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CASE REPORT

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Immunogenicity and safety of BNT162b2 mRNA COVID-19 vaccine in a subject affected by Shapiro's syndrome: A case report

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ABSTRACT

Shapiro's syndrome (SS) is a rare neurological disorder characterized by spontaneous periodic hypothermia and hyperhidrosis without identifiable systemic causes or brain injuries. We present the case of F. a young patient, without agenesis of the corpus callosum and with episodes of recurrent hypothermia, who was successfully immunized against SARS-CoV-2 via vaccination. F. was born on 2012 and started suffering from episodes of hypothermia at the age of three, with body temperature reaching as low as 32.8°C. Hypothermia episodes were initially associated with ibuprofen intake, but were later defined as symptoms of SS. No SARS-CoV-2 infections had been reported before vaccination. The subject received the first dose of pediatric formulation anti-SARS-CoV-2 Comirnaty vaccine on 11 January 2022 and the second dose on 5 February 2022. A one-week follow-up for adverse events was performed via telephone contact after both administrations. Further contact occurred one month after immunization. Anti-SARS-CoV-2 IgG titers were evaluated fifteen days after administration of the second dose. Following vaccination, slight fluctuations in body temperature and local adverse events were noted. These adverse events were not worrying; the vaccine's safety profile is therefore confirmed. The child also developed an excellent antibody titer ($>28 \times 10^3$ AU/ml), thus suggesting a good immune response.

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Introduction

Shapiro's syndrome (SS), or Spontaneous periodic hypothermia (SPH), is a rare neurological disorder characterized by spontaneous periodic hypothermia and hyperhidrosis in the absence of an identifiable systemic cause or brain injury. It was first described by Shapiro et al.¹ who reported, in 1969, the first two cases of agenesis of the corpus callosum (ACC) associated with episodes of hyperhidrosis and hypothermia. However, agenesis of the corpus callosum only occurs in some patients and is not a diagnostic criterion.^{2–4} Moreover, the hypothermia-hypersudation-corpora callosa agenesis triad was reported in less than half of the cases.⁵ The prevalence of the disease is estimated to be $< 1/1,000,000$ and between 50 and 70 cases are described in literature worldwide.^{2,3,5} It can occur at any age but has most frequently been reported in early childhood, with no gender prevalence.^{2,6} The duration and frequency of the episodes may differ. Episodes of hypothermia can occur without any trigger and in absence of exposure to a known causative factor of hypothermia. The cause and pathophysiological mechanisms of the syndrome remain unknown. The hypothesized causes include hypothalamic dysfunction, neurochemical abnormalities, inflammatory processes and epileptic activity.^{3,6,7,8} Episodic and paroxysmal hypothermia is considered the hallmark of typical and variant SS while other signs and symptoms associated with SS occur with variable frequency during hypothermia.² The clinical signs most frequently associated with hypothermia (defined by the detection of an internal temperature $< 35^\circ\text{C}$) are profuse sweating, nausea and vomiting,

a "strange sensation" referred to the head that is difficult to identify, weakness, unsteady gait, drowsiness, bradycardia, pale and cold skin. In one case, polyuria and polydipsia were described during the episodes.^{9,10} Periodicity of hypothermic episodes may range from hours to years and the episodes themselves may last from hours to weeks. Warming procedures are used during crises. No definitive treatment has been identified for this disorder and various pharmacological approaches have been tested with modest and variable results. Anticonvulsant agents seem to have the highest probability of success.^{11,12} Improvements have been described with the use of clonidine, cyproheptadine, carbamazepine, amobarbital, glycopyrrolate, clomipramine and acetazolamide.² However, the disease has a generally benign course and may resolve spontaneously.¹³

Due to the extremely rare prevalence, there is no data about the safety and the immunogenicity of vaccination among patients affected by SS, and vaccination can be suspected to be a trigger of crisis.

