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IgA-diseases associated to SARS-CoV-2 infection or vaccination: a systematic literature review

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Abstract

Coronavirus disease 2019 (COVID-19) and vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been associated with autoimmune phenomena. However, the interplay between SARS-CoV-2 infection or vaccination against it and Berger glomerulonephritis or Henoch-Schönlein vasculitis, two diseases mediated by immunoglobulin A, has never been comprehensively investigated. Therefore, we carried out a systematic review of the literature on this topic. Following databases were used: Google Scholar, Excerpta Medica and the United States National Library of Medicine. Eighty-seven patients with immunoglobulin A-mediated diseases associated with SARS-CoV-2 infection or vaccination against it were sorted out (53% males, 47% females; 34 [17-51] years of age, median and interquartile range): 47 cases of Berger glomerulonephritis and 40 of Henoch-Schönlein vasculitis. Approximately 50% (N=24) of Berger glomerulonephritis and 10% (N=4) of Henoch-Schönlein vasculitis patients presented with a pre-existing history of immunoglobulin A-mediated disease. Almost all cases of Berger glomerulonephritis were vaccine-associated (N=44; 94%), while most cases of Henoch-Schönlein vasculitis were infection-associated (N=23; 57%). Among vaccine-associated immunoglobulin A diseases, about 90% were associated to mRNA-based vaccines. Our analysis supports the hypothesis that SARS-CoV-2 infection coronavirus disease 2019 and vaccination against it may trigger or exacerbate an immunoglobulin A-mediated diseases.

Keywords

Berger glomerulonephritis ● Coronavirus 2019 ● COVID 19 ● Henoch-Schönlein vasculitis ● Immunoglobulin A nephritis ● Immunoglobulin A vasculitis ● Vaccination ● SARS-CoV-2
Introduction

Henoch-Schönlein vasculitis and Berger glomerulonephritis are characterized by tissue deposition of immunoglobulin A [1, 2]. The onset of Henoch-Schönlein vasculitis [1] is often preceded by a common respiratory disease or a vaccination. Similarly, both the acute onset and the recurrences of Berger glomerulonephritis, may be preceded by a respiratory disease or a vaccination [2].

Coronavirus disease 2019 (COVID-19) and vaccination against the virus causing it, i.e. severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may trigger autoimmune phenomena [3]. However, little is known about the interplay between SARS-CoV-2 and immunoglobulin A-mediated diseases. Hence, we carried out a systematic review of the literature to determine whether COVID-19 or vaccination against SARS-CoV-2 may be temporally related to a new-onset, or a flare, of an immunoglobulin A-mediated disorder.

Methods
Search strategy

This review was undertaken in agreement with the 2020 edition of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses methodology [4]. Google Scholar, Excerpta Medica and the United States National Library of Medicine were explored in March 2022 (and before submission) without limitations for original articles or letters using following terms entered in separate pairs: “anaphylactoid purpura” OR “Henoch-Schönlein” OR “Henoch” OR “IgA purpura” OR “IgA vasculitis” OR “immunoglobulin A purpura” OR “immunoglobulin A vasculitis” OR “rheumatoid purpura” OR “Henoch-Schönlein” OR “Berger disease” OR “Berger nephritis” OR “Berger glomerulonephritis” OR “IgA purpura” OR “immunoglobulin A nephritis” AND “coronavirus disease 2019” OR “COVID-19” OR “severe acute respiratory syndrome coronavirus 2” OR “SARS-CoV-2”. References listed within bibliographies of the retrieved records and articles already known to the authors were also considered for inclusion.

Selection criteria – diagnostic criteria

Of interest were cases of immunoglobulin A-mediated diseases preceded by COVID-19 or a vaccination against SARS-CoV-2 with a latency of four weeks or less. The time latency from symptomatic COVID-19 to onset of immunoglobulin A-mediated disease was calculated based on the onset of symptoms or signs. Cases preceded by an infection other than SARS-CoV-2 or by a vaccination against a microorganism other than SARS-CoV-2 with a latency of four weeks or less were excluded. The diagnosis of Henoch-Schönlein vasculitis [1] was made in subjects with palpable purpura and at least one of the following features: abdominal pain, acute arthritis or arthralgia in any joint, and kidney involvement as evidenced by hematuria (with or without associated pathological proteinuria). A biopsy study was not a prerequisite for the diagnosis of Henoch-Schönlein vasculitis. The diagnosis of Berger glomerulonephritis [2] was made in patients with acute onset of otherwise
unexplained gross hematuria and proteinuria supported, if possible, by histologic and immunochemical evidence.

