Hyper Production of Anti Spike Antibodies and Rheumatological Manifestations: Coincidence or Pathogenesis?

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Article

Hyper Production of Anti Spike Antibodies and Rheumatological Manifestations: Coincidence or Pathogenesis?

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Abstract

Introduction: Vaccine is the most widely used public health measure to control the global COVID-19 pandemic. Most of the vaccines used in Europe and North America are mRNA-based vaccine A mass vaccination campaign was carried out between 2021 and 2024. Some adverse events have been reported. We question the role of vaccines in the pathogenesis of rheumatological manifestations observed following one or more injections. Material and methods: A prospective observational study involving two cohorts was initiated, with the first cohort observed from 13th September 2021 to 30th September 2022, and the second cohort from 1st October 2022 to 30th September 2023. The study also focused on the interval between the last vaccine injection and the onset of rheumatic symptoms. None of the patients had a history of rheumatic or inflammatory diseases. We compare both cohorts and ankle arthritis case series to analyze the differences between early and late onset adverse events patients. Results: In both cohorts and case series, the majority of patients are women. The most common symptoms include diffuse muscle pain, which mimics polymyalgia rheumatica and ankle arthritis. Very high levels of anti-Spike antibodies (> 2080 BAU/ml) were generally detected. Pearson correlation coefficient between both cohorts and case series is very high, confirming the reproducibility of post-vaccine clinical and biological features. Conclusion: These rheumatological manifestations might be triggered by inappropriate individual immune responses to the vaccine's Spike protein and/or the overproduction of Spike protein, which can mediate a pro-inflammatory reaction explaining early and late-onset effects.

Keywords: COVID 19-vaccine; anti-Spike antibodies; averse events; arthritis

Introduction

Vaccine is the most widely used public health measure to control the global COVID-19 pandemic. Most of the vaccines used in Europe and North America are mRNA-based vaccines (BNT162b2 and mRNA-1273), but DNA vaccines (ChadOx1 and CoV-19) are also used [1,2]. A mass vaccination campaign was launched between 2021 and 2024. Some adverse events have been reported in relation to this vaccine and several rheumatological events have been documented [3,4]. We question the role of Covid 19 vaccines in the pathogenesis of rheumatological manifestations observed following one or more injections.

Material and Methods

This clinical study was approved by Saint-Jean hospital's ethical board in accordance with the Belgian Law regarding the use of medical data which is available for any additional request. All patients were examined and followed in the same rheumatology department. A prospective observational study of 2 cohorts was launched from 13th September 2021 to 30th of September 2022 for the first one and from 1st October 2022 to 30th of September 2023 for the second one. After the first