Patient history and case presentation

We present the case of a young patient, without agenesis of the corpus callosum and with episodes of recurrent hypothermia, who was successfully immunized against SARS-CoV-2 via vaccination. F. was born on 2012 at the 40th week of gestation by urgent cesarean section for pregnancy characterized by gestosis. The weight at birth was 3,290 kg. Jaundice was detected and treated with phototherapy; otherwise, perinatal anamnesis was normal.

The first stages of neuropsychomotor development were reported at the appropriate time and vaccinations were carried out according to the vaccination schedule without any significant adverse events. Starting at 3 years of age, episodes of hypothermia (with a minimum temperature reached of 32.8 °C) were reported and were initially associated with ibuprofen intake, during febrile or afebrile inflammatory events. Typically, hypothermia was associated with severe asthenia, algid sweating, bradycardia and drowsiness that resolved with active and passive heating maneuvers, and temperature rose gradually over a few days. During the first episode, the child was 3 years old. Following an episode of hyperthermia (40°C) that did not resolve with paracetamol, the child was conducted in an emergency department where he received ibuprofen. Shortly afterward, the temperature dropped sharply to 33.5°C and symptoms appeared.

Subsequently, other episodes of hypothermia appeared, characterized by asthenia, frontal headache, painful sensation in the eyeballs, bradycardia, abdominalgia and vomiting, lasting a few hours. These symptoms resolved after heating maneuvers. Because of the recurrence of these episodes, the patient underwent cardiological evaluation (ECG, echocardiography, dynamic Holter), which proved negative. During neurological evaluation, Shapiro's syndrome was suspected. Routine haematochemical examinations were also prescribed, and a modestly elevated (10%) eosinophil count (860 E/mm³) was noted. Following pneumo-immunoallergological assessment, the occasional finding of eosinophilia in the absence of other symptoms was considered of no clinical significance, while the hypothermia finding, apparently correlated with the administration of ibuprofen, was considered to be linked to an idiosyncratic reaction that was probably nonimmune-mediated. Skin allergy tests for inhalants were also negative. The neurologist and allergologist agreed that non-steroid anti-inflammatory drugs (NSAIDs) had to be avoided, and only paracetamol should have been used as an antipyretic and analgesic.

In April 2021, the patient was admitted to the Neurology Unit of "Giovanni XXIII" Hospital of Bari Policlinico for diagnostic evaluation. At the admission, his body temperature, heart rate, blood pressure and heart rate were monitored and found to be within normal limits. The electrocardiogram and brain MRI did not reveal any abnormalities. In particular, MRI of the brain performed without contrast agent and completed with diffusion study did not reveal areas of altered signal intensity or reduced diffusivity in either the supra- or sub-tentorial brain tissue. The midline structures were on axis, the ventricular system was symmetrical and undilated, and the pericerebral subarachnoid spaces were regularly represented. The haematochemical examinations showed pathological values of Vanilmandelic acid (12.7 mg/24 h, with normal value <6,4 mg/24 h), C-Peptide (5.4 ng/mL with a normal range of 1.1–4.4 ng/mL), cortisol (256 µg/µL with a normal range of 48–195), insulin (51.9 microUI/mL with a normal range of 2.6–24.9 microUI/mL) and glycemia (121 mg/dL, with a normal range of 74–106 mg/dL). Genetic-metabolic counseling was therefore requested and in-depth tests were scheduled to investigate the occasional finding of hyperglycemia with probable reactive hyperinsulinism and hypercortisolism. The glycosylated hemoglobin assay, however, showed a normal value (5.1%, normal range 4–6%). The conclusion

was "occasional hyperglycemia and hypercortisolism in the diagnostic phase." The child was discharged with the diagnosis of suspected Shapiro's syndrome. The mother frequently measured the child's temperature and found, under normal conditions and in the absence of symptoms, axillary temperatures between 35°C and 36°C. In the child's history, conditions of sudden changes of the body temperature have been recognized as triggers capable of causing symptoms. In particular, those induced by febrile episodes, and especially in the defervescence phase, intake of antipyretic drugs, and environmental exposure to sudden temperature changes, such as moving from an air-conditioned indoor environment to outdoor spaces. In the last year, however, a more rapid recovery from hypothermia after warming maneuvers was reported than in the past.