The diagnosis of new onset Henoch-Schönlein vasculitis or Berger glomerulonephritis temporally associated with COVID-19 or vaccination against SARS-CoV-2 was retained in subjects without a history of the mentioned conditions. On the other hand, the diagnosis of Henoch-Schönlein vasculitis flare or Berger glomerulonephritis flare was retained in subjects with a history of the mentioned conditions. Cases of Henoch-Schönlein vasculitis or acute Berger glomerulonephritis temporally associated with COVID-19 were categorized as intra- (immunoglobulin A-mediated disease starting or flaring before resolution of COVID-19) or post-infectious (immunoglobulin A-mediated disease after resolution of COVID-19).

A positive microbiologic testing was a prerequisite for the diagnosis of COVID-19. Its severity was categorized in five stages as recommended by the National Institutes of Health: 1. asymptomatic (without signs and symptoms but recent strict contact to symptomatic cases); 2. mild (any sign or symptom such as fever, cough, sore throat, malaise, headache, muscle pain without shortness of breath, dyspnea, or abnormal chest imaging); 3. moderate (evidence of lower respiratory disease by clinical assessment or imaging, and transcutaneous O₂-saturation ≥94 percent on room air); 4. severe illness (breathing rate >30 /minute, O₂-saturation <94 percent on room air, or pulmonary infiltrates >50 percent); 5. critical (hypercapnic respiratory failure, septic shock, or multiple organ dysfunction).

Data extraction

For each case of new onset or flare of an immunoglobulin A-mediated disease temporally related to COVID-19, following information was collected: medical history with emphasis on a pre-existing immunoglobulin A-mediated disease; presentation and duration of the immunoglobulin A-mediated disease, testing for COVID-19; temporal relationship between COVID-19 and onset of immunoglobulin A-mediated disease. Similarly, for each case of new onset or flare of immunoglobulin A-mediated disease preceded by a vaccination against coronavirus, following information was collected: medical history with emphasis on a pre-existing immunoglobulin A-mediated disease; presentation and duration of the immunoglobulin A-mediated disease, type of vaccine and dose (first, second, or third); temporal relationship between vaccination and first symptoms and signs of immunoglobulin A-mediated disease.

Attempts also were made to contact original authors to acquire missing data. Two authors independently carried out the literature search, the selection of articles retained for analysis and the data extraction. One author entered the data into a pilot-tested database, and the second author verified the accuracy of data entry. Discrepancies were resolved by consensus and, where necessary, a third author was consulted.

Analysis

Pairwise deletion was used to deal with missing data that were not obtained from the corresponding authors. Categorical data are presented as counts and were analyzed using the Fisher exact test. Continuous data are shown as medians and interquartile ranges and were compared using the Mann-Whitney-Wilcoxon test. Statistical significance was defined by two-sided P-values of <0.05.
Results

Search results

The literature search returned 2570 potentially relevant records (Figure 1). In the first selection round, reports were screened based on titles and abstracts. In the second selection round, full-text articles of the remaining papers were assessed. For the final analysis, we retained 67 reports [5-72]: 25 from Europe (France, N=7; Spain, N=5; Italy, N=4; Turkey, N=3; Switzerland, N=2; United Kingdom, N=2; Germany, N=1; Luxemburg, N=1), 16 from North America (United States of America, N=14; Canada, N=1; Mexico, N=1), 23 from Asia (Japan, N=13; India, N=2; Jordan, N=2; Bahrain, N=1; Islamic Republic of Iran, N=1; Israel, N=1; Lebanon, N=1; People’s Republic of China, N=1; Singapore, N=1), two from Africa (Egypt, N=1; Morocco, N=1), two from Oceania (Australia, N=2) and two from South America (Brazil, N=1; Peru, N=1). They were published in English (N=64) and Spanish (N=3).