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year, we focused also the observational study on the delay between the last vaccine injection and the beginning of rheumatic symptoms. We exclude of the studies all patients having a past of rheumatic or inflammatory diseases. Patients treated for depression, fibromyalgia or chronical widespread pain were also excluded. Out of a series of 184 patients having muscle, joint and skeletal claims after Covid vaccination we report a first cohort of 124 patients without interferent diseases having developed rheumatological manifestations which occurred after vaccination with an RNA vaccine coding for the SARS-CoV-2 spike protein (120/124) or an DNA vaccine (4/124). Out of 156 patients, 31 were excluded using the same criteria and a second cohort of 125 patients having developed late onset adverse events is studied. None of the patients had a history of rheumatological disease or developed rheumatological disease during the follow-up. All causes of rheumatic diseases were excluded by a full biological examination, adequate imaging according to the clinic. A post-vaccination blood serological follow-up for anti-spike antibodies was requested a several times for all patients at the diagnosis and during the follow-up. None of the subjects had a suspicion of viral infection as confirmed by the diverse samplings collected. All the patients were treated with an oral low dose of methylprednisolone 8mg/day reduced to 4 mg/day after 2 weeks. We double checked the medical history of each patient by consulting ABRUMET (professional access to general patient medical data base) according to the Belgian law. None of the patients developed any other disease after at least 18 months of follow-up. All patients underwent serological testing for SARS-CoV-2 after vaccination. IgG antibodies anti-Spike to SARS-CoV-2 were determined on LIAISON XL (DiaSorin S.p.A., Saluggia, Italy) using the IgG SARS-CoV-2 Trimerics reagent (DiaSorin S.p.A.). The measurement range was between 4.81 and 2080 BAU/mL, with a threshold of 33.8 BAU/ml. According to the company, a value of 520 BAU/mL or more corresponds to a high neutralization capacity of the antibodies. As this serological test is not reimbursed by the Belgian social security, each patient had to pay for it. Because of ethical board restriction, we were only allowed to use the serological results of our own vaccinated patients as control group followed at the consultation with other diagnoses. A vaccinated control group of 59 subjects (mean age 56 years old, 43 females and 16 males) does not reveal such a high level of anti-Spike antibodies in the blood sample. The mean anti-spike antibody level in the control group was 486,7 BAU/ml (4.8 – 842). We also tested 6 unvaccinated patients of our own consultation to assess the control group (mean value 54 BAU/ml). We questioned each patient about any declaration of adverse events. We use the Pearson test to compare early and late onset cohorts and bilateral ankle arthritis after vaccination and examine the potential link between Covid-19 vaccines and new or recurrent sarcoidosis.

Results: Tables 1–3.

Table 1. Cohort description.

	Patients	Age		gender		Ethnic			Vaccines		Vaccine doses / delay days	
		F	M	F	M	Caucasian	Black African	Asian	mRNA	DNA	1st/delay 3d/delay	2d/delay 4th/delay
Cohort1	124	54,6	59,6	87	37	79F/32M	7F/3M	1F/1M	120	4	17/12,5d 55/30,5d	50/20,3d 4/30,5d
Cohort2	125	41,2	50,6	94	31	86F/29M	7F/0M	1F/2M	123	2	4/12,5d 58/>113d	45/>122d 18/>126d

Table 2. Clinical features.

	Polymyalgia	Ankle arthritis	Fingers hands wrist	Knees arthritis	Hips arthritis	Ploy - oligo arthritis	Combination	diverse
Cohort1	73	38+1	13	9+1	2	1	19	0
Cohort2	53	37	33	15+9	3	1	24	2

Ankle arthritis ; 38 bilateral + 1 unilateral;Fingers , hand and wrist : arthritis and arthralgia; knees arthritis: 9 and 15 bilateral , 1 and 9 unilateral arthritis.

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Table 3. Biological characteristics.

	Anti-Spike BAU/ml		High SR mm/h		High CRP mg/l		ANA	RF	Anti CCP
	>2080	1000 -2080	Patient/ mean value		Patient/ mean value				
Cohort 1	104	20/ 1318	32F/41mm/h	8M/46,mm/h	32F/14,6mg/l	8M/26,3 mg/l	3	0	2
Cohort 2	96	29/1434	35F/19mm/h	9M/15,7mm/h	35F/7,04mg/l	9M/12,2 mg/l	8	1	3

Anti Spike antibodies :plasmatic level in BAU/ml , high RS or CRP : cohort 1 40pateitns cohort 2 46 patients , ANA antinuclear antibodies , RF rheumatoid factor , anti CCP anti citrullinated peptide.