No SARS-CoV-2 infections have been reported for the child since March 2020 to December 2021. The child received the first dose of pediatric formulation anti-SARS-CoV-2 Comirnaty vaccine on 11 January 2022 and the second dose on 5 February 2022.

Comirnaty is a messenger RNA (mRNA) based vaccine against coronavirus disease, manufactured by Pfizer for BioNTech.¹⁴ The first dose of vaccine was administered during a Day-Hospital hospitalization in the Neurology Unit of Children Hospital "Giovanni XXIII" - Bari Policlinico University Hospital. On admission, the child's parents reported two further episodes of hypothermia following the previous hospitalization, which were resolved after a few minutes through warming maneuvers. During hospitalization, after the vaccine's administration, neurological examination and electrocardiogram were performed, highlighting no pathological signs; therefore, the child was sent back home. Follow-up by telephone calls to monitor symptoms was carried out.

Results

Pain near the injection site was reported on the first day following immunization. During the first 48 hours after the vaccine, the body temperature was kept under control: measures at the hospital and at home ranged from 36.3°C to 36.7°C the average of the measurement was higher than the child's usual temperature. On the third day after vaccination, the temperature ranged between 35°C and 36°C. Until the second dose was administered, no further pathological fluctuations of the body temperature were reported, with values close to 36°C. On 5 February 2022, at 10:52 a.m., the child returned to the Hospital Vaccination Point of Bari Policlinico in order to complete the vaccination cycle and he received the second dose of vaccine on an outpatient basis. On Saturday (5th) and Sunday morning (6th), the child showed no symptoms. On Sunday afternoon, the body temperature was 37.2°C with no other symptoms of clinical significance. Half an hour after the appearance of fever, the temperature was back to 36°C. At the same time, abdominal pain and tension, localized eyesore, a feeling of thirst with polydipsia and subsequent polyuria were reported. Over the next thirty minutes, the body temperature rose to 37°C and then fell to the lowest temperature of the day, 35.7°C. On Sunday evening, a stable 36°C body temperature was measured. On Monday 7th, Tuesday 8th and Wednesday 9th February, the child felt fine, with a stable

body temperature of 36.5°C From Thursday 10th to Sunday 13th, the temperature fell and then stabilized at 35.6–35.7°C On Sunday afternoon, the temperature fell to 34°C Skin paleness and a feeling of cold appeared. Warming maneuvers with blankets and hot drinks were carried out causing the temperature to rise to 35.6°C On February 14th morning, the temperature reached 35.7 and remained fairly stable during the following days. One month later the mother was contacted again for further updates. The mother reported that the child was fine and that there had been no need for further temperature monitoring. 15 days after the administration of the second dose, a blood sample was taken to assess the antibody titer developed after the immunization program. The assay we employed is called SARS-CoV-2 IgG II Quant, a chemiluminescent microparticle immunoassay (CMIA), used for the qualitative and quantitative determination of IgG antibodies to SARS-CoV-2 in human serum on the ARCHITECT I System; this assay is used to monitor antibody response in individuals that have received the COVID-19 vaccine, by quantitatively measuring IgG antibodies against the spike receptor-binding domain (RBD) of SARS-CoV-2. The quantitative anti-SARS-CoV-2 IgG assay of the patient after two weeks from the 2nd dose tested positive, with a titer of $28,9 \times 10^3$ AU/ml.¹⁵