Findings

General findings

The reports provided information on 87 cases: 47 cases of Berger glomerulonephritis [5-32] and 40 cases of Henoch-Schönlein [33-72] vasculitis (table 1). Henoch-Schönlein and Berger cases did not significantly differ with respect to age and female to male ratio. Twenty-eight cases occurred in patients with medical history of an immunoglobulin A-mediated disease: this trend was significantly (P=0.0001) more common in Berger glomerulonephritis (N=24; 51%) than in Henoch-Schönlein vasculitis (N=4; 10%). A pre-existing autoimmune disease was present in six cases: rheumatoid arthritis in two [36; 40], and antiphospholipid syndrome [14], Crohn disease [52], Hashimoto thyroiditis [39] or ulcerative colitis [25] in each one case.

Approximately three out of four cases were preceded by a vaccination: this tendency was more common (P=0.0001) in Berger glomerulonephritis (N=44; 94%) than in Henoch-Schönlein vasculitis (N=17; 43%). The time latency from precursor was similar in Henoch-Schönlein vasculitis and in Berger glomerulonephritis (table 1). The disease duration was more frequently >4 weeks in Berger glomerulonephritis than in Henoch-Schönlein vasculitis (P=0.0362).

The test employed for the diagnosis of COVID-19 was a polymerase chain reaction in 24 (Henoch-Schönlein vasculitis, N=21; Berger glomerulonephritis, N=3) and both an immunoglobulin M and an immunoglobulin G serology a specific serology validated for the diagnosis of an acute coronavirus infection [73] in two patients with Henoch-Schönlein vasculitis. Two cases presented with a critical, two with a severe, three with a moderate, 13 with a mild and five with an asymptomatic COVID-19 (this piece of information was not available for one case). The immunoglobulin A-mediated disease was intra-infectious in 20 (Henoch-Schönlein vasculitis, N=18; Berger glomerulonephritis, N=2) and post-infectious in the remaining 6 cases (Henoch-Schönlein vasculitis, N=5; Berger glomerulonephritis, N=1).

About 90% of vaccine-associated cases (table 2) occurred after a mRNA-1273 or a mRNA-BNT162b2 vaccine. Forty cases were observed after the second (Berger glomerulonephritis, N=34; Henoch-Schönlein vasculitis, N=6) and 13 after the first dose (Henoch-Schönlein vasculitis, N=7;
Berger glomerulonephritis, N=6) of vaccine. No case was observed after the third vaccine dose. In seven cases, the disease occurred both after the first and the second vaccine dose (Henoch-Schönlein vasculitis, N=4; Berger glomerulonephritis, N=3). No information on the vaccine dose was available in the remaining case of Henoch-Schönlein vasculitis.

**Henoch-Schönlein vasculitis**

Henoch-Schönlein vasculitis was associated with a kidney involvement in 50% (N=20) of cases. It was vaccine-associated in about 40% and infection-associated in the remaining 60% of cases (table 3). Vaccine-associated cases were older (P=0.0008), occurred after a longer latency time (P=0.048) and presented less frequently (P=0.022) with an abdominal involvement than infection-associated cases. In contrast, no significant differences were noted between vaccine- and infection-associated cases with respect to gender, prevalence of pre-existing Henoch-Schönlein vasculitis, articular or renal involvement, and disease duration.

**Berger glomerulonephritis**

As previously stated, all but three cases (94%) of Berger glomerulonephritis were vaccine-associated (table 4). Approximately 55% of cases had a history of pre-existing Berger glomerulonephritis. Most cases remitted within 4 weeks.

**Discussion**

This review documents 87 patients, mostly adults, with 94 cases of immunoglobulin A-mediated diseases, which were temporally associated with a vaccination against SARS-CoV-2 (mostly a mRNA vaccine) or, less frequently, with COVID-19. Two-thirds of cases occurred in subjects without history of a pre-existing immunoglobulin A-mediated disease. Furthermore, most cases were benign, as indicated by the fact that they remitted within 4 weeks [1, 2]. Moreover, almost all published cases of Berger glomerulonephritis were vaccine-associated while most Henoch-Schönlein cases were infection-associated. Finally, immunoglobulin A disease occasionally occurred both after the first and the second vaccine dose, further supporting not only a temporal but also a causal relationship.