Cohort 1

Among the 124 patients (median age 51.6 years [17-86 years]), 37 are men (33 Caucasians, 3 Africans, 1 Asian) and 87 (70%) are women (median age 54.6 years [20-80 years]), including 79 Caucasians, 7 Africans, and 1 Asian. Of these patients, 73 (58.9%) had polymyalgia, 38 (30.6%) had bilateral ankle arthritis, 1 had monoarthritic of the ankle, 13 (10.4%) had arthritis of the fingers, hand, or wrist, 9 (7%) had arthritis of both knees, 1 had monoarthritic of the knee, 2 had arthritis of the hips, and 1 had seronegative polyarthritis. A combination of rheumatological symptoms occurred in 19 patients. Antinuclear antibodies (ANA) were detected in 3 patients, and anti-citrullinated peptide antibodies (anti-CCP) were detected in 2 patients. Most symptoms appeared after the 2nd or 3rd dose of the vaccine: 17 cases on average 12.5 days (range 1-42 days) after the first dose, 50 cases on average 20.3 days (range 1-90 days) after the second dose, 53 cases on average 30.5 days (range 1-90 days) after the third dose, and 4 cases on average 30.5 days (range 1-90 days) after the fourth dose. Very high levels of anti-Spike antibodies (> 2080 BAU/ml) were found in 104 cases (84%), and high levels (average 1318 BAU/ml) were found in 20 cases (16%). In some cases, the anti-Spike antibody level increased during follow-up in the absence of a proven COVID-19 infection or vaccine booster and correlated with an outbreak of muscle or joint pain. At the beginning of the follow-up, a biological inflammatory syndrome characterized by elevated sedimentation rate (SR) and/or C-reactive protein (CRP) was found in 40 out of 124 patients (32%), especially in women (32 out of 40, 80%). The mean SR/CRP values were 41 mm/h / 14.6 mg/l in women and 46.5 mm/h / 21.3 mg/l in men. Even if most patients had no inflammatory abnormalities, they were symptomatic and responded to a low dose of 8 mg methylprednisolone per day, which was rapidly reduced to 4 mg per day."

Cohort 2

Among the 125 patients (median age 50.6 years [28-85 years]), 31 are men (29 Caucasians and 2 Asians) and 94(75%) are women (median age 41.2 years [17-85 years]), including 86 Caucasians, 7 Africans, and 1 Asian. Of these patients, 53 (42.4%) had polymyalgia, 37 (29.6%) had bilateral ankle arthritis, 33 (26.4%) had arthralgia or arthritis of the fingers, hand, or wrist, 15 (12%) had arthritis of both knees, 9 (7.2%) had monoarthritic of the knee, 3 had arthritis of the hips, and 1 had seronegative polyarthritis. A combination of these rheumatological symptoms occurred in 24 patients. Anti-nuclear antibodies (ANA) were detected in 8 patients, rheumatoid factor in 1 patient, and anti-citrullinated peptide antibodies (anti-CCP) in 3 patients (2 slightly positive and 1 with high levels). Most symptoms appeared after the 2nd or 3rd dose of the vaccine: 4 cases on average 12.5 days after the first dose, 45 cases on average at least 122 days after the second dose, 58 cases on average at least 113 days after the third dose, and 18 cases on average at least 126 days after the fourth dose. Very high levels of anti-Spike antibodies (> 2080 BAU/ml) were found in 96 cases (76.8%), and high levels (average 1435 BAU/ml) were found in 29 cases (23.2%).A biological inflammatory syndrome characterized by elevated sedimentation rate (SR) and/or C-reactive protein (CRP) was found in 46 out of 125 patients (36.8%), with 35 out of 49 women (71.4%) affected. The mean SR/CRP values were 19 mm/h / 7.04 mg/l in women and 15.7 mm/h / 12.2 mg/l in men. Most patients in the second cohort had no inflammatory abnormalities; they were symptomatic and responded equally to a low dose of 8 mg methylprednisolone per day, which was rapidly reduced to 4 mg per day (the same treatment and follow-up as for the first group).In both cohorts, none of the patients reported any adverse events related to COVID-19 vaccines due to fear and lack of knowledge about the reporting process. No

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serum sickness related to high levels of anti-Spike antibodies was observed. The Pearson correlation coefficient between both cohorts is very high (0.95), confirming the reproducibility of clinical and biological features.

Comparison between early and late onset bilateral ankle arthritis (Tables 4 and 5).

