vaccine in 101 participants, a case of transient grade 2 Bell's palsy was reported 7 days after the second dose [7]. The strong similarities in terms of time of onset and outcome suggest that Bell's palsy may be a class effect of mRNA vaccines.

To conclude, considering the converging evidence of temporal association and biological plausibility, the contribution of mRNA COVID-19 vaccines to Bell's palsy cannot be excluded, and constitute a signal of pharmacovigilance [8]. Beside idiopathic causes and viral infections including COVID-19 itself [9], mRNA COVID-19 vaccine should therefore be considered as an additional possible cause in the etiology of Bell's palsy.

Disclosure of interest

The authors declare that they have no competing interest.

References

[1] FDA. Vaccines and related biological products advisory committee December 10, 2020 meeting announcement; 2021. https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-december-10-2020-meeting-announcement. [Accessed March 29, 2021].

[2] FDA. Vaccines and related biological products advisory committee December 17, 2020 meeting announcement; 2021. https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-december-17-2020-meeting-announcement. [Accessed March 29, 2021].

[3] De Beuckelaer A, Grooten J, De Koker S. Type I interferons modulate CD8 + T cell immunity to mRNA vaccines. Trends Mol Med 2017;23:216—26.

[4] Kamphuis E, Junt T, Waibler Z, Forster R, Kalinke U. Type I interferons directly regulate lymphocyte recirculation and cause transient blood lymphopenia. Blood 2006;108:3253—61.

[5] Greco A, Gallo A, Fusconi M, Marinelli C, Macri GF, de Vincentiis M. Bell's palsy and autoimmunity. Autoimmun Rev 2012;12:323—8.

[6] Hoare M, Woodall T, Alexander GJM. Case report: Bell's palsy associated with IFN-α and ribavirin therapy for hepatitis C virus infection. J Interferon Cytokine Res 2005;25:174—6.

[7] Alberer M, Gnad-Vogt U, Hong HS, Mehr KT, Backert L, Finak G, et al. Safety and immunogenicity of a mRNA rabies vaccine in healthy adults: an open-label, non-randomised, prospective, first-in-human phase 1 clinical trial. Lancet 2017;390:1511—20.

[8] Moore N, Berdaï D, Blin P, Droz C. Pharmacovigilance — The next chapter. Therapies 2019;74:557—67.
[9] Goh Y, Beh DLL, Makmur A, Somani J, Chan ACY. Pearls & Oy-sters: facial nerve palsy in COVID-19 infection. Neurology 2020;95:364—7.

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Thrombotic events after AstraZeneca vaccine: What if it was related to dysfunctional immune response?

Keywords Thrombosis; Vaccines; COVID-19; Physiopathology; Neutrophil activation

Abbreviations

ACE2	angiotensin-converting enzyme type 2
ADRs	adverse drug reactions
COVID-19	coronavirus disease 2019
EMA	European Medicines Agency
HIT	heparin-induced thrombocytopenia
NET	neutrophil extracellular traps
SARS-COV 2	severe acute respiratory syndrome coronavirus 2
WHO	World Health Organization

As a new wave of the SARS-COV-2 epidemic overwhelms Europe, the vaccine from the Anglo-Swedish laboratory AstraZeneca has come under the spotlight, suspected of having serious thrombotic adverse drug reactions (ADRs) [1]. The first reports of coagulation problems were described in Austria, Italy and the Nordic countries. An unusual number of cerebral venous sinus thrombosis associated with platelet deficiency (thrombocytopenia) and bleeding was reported in Germany. This association was found in 7 cases by 15 March 2021 (date of suspension in Germany) with a temporal association consistent with AstraZeneca vaccination. The 7 affected individuals were women aged 20-50 years; 6 had cerebral venous sinus thrombosis, occurring 4-16 days after vaccination; 3 died. The World Health Organization (WHO) and the European Medicines Agency (EMA) were quick to point out the benefits-risks balance remained in favour of the vaccine, and that there was currently no proven cause-and-effect relationship [1].

In France, over 1,923 million people received the AstraZeneca vaccine between 6 February and 25 March 2021 [2]. A total of 7,439 ADRs were reported of which 91 cases of serious thromboembolic events, including 9 cases of cerebral venous sinus thrombosis, 2 cases of splanchnic venous thrombosis and 1 case of combined stroke/pulmonary embolism/splanchnic venous thrombosis in the context of disseminated intravascular coagulation [2]. These 12 cases of thrombosis of the large veins were atypical in their location (mainly cerebral, but also digestive) and may be associated with thrombocytopenia or coagulation disorders [2]. These cases occurred mostly in women, within a median of 9 days after vaccination in patients mainly under 55 years of age (9 patients vs. 3 over 55 years of age), with no particular history identified to date, apart from oral contraception in 4 cases, associated with a protein C/S deficiency in one fifth and obesity in 1 case. Lymphadenopathy is regularly described. Among them, 4 people died [2]. The very atypical character of these thromboses, their common clinical picture and the homogeneous time of occurrence lead the monitoring committee to confirm the very rare occurrence of this thrombotic risk in people vaccinated with AstraZeneca vaccine [2].

Thrombosis can occur at almost any age depending on comorbidities or genetic factors, in particular sepsis, cancer, prolonged bed rest, active smoking, combined oral contraception, etc. Even if these causes were a priori excluded in these ADRs, the occurrence of thrombosis may be related to one or more of unknown factors. These ADRs may be concomitant with vaccination in the context of a mass campaign during a pandemic. Nevertheless, in order to support the hypothesis of causality between AstraZeneca vaccination and the occurrence of thrombotic events, we propose below a pathophysiological hypothesis involving neutrophils, neutrophil extracellular traps (NET), platelets and innate immunity.

The AstraZeneca vaccine is based on an adenovirus expressing the Spike protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which allows development of a humoral and cellular immune response against