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The impact of the COVID-19 pandemic on the incidence and clinical course of IgA vasculitis in paediatric patients

Wpływ pandemii COVID-19 na częstość występowania i przebieg kliniczny zapalenia naczyń związanego z IgA u pacjentów pediatrycznych

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Abstract

Introduction and objective: Immunoglobulin A vasculitis is an autoimmune disorder resulting from immune complex accumulation in small blood vessels, causing skin, joint, abdominal, and kidney manifestations. This study evaluated the impact of the COVID-19 pandemic on the incidence and clinical course of immunoglobulin A vasculitis in paediatric patients. **Materials and methods:** A retrospective analysis of medical records from a single university paediatric hospital was performed to compare 117 patients presenting with immunoglobulin A vasculitis before and 57 after the COVID-19 epidemic announcement in Poland on 20 March 2020. Laboratory results, hospitalisation duration, preceding infections, clinical presentation, history of allergies and COVID-19 vaccinations, and the proportion of immunoglobulin A vasculitis patients among all admissions were analysed. **Results:** The study of 174 patients showed that their average age during the pandemic (5.51 ± 3.10) was significantly lower than pre-pandemically (6.98 ± 3.67) ($p < 0.05$). Before the pandemic, more hospitalised patients had immunoglobulin A vasculitis (1.14%) compared to during the pandemic (0.47%) ($p < 0.05$). Food allergies were also more common during the pandemic (20.8%) than before (8.8%) ($p < 0.05$). No significant differences were found in hospitalisation duration, and the incidence of immunoglobulin A vasculitis nephritis and abdominal symptoms ($p = 0.194$, $p = 0.381$, $p = 0.968$, respectively). Three patients had COVID-19 infection at admission. **Conclusions:** The pandemic led to fewer immunoglobulin A vasculitis hospitalisations but did not alter the clinical course of the disease or the incidence of immunoglobulin A vasculitis nephritis. In the context of the resurgence of COVID-19 infections, it is important to consider them as potential factors affecting immunoglobulin A vasculitis. Ongoing research is essential to understand these dynamics and guide effective clinical management of immunoglobulin A vasculitis amidst the evolving COVID-19 setting.

Keywords: COVID-19, SARS-CoV-2, paediatrics, IgA vasculitis

Streszczenie

Wprowadzenie i cel: Zapalenie naczyń związane z IgA jest chorobą autoimmunologiczną wynikającą z gromadzenia się kompleksów immunologicznych w małych naczyniach krwionośnych, powodującą objawy skórne, stawowe, brzuszne i nerkowe. Celem badania była ocena wpływu pandemii COVID-19 na częstość występowania i przebieg kliniczny tego zapalenia u pacjentów pediatrycznych. **Materiał i metody:** Retrospektywna analiza dokumentacji medycznej pacjentów z zapaleniem naczyń związanym z IgA jednego uniwersyteckiego szpitala pediatrycznego w ciągu dwóch lat przed ogłoszeniem epidemii COVID-19 w Polsce, co miało miejsce 20 marca 2020 roku (117 pacjentów), i dwóch następnych lat (57 pacjentów). Porównano wyniki badań laboratoryjnych, czas trwania hospitalizacji, poprzedzające infekcje, stan zakażenia, obraz kliniczny, historię alergii i szczepień przeciwko COVID-19 oraz odsetek pacjentów z zapaleniem naczyń związanym z IgA wśród wszystkich przyjętych do szpitala. **Wyniki:** Analiza 174 przypadków wykazała, że średni wiek pacjenta podczas