Table 4. comparison control group, early-onset, and late-onset case series.

Patients			**VS/CRP**		**Number Vaccine doses**				**Anti Spike anti bodies BAU/ml**		
	Age	gender	VS mm/h	CRP mg/l	Johnson	Astra Zeneca	Moderna	Pfizer	>2080	1000-2080	<1000
59 Control	56	43F/16M			2	32	23	72	0	0	59
17 Early	51,8	13F /4M	27,7 (3-85)	23,7(2-69)	0	2	3	20	13	1	2
17 Late	57,1	14F /3M	26,6 (2-73)	9 (2-52)	0	8	4	35	10	5	2

Table 5. Clinical characteristics of the late-onset arthritis patients.

Case	Sex/Age	Ethnic	vaccine	Clinical features	ESR (mm/h)/ CRP (mg/l)	SarsCov2 S IGG AB (delay)
1	F/48	Caucasian	Pfizer x2	Ankle R+L	73/4	>2080(17months)
2	F/75	Caucasian	Pfizer x3	Ankle R +L	48/9	>2080(19months)
3	M/60	Caucasian	Pfizer x3	Ankle R +L	7/2	1300 (22months)
4	F/52	Caucasian	Pfizer x3	Ankle R+L	22/4	>2080(13months)
5	F/53	Caucasian	Pfizer x3	Ankle R+L	15/2	425(15months)
6	M/50	Caucasian	Pfizer x3	Ankle R +L	26/21	>2080(13months)
7	F/80	Caucasian	Moderna x3	Ankle R+L	30/04	>2080(16months)
8	F/74	Caucasian	Pfizer x3	Ankle R +L	11/52	>2080(15months)
9	F/54	Caucasian	AZ x2	Ankle R +L	39/15	1280(22months)
10	F/68	Caucasian	AZ x2 Pfizerx1	Ankle R +L Knee R	21/02	1680(17months)
11	F/55	Caucasian	Pfizer x2	Ankle R +L	39/4	>2080(25months)
12	M/69	Caucasian	AZx2 Pfizerx2	Ankle R +L	6/2	641(8months)
13	F/39	Asian	Pfizerx2Modernax1	Ankle R +L	30/06	>2080(17months)
14	F/48	African	Pfizer x2	Ankle R +L	56/8	1530(20months)
15	F/38	African	Pfizer x3	Ankle R +L	19/10	1550(11months)
16	F/49	African	AZx2Pfizerx1	Ankle R +L	2/6	>2080(19months)
17	F/57	Caucasian	Pfizerx2Modernax1	Ankle R +L. Knee R+L	9/3	>2080(21months)

We compare the 17 first patients of cohort having late-onset bilateral ankle arthritis with

our initial case series. Among the 17 patients (median age 57.1 years [38-85 years]), 14 are women, with 10 identifying as Caucasian, 3 as Black African, and 1 as Asian. The 3 men are all Caucasian. Three women developed bilateral ankle arthritis six months or more after receiving two doses of mRNA vaccines, one after two doses of DNA vaccines, twelve (ten women and two men) after three doses, and one man after four doses. Only three patients had received a DNA vaccine before the mRNA boosters (one or two doses). The late-onset case series is compared with our initial published series of early post-vaccine ankle arthritis. Clinical and biological features between early and long-latency patients are summarized in Table 4. High levels of anti-Spike antibodies were detected in blood samples at the time of diagnosis, and these elevated levels persisted in 9 of the 17 patients studied for more than 11 months after the diagnosis of ankle arthritis. Among these cases, four experienced a relapse of bilateral ankle arthritis. The number of vaccine doses is higher in the late-onset series (47) than in the early-onset group (25). The number of DNA and RNA vaccine doses received is also higher in the late-onset group (8 DNA/39 RNA doses) than in the early-onset case series (2 DNA/23 RNA doses). We also focused on the delay between the last vaccine dose and the rheumatological diagnosis. The mean delay

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is 17 months in the late-onset group and 0.44 months in the early-onset case series. Excluding the delay parameter, the Pearson correlation coefficient (0.91) between both case series confirms clinical reproducibility.