The mechanisms by which SARS-CoV-2 infection or vaccination against it predispose to autoimmune phenomena including immunoglobulin A-mediated disease are currently unclear. However, SARS-CoV-2 shares with Epstein-Barr virus and many common respiratory tract viruses features that may trigger autoimmunity including superantigen activity, functional and molecular mimicry, and activation of inflammatory signaling [3]. The occurrence of an immunoglobulin A-mediated disease in association with SARS-CoV-2 infection or vaccination is likely explained by the fact that an immunoglobulin A response is observed three days or more after disease onset [73] [74] or vaccination [74] [75]. In immunoglobulin A-mediated diseases, the initiating event is the deposition of abnormally glycosylated immunoglobulin A1 containing polymeric immune complexes, which are larger and contain a higher concentration of immunoglobulin E in Henoch-Schönlein vasculitis than in Berger glomerulonephritis [1]. Little is known about the overall incidence of immunoglobulin A-mediated diseases during the pandemic. However, limited evidence suggests a decreased incidence of Henoch-Schönlein vasculitis in childhood [77].
Vaccine-associated immunoglobulin A mediated diseases were mostly observed after a mRNA vaccine. The link is likely explained either by the fact that these vaccines are used very often or/and by the fact that they are strongly immunogenic [77].

The major novelty of the present observations lies in the ability to demonstrate a possible causal association between SARS-CoV-2 infection or vaccination and immunoglobulin A-mediated diseases. In contrast, information from case reports is prone to bias, cannot be inferred to determine prevalence and cannot be extrapolated to general experience [75] [78]. For example, the present data do not prove that fewer cases of immunoglobulin A disease occur after SARS-CoV-2 infection than after vaccination against it. Although Henoch-Schönlein vasculitis mostly affects children [1], Henoch-Schönlein patients included in this survey were frequently adult. This likely results from publication bias and from the fact that COVID-19 rarely affects children and that this age group infrequently gets vaccinated against SARS-CoV-2 [76] [79].

Available data point out that immunization is the most effective intervention to reduce or eliminate the burden of many infectious disease including coronavirus disease 2019 [77].

Conclusion

These data suggest that SARS-CoV-2 infection and vaccination against it add to the list of triggers of immunoglobulin A diseases. Considering that the outcome of COVID-19 is more severe in subjects with aberrant immune response, they should continue to be offered the vaccine, but warrant close monitoring.

Author Contribution

G.B., P.B.F., G.D.S., M.G.B., and G.P.M. conceptualized the study design; G.B., S.A.G.L., and G.P.M. carried out the literature search; G.B., P.B.F., and M.S. extracted and analyzed the data; G.B., S.A.G.L., and M.G.B. wrote the manuscript; G.D.S, B.T.B.P., and C.A. reviewed the manuscript for important intellectual content; all authors accepted the final version of the manuscript.

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**Figure 1 - Legend**

Severe acute respiratory syndrome coronavirus 2 and immunoglobulin A-mediated diseases. Flowchart of the literature search process.
Table 1: Characteristics of 87 patients with an immunoglobulin A-mediated disease preceded by a coronavirus disease 2019 or a vaccination for it against severe acute respiratory syndrome coronavirus 2. Data are presented as frequency or as median with interquartile range.

|                           | All  | Berger Glomerulonephritis | Henoch-Schönlein Vasculitis | P-value |
|---------------------------|------|----------------------------|----------------------------|---------|
| N                         | 87   | 47                         | 40                         |         |
| Males : females, N        | 45 : 40 | 20 : 25                   | 25 : 15                    | 0.128   |
| Age                       | 34 [17-51] | 35 [19-46]                | 33 [13-65]                 | 0.881   |
| ≤18 years, N              | 23   | 10                         | 13                         | 0.812   |
| Underlying autoimmune diseases-, N | 6     | 2                          | 4                          | 0.9999  |
| Immunoglobulin A mediated disease |       |                             |                            | 0.0001  |
| Pre-existing, N           | 28   | 24                         | 4                          |         |
| De novo, N                | 59   | 23                         | 36                         |         |
| Precursor                 |       |                             |                            | 0.0001  |
| Infection, N              | 26   | 3                          | 23                         |         |
| Vaccination, N            | 61   | 44                         | 17                         |         |
| Time latency, days        | 2 [1-9] | 2 [1-5]                   | 3 [1-10]                   | 0.178   |
| Disease duration >4 weeks, N | 25   | 18                         | 7                          | 0.0362  |