Discussion

Shapiro syndrome is a rare, orphan disease and guidelines for the immunization of patients affected by this condition are not available, due to its rarity. The idea that the vaccine could be a trigger of hypothermia may cause fear among parents and healthcare workers; this could determine vaccine refusal, as the fear of adverse events is proven to be the most important cause of vaccine hesitancy.^{16–18} In our experience, vaccination was showed to be safe. The analysis of the case report revealed that in the days following the first dose of COVID vaccine, slight fluctuations in body temperature were noted, but always within physiological range (T max 36.7°C - T min 35 °C) and in absence of associated symptoms. The day after the administration of the second dose, the child developed fever (37.2°C). This adverse event is also documented and reported as very common; the slight increase in temperature regressed without drug treatment within 30 minutes. Subsequently, temperature fluctuations were recorded (minimum temperature reached 35.7°C) in association with the symptoms usually reported during previous temperature excursions, especially when the decrease in body temperature is particularly rapid (abdominalgia, abdominal tension, localized pain in the eyeballs, thirst with polydipsia and polyuria). However, temperature changes and symptoms resolved independently by nightfall. After the first dose, our patient developed arm pain, which is among the very common reactions ($\geq 1/10$) reported in the package insert of the product Comirnaty.¹⁹ Eight days after vaccination, a new drop in temperature (34°C) appeared, in association with skin pallor and feeling of cold. It disappeared with warming maneuvers shortly afterward: using blankets and hot drinks the temperature rose again to 35.6°C.

The adverse events developed after vaccination and the temperature oscillations reported by the patient were not serious or worrying, therefore the safety profile of the vaccine seems acceptable. The antibody titer developed by our patient is suggestive of a good immune response elicited by the vaccine. Therefore, the immunogenicity profile was maintained. The importance of vaccination in our patient is corroborated by the theoretical risk of developing critical episodes of hypothermia during COVID-19 disease. People with COVID-19 have reported a wide range of symptoms, ranging from mild symptoms to severe illness. Symptoms of COVID-19 include fever, chills, cough, shortness of breath or difficulty breathing, sore throat, congestion, nausea, vomiting, diarrhea, fatigue, muscle or body aches, headache and others. Moreover, persistence of symptoms after the acute phase of the infection is not rare.^{20–22} A large number of effects related to nervous system involvement have been described, too. Predicting the risks and evolution of the disease in a child with our patient's susceptibility factors is difficult.

Lamotte et al.²³ described the case of a woman with exacerbation of paroxysmal hyperhidrosis and hypothermia after COVID-19 infection, which required an increase in the dosage of clonidine normally administered. Scientists correlated the pathophysiology of Shapiro syndrome, probably in part related to hypothalamic dysfunction,¹ with the evidence that SARS-CoV-2 can lead to hypothalamic dysfunction via direct invasion of the virus and/or reactive inflammation with the olfactory tracts as a port of central nervous system entry. In their study it was hypothesized that COVID-19 infection could have exacerbated dysfunction in the medial preoptic area containing warm-sensitive neurons, triggering excessive sweating and thus hypothermia and exacerbating the preexisting symptoms of Shapiro syndrome.^{24,25}

Shapiro syndrome is extremely rare and a significant limitation in vaccinating individuals with rare diseases is the lack of scientific evidence to support the choices of health care providers and patients. This problem also applies to COVID vaccines. In fact, there is no data about immune response of patient with SS to active immunization, in general; moreover, as far as we know, this report is the first that documented a pediatric SS patient's response to COVID19 vaccine. Currently, the Pfizer-BioNTech COVID-19 vaccine is the only one available for the vaccination of children aged 5–11 years in Europe. For such a recently approved vaccine and for such a rare disease, it is hard to have data on the safety, the effectiveness, the possible side effects and the benefits of getting vaccinated. Therefore, in the absence of scientific evidence, we must rely on assessments of precaution and biological plausibility. Our patient had received all the routine vaccinations required by the childhood schedule without reporting any notable adverse events, but at the time of immunization the diagnosis of Shapiro Syndrome was not made. Due to the diagnosis, Family Pediatrician and out-hospital vaccination clinic required that the patient were evaluated in the Hospital Center for vaccination, because of the fear of adverse events. While we had no reason to believe that the patient would have an impaired immune response to vaccination, our main focus was investigating the safety profile of vaccination with recently approved vaccine in a patient with a very rare disease. Our case report seems to show that administration of the anti-SARS-

CoV-2 vaccine was safe and effective for our patient, as supported by the presence of minimal adverse effects and the development of a good antibody response.

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