Flare and new onset of sarcoidosis (Table 6).

Table 6. Flare and new onset of sarcoidosis.

	age	gender	ethnic	biology		Anti spike BAU/ml	clinical	vacce	delay
				SR mm/h	CRP mg/l				
1	27	F	Black African	27	16	>2080	Ankle L+R	Modernax2	7days
2	66	F	Black African	44	17	1780	Ankle L+R	AZx2	5 days
3	38	F	Black African	6	4	>2080	Ankle L+R	Pfizerx2	7 days
4	33	F	Maghreban	50	24	>2080	Ankle L+R and mediastinal lymphadenopathy	Pfizerx2	3months
5	43	M	Black African	32	24	1250	Ankle L+R	Modernax2	>6months
6	48	F	Black African	20	2	>2080	Ankle L+R	PfizerX2	?

Patients experiencing a new onset or flare of sarcoidosis after receiving COVID-19 vaccines developed also bilateral ankle arthritis. Three patients developed symptoms shortly after the second dose of the COVID-19 vaccine (one DNA and two mRNA), while two others had a delayed onset (both with mRNA vaccines). The sixth patient could not specify the delay between the last vaccine and the onset of the articular flare. All individuals exhibited elevated levels of anti-Spike protein, with women constituting most participants (five out of six). The clinical evolution was favorable under treatment with a low dose of prednisolone.

Discussion

In both cohorts and case series, a vast majority of patient are women, experiencing more often than men, a biological inflammatory syndrome. The strong affinity of Spike protein to estrogenic alpha receptors [5] may explain the female gender ratio of the rheumatologic adverse event. The most common complaint is diffuse muscle pain mimicking polymyalgia rheumatica [6,7] in presentation but occurring on average in the early 50s and often without inflammatory syndrome. As most causes of diffuse pain have been excluded, low-dose corticosteroid treatment (8 mg methyl prednisolone/day reduced to 4 mg/day) has been administered as for the other clinical manifestations and has been effective in most cases 65 /73 (cohort 1) and 35/53 (cohort 2).The most frequent joint involvement is bi arthritis of the ankles [8] (38 +1unilateral ankle arthritis -31% in cohort1 and 37 cases- 29,6 % in cohort2. New cases of inflammatory mono/oligo arthritis involving the ankle are more likely to be due to reactive undifferentiated arthritis or spondylarthritis than rheumatoid arthritis and microcrystalline arthritis [9]. Abhishek and colleagues reported that in the Birmingham early inflammatory arthritis (BEACON) cohort, patients with bilateral ankle synovitis were more likely to be classified as having acute sarcoid arthritis [10]. We remind that all those diagnoses were excluded from both cohorts. About 75 cases of acute sarcoidosis are expected to be diagnosed in one year for the Brussels region and shared into 13 hospitals. The 6 patients (excluded of both cohorts) having previously an articular sarcoidosis and those who developed a flare or a sarcoidosis after vaccination [11–13] confirm the normal incidence of the disease diagnosed in our department and are questioning about the significance of the high level of anti-Spike antibodies and the role of spike protein in the occurrence of inflammatory articular manifestations. We find totally 46 (13 early onset cohort +33 late onset cohort) cases of arthralgia, arthritic fingers and wrists without any erosions. No other cause is discovered during the follow-up as well for patients having other articular locations (knees or hips). No patients exhibited serum sickness symptoms associated with elevated anti-Spike protein levels. These biological findings do not monster abnormal frequency of ANA, RF or anti CCP and suggest a cellular rather than humoral inflammatory reaction [14]. Mostly, the evolution