pandemii (5,51 ± 3,10 roku) był istotnie niższy niż przed pandemią (6,98 ± 3,67 roku; $p < 0,05$). Przed pandemią odsetek hospitalizowanych pacjentów z zapaleniem naczyń związanym z IgA był wyższy w porównaniu z czasem pandemii (1,14% *vs* 0,47%; $p < 0,05$). Pacjenci z alergiami pokarmowymi stanowili większy odsetek podczas pandemii niż przed nią (20,8% *vs* 8,8%; $p < 0,05$). Różnice między długością hospitalizacji, zajęciem nerek i obecnością objawów brzusznych nie były istotne statystycznie (odpowiednio $p = 0,194$, $p = 0,381$, $p = 0,968$). U trzech pacjentów podczas przyjęcia do szpitala wynik testu na COVID-19 był dodatni. **Wnioski:** Pandemia COVID-19 spowodowała spadek liczby hospitalizacji z powodu zapalenia naczyń związanego z IgA, nie wpłynęła jednak na przebieg kliniczny choroby ani na częstość zajęcia nerek w jej przebiegu. W kontekście ponownego wzrostu zakażeń SARS-CoV-2 istotne jest ich uwzględnienie jako potencjalnego czynnika wpływającego na zapalenie naczyń związane z IgA. Wobec ciągle ewoluującego obrazu COVID-19 dla lepszego poznania zapalenia naczyń związanego z IgA oraz opracowania skutecznych strategii postępowania w jego leczeniu konieczne są dalsze badania z udziałem większej grupy pacjentów.

Słowa kluczowe: COVID-19, SARS-CoV-2, pediatria, zapalenie naczyń związane z IgA

INTRODUCTION

Immunoglobulin A vasculitis (IgAV), previously known as Henoch–Schönlein purpura (HSP), is a type of autoimmune small blood vessel inflammation. It is characterised by the accumulation of IgA1 immune deposits primarily at the walls of affected blood vessels[1]. Despite extensive research efforts to uncover its causes, the exact aetiology of IgAV remains unknown[2]. Among childhood vasculitis, IgAV is the most prevalent form[3] and affects children more frequently than adults[4]. The disease can affect the skin (Fig. 1), gastrointestinal tract, joints, and kidneys[5].

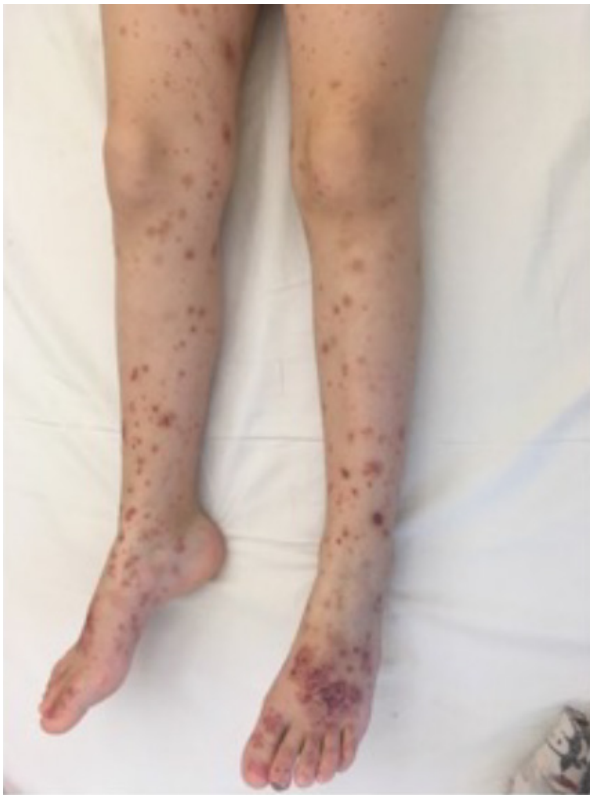

Fig. 1. Spotted purpura in the course of IgA vasculitis

The prognosis in the long term depends on the presence of renal involvement. IgA vasculitis nephritis (IgAVN) may present with either microscopic or gross haematuria, proteinuria, nephrotic or nephritic syndrome, and can even lead to acute renal failure. The primary indication of kidney involvement is the presence of microscopic or gross haematuria, often accompanied by proteinuria (in up to two-thirds of cases). The severity of symptoms at the onset of IgA vasculitis nephritis directly correlates with the gravity of the prognosis. In 30–50% of patients with IgAV presenting with renal changes, chronic glomerulonephritis develops, yet only 1–7% ultimately reach end-stage renal disease. Key determinants of poor prognosis include a reduced glomerular filtration rate (GFR), the presence of nephrotic syndrome or nephrotic syndrome, crescents observed in kidney biopsy, and the identification of advanced lesions in kidney biopsy (ISKDC grades III–VI)[6]. HSP can be triggered by bacterial and viral infections (e.g. parvovirus B19, *Bartonella henselae*, *Helicobacter pylori*, *Haemophilus parainfluenza*, Coxsackie virus, adenovirus, hepatitis A and B viruses, mycoplasma, Epstein–Barr virus, varicella, campylobacter, and methicillin-resistant *Staphylococcus aureus*)[7].