* The diagnosis of Henoch-Schönlein vasculitis was supported by a kidney biopsy in one case (no skin biopsy was performed); ◆ other than immunoglobulin A-mediated diseases; † the diagnosis of Berger glomerulonephritis was supported by a kidney biopsy in the 24 cases; ‡ the diagnosis of de novo Henoch-Schönlein vasculitis was supported by a biopsy in 23 of the 36 cases: skin biopsy, N=16; both skin and kidney biopsy, N=7; † the diagnosis of de novo Berger glomerulonephritis was supported by a kidney biopsy in 21 of the 23 cases with new onset glomerulonephritis.
Table 2: Vaccines against severe acute respiratory syndrome coronavirus 2 disease 2019 implicated in Berger glomerulonephritis and Henoch-Schönlein vasculitis.

| Vaccine                        | All | Berger Glomerulonephritis | Henoch-Schönlein Vasculitis |
|-------------------------------|-----|---------------------------|-----------------------------|
| mRNA - BNT162b2               | 28  | 23                        | 5                           |
| mRNA – 1273                   | 23  | 19                        | 4                           |
| ChadOx1 nCoV-19               | 6   | 0                         | 6                           |
| mRNA based COVID-19 vaccine*  | 2   | 2                         | 0                           |
| Ad26.COV2.S                   | 1   | 0                         | 1                           |
| Inactivated COVID-19 vaccine* | 1   | 0                         | 1                           |

* not otherwise specified
Table 3: Clinical features of 40 cases of Henoch-Schönlein vasculitis preceded by a coronavirus disease 2019 or a vaccination against it severe acute respiratory syndrome coronavirus 2. Data are presented as frequency or as median with interquartile range.

|                                | Vaccination-associated | Infection-associated | P-value |
|--------------------------------|------------------------|----------------------|---------|
| N                              | 17                     | 23                   |         |
| Males : females, N             | 9 : 8                  | 16 : 7               | 0.503   |
| Age, years of age              | 60 [40-70]             | 13 [7-30]            | 0.0008  |
| Latency, days                  | 8 [2-11]               | 3 [0-9]              | 0.048   |
| Henoch-Schönlein vasculitis    |                        |                      | 0.294   |
| Pre-existing, N                | 3                      | 1                    |         |
| De novo, N                     | 14                     | 22                   |         |
| Extracutaneous involvement     |                        |                      |         |
| Abdominal, N                   | 3                      | 13                   | 0.022   |
| Articular, N                   | 6                      | 12                   | 0.347   |
| Renal, N                       | 9                      | 9                    | 0.523   |
| Disease duration >4 weeks, N   | 2                      | 5                    | 0.677   |
Table 4: Clinical features of 47 cases of Berger glomerulonephritis preceded by a coronavirus disease 2019 or a vaccination against it severe acute respiratory syndrome coronavirus 2. Data are presented as frequency or as median with interquartile range (vaccination-associated cases) or as individual values (infection-associated cases). Information on sex was not available in two vaccination-associated cases.

|                                | Vaccination-associated | Infection-associated |
|--------------------------------|------------------------|----------------------|
| N                              | 44                     | 3                    |
| Males : females, N             | 18 : 24                | 2 : 1                |
| Age, years of age              | 33 [19–45]             | 18; 65; 88           |
| Latency, days                  | 2 [1–4]                | 1; 3; 21             |
| Berger glomerulonephritis      |                        |                      |
| Pre-existing, N                | 24                     | 0                    |
| De novo, N                     | 20                     | 3                    |
| Disease duration >4 weeks, N   | 16                     | 2                    |
Records identified through search in the Google Scholar Database (N=2777)

Records identified through search in the Excerpta Medica Database (N=148)

Records identified through search in the National Library Database (N=78)

Records screened after duplicates removed (N=2570)

Records excluded after title or abstract screening (N=2472)

Full-text assessed in detail for eligibility (N=98)

Records excluded (N=43)
Not including original cases (N=18)
Not pertaining (N=11)
Not case reports (N=5)

Personal files (N=2)

Full-text articles included (N=67)
- Systematic literature review on IgA-diseases associated to SARS-CoV-2 infection or vaccination

- 47 cases of Berger glomerulonephritis identified, of whom 44 in temporal association with vaccination, and 3 with infection

- 40 cases of Henoch-Schönlein purpura identified, of whom 17 in temporal association with vaccination, and 23 with infection