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was favorable each time when low-dose corticosteroids were taken. The lack of satisfactory response to corticosteroids seems to be related to the long persistence or increased of very high levels of anti-Spike (> 2080 BAU/ml). Whatever, the significance of anti-Spike antibodies remains unclear, a high level of anti-Spike IGG antibodies was also detected in young patients who have developed post-vaccination myocarditis, especially in the presence of a high amount of Spike protein [15]. Even if the average age of late-onset patients is higher (51 years), we can also accredit the presence of high levels of anti-Spike IGG antibodies at the time of diagnosis and during the follow-up. Although we cannot exclude the possibility that the onset of arthritis/polymyalgia after mRNA vaccination is a coincidence, the similarities between these 2 cohorts and the number of cases post vaccine over a short period of time might suggest some pathogenic causation. Normally, the level of post-vaccine induced IGG anti-Spike lowered in 5 to 6 months, justifying the booster vaccine program [16] and after a 3rd dose of RNA vaccine, there is a reduction in anti-spike levels from the 3rd month [17]. The presence of SARS-CoV-2 Spike antibodies at least more than 8 months after a vaccine dose is questioning the physiopathology of early and late-onset arthritis post-RNA vaccine. Vaccine dose count is higher in the late-onset ankle arthritis case series (47injections) than in the early-onset group (25 injections). The comparison of early and late-onset ankle arthritis reveals that the late-onset group received a higher number of DNA and RNA vaccine doses (8 DNA/39 RNA doses) compared to the early-onset case series (2 DNA/23 RNA doses). Additionally, the mean delay between the last vaccine dose and the rheumatological diagnosis is 17 months in the late-onset group, while it is only 0.44 months in the early-onset case series. The mechanism of COVID-19 vaccines is entirely different from that of live attenuated virus vaccines thus rendering the analogical reasoning regarding the potential side effects incomplete. Post COVID-19 vaccine late-onset adverse events prompt us to explore alternative pathway [18]. In vitro studies demonstrate the integration of RNA spike sequences in human cells [19,20]. Spike protein could be the key to fixing the Angiotensin 2 receptors [17,21] and Toll-Like receptors 4 and 2 [17,22] implicated in an increased production of pro-inflammatory cytokines. Moreover, the strong affinity of Spike protein to Estrogen receptor alpha [5,7] may explain why women are mostly involved. The number of injected DNA and RNA vaccine doses and the delay between the date of the last vaccine dose and the time of the rheumatological diagnosis might also argue that Spike protein could mediate early and delayed adverse events.

Bradford Hill Criteria

This observational study satisfies all the Bradford Hill criteria. The high correlation coefficient observed in both cohorts and case series demonstrates the coherence and reproducibility of clinical and biologicals rheumatologic symptoms that manifest post-vaccination indicating temporality. Most of patients experienced adverse events following the 2^{d} or 3^{d} doses and those with delayed onset ankle arthritis were vaccinated more frequently than those with early onset symptoms (dose effect). Recent works demonstrate the plausibility of the facts and the pro inflammatory potential of spike protein

Conclusions

When encountering new cases of polymyalgia, arthritis, and particularly bilateral ankle arthritis in healthy individuals without any personal or family history of inflammatory diseases, it is essential to consider other potential causes of rheumatic or inflammatory diseases alongside post-vaccine adverse events. A strong positive result for plasmatic level of anti-Spike protein suggests that these rheumatological manifestations might be triggered by inappropriate individual immune responses to the vaccine's Spike protein and/or the overproduction of Spike protein, which can mediate a pro-inflammatory immune response explaining early and late-onset effects tables.

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Institutional Review Board Statement: The study was approved by the ethical board of the Clinique Saint-Jean according to the Belgian law. As specified in the observational study protocol submitted to the ethical board, anonymous data and clinical features as pictures of the patients were allowed to be collected during the consultation.

Informed Consent Statement: Pictures of the joints were performed during common consultation with the consent of the patients.

Conflicts of Interest: The authors declare no conflict of interest

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