Over the past few years, the world has faced the COVID-19 pandemic, which originated in Wuhan, China, in November 2019, and rapidly attained a global scope. In Poland, the epidemic was declared on 20 March 2020, only 16 days following the first reported case. COVID-19, caused by the SARS-CoV-2 virus, typically results in mild symptoms such as fever, cough, and fatigue. However, older and obese individuals often experience a more severe disease progression, potentially leading to pneumonia, acute respiratory distress, septic shock, and even death[8]. COVID-19 shares similarities with autoimmune diseases in clinical manifestations, immune responses, and pathogenic mechanisms[9]. There have been reported cases of individuals developing autoimmune disorders, including Guillain–Barré syndrome or systemic lupus erythematosus, following a previous infection with COVID-19[9]. Other studies have presented cohorts of patients who developed new-onset autoimmune rheumatic diseases following the administration of COVID-19

vaccines[10]. It remains unclear whether the COVID-19 infection triggers the production of IgA antibodies or the formation of pathogenic IgA, or whether the immune response to the infection or the vaccine simply reveals pre-existing deposits[11].

The COVID-19 pandemic, with its stringent lockdowns and social distancing measures, fundamentally altered the functioning of individuals and healthcare systems, also in Poland.

The changes associated with the pandemic, along with the reorientation of healthcare services to prioritise the treatment and prevention of COVID-19, offer a unique context for examining the incidence and course of paediatric autoimmune diseases during this unique period.

The aim of this study was to comprehensively investigate the effects of the COVID-19 pandemic on the incidence and clinical course of IgA vasculitis among paediatric patients.

MATERIALS AND METHODS

Medical records of patients presenting with IgA vasculitis at the Children's Clinical Hospital of the Medical University of Warsaw were retrospectively reviewed for the period between March 2018 and March 2022. This timeframe includes two years before the pandemic and the first two years of the pandemic, following the announcement of the COVID-19 epidemic in Poland on 20 March 2020. A total of 174 patients were divided into two groups according to the year of diagnosis (20 March 2018 to 19 March 2020; 20 March 2020 to 20 March 2022). The group of patients diagnosed prior to the pandemic (the pre-pandemic group) consisted of 117 children. The other group, with patients diagnosed after the announcement of the state of pandemic in Poland (the during-pandemic group), consisted of 57 individuals. The inclusion criteria were as follows: 1) children younger than 18 years of age; 2) patients with confirmed IgAV diagnosis within either of the two periods.

Based on medical documentation, the following clinical parameters were compared: age of onset, skin symptoms, abdominal symptoms, joint symptoms, kidney symptoms, food allergies, respiratory allergies, and skin allergies. The frequency of occurrence of IgAVN was compared. The number of patients in the pre-pandemic group and the during-pandemic group was also compared against the total number of patients admitted to the hospital during corresponding periods.

The following laboratory test results of patients in both groups were compared: number of erythrocytes and urine concentrations of protein, creatinine, urea, IgA, IgG, IgM, complement C3 and C4, white blood cells (WBC), haemoglobin (HGB), platelet (PLT) level in serum, and estimated GFR (eGFR). Creatinine levels were determined by an enzymatic method using the Cobas (Roche, Switzerland) analyser. The eGFR was calculated with the Schwartz method. Urea concentration was measured kinetically, utilising urease and glutamate dehydrogenase, again with the Cobas system. For immunoglobulins, the immunonephelometric method was used. This applies to IgA, IgG, and IgM, all of which were measured using the BN II device (Siemens, Germany). Similarly, the complement components C3 and C4 were determined using the immunonephelometric method with the BN II device. WBC count was conducted through fluorescence flow cytometry using a semiconductor laser, specifically with the Sysmex XN-1500 analyser (Sysmex, Japan). HGB concentration was measured using the SLS HGB method, which involves absorbance measurement with sodium lauryl sulphate, also utilising the Sysmex XN-1500 system. PLT count was determined using either the impedance method with hydrodynamic focusing, or optical or fluorescence methods, all conducted with the Sysmex XN-1500 device. For assessing haematuria, two approaches were taken. The qualitative assessment of blood in urine was done by reading strips using reflectance photometry with the Atellica 1500 system (Siemens, Germany) with the CliniteK NOVUS module. For quantitative assessment, which involved counting the number of cells per microlitre, an automated microscopy method was used. This approach is based on automated classification of formed elements in urine, which relies on digital images from 15 evaluated fields. This was performed with the Atellica 1500 system (Siemens, Germany) with the Atellica UAS 800 module. Urine protein analysis was done both qualitatively and quantitatively. The qualitative analysis involved reading strips using reflectance photometry, carried out with the Atellica 1500 system (Siemens, Germany) and the CliniteK NOVUS module. For quantitative analysis, the turbidimetric method was used with the Cobas analyser (Roche, Switzerland).

To check the virus infection status, nasopharyngeal swab specimens were collected with flocked swabs. The material was deposited in a viral transport medium (Biocomma, China). Immediately after collection, the swabs were placed at 2–8°C and transported to the laboratory within two hours. RNA was extracted with the Nuclisens EasyMag automatic nucleic acid extraction system (bioMérieux, France). The RT-PCR SARS-CoV-2 analysis was performed using the Liferiver Novel Coronavirus (2019-nCoV) Real Time Multiplex RT-PCR Kit (Shanghai ZJ Bio-Tech C, Shanghai, China) in accordance with the manufacturer's protocol. Thermocycling was performed in the CFX96™ Real-Time PCR Detection System (Bio-Rad, USA). The test detects three target genes: SARS-CoV-2 gene *E*, gene *N*, and *ORF1ab*. The limit of detection is 1,000 copies/mL. As positive result was regarded detection at least two specific genes, detection of one gene was reported as inconclusive. Internal control was applied at the isolation and amplification stages.

All comparisons were evaluated as either statistically significant or insignificant using the chi-squared, Mann–Whitney or the *t*-Student test. A p-value <0.05 was considered to represent a statistically significant result.

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	Average		*t*-Student test results	
	Pre-pandemic	**During-pandemic**	***t***	***p***
Age [years]	**6.98 ± 3.67**	**5.51 ± 3.10**	**2.59**	**0.010**
Length of hospitalisation [days]	6.58 ± 6.16	8.05 ± 8.40	–1.30	0.194
Body weight [kg]	26.36 ± 15.06	22.95 ± 13.02	1.22	0.226
Height [cm]	**125.10 ± 25.4**	**114.0 ± 19.1**	**2.27**	**0.026**
WBC [10^3/μL]	10.75 ± 4.13	10.24 ± 3.41	0.79	0.431
HGB [g/dL]	12.42 ± 1.1	12.32 ± 1.17	0.58	0.564
PLT [10^3/μL]	375.39 ± 124.3	362.1 ± 102.5	0.69	0.492
Lymphocytes [%]	35.11 ± 10.69	35.63 ± 12.90	–0.28	0.783
Neutrophils [%]	52.95 ± 12.77	53.48 ± 13.82	–0.24	0.807
Urea [mg/dL]	26.98 ± 7.61	29.19 ± 8.55	–1.53	0.128
Creatinine [mg/dL]	0.42 ± 0.17	0.36 ± 0.17	1.82	0.070
GFR [mL/min/1.73 m^2]	**125.48 ± 31.33**	**140.01 ± 38.27**	**–2.01**	**0.047**
IgA [mg/dL]	204.63 ± 109.6	173.06 ± 83.15	1.59	0.114
IgG [mg/dL]	**1,124.34 ± 334.0**	**945.52 ± 249.47**	**2.63**	**0.010**
IgM [mg/dL]	120.18 ± 61.5	108.3 ± 45.9	0.99	0.325
C3 [mg/dL]	116.57 ± 23.6	105.0 ± 28.4	2.18	0.031
C4 [mg/dL]	24.01 ± 6.8	128.3 ± 588.0	–1.50	0.136
			Mann–Whitney test results	
			U	***p***
Urine protein [mg/dL]	36.71 ± 136.50	24.50 ± 90.85	3,154.00	0.901

C3 – complement component 3; **C4** – complement component 4; **GFR** – glomerular filtration rate; **HGB** – haemoglobin; **IgA** – immunoglobulin A; **IgG** – immunoglobulin G; **IgM** – immunoglobulin M; **PLT** – platelets; **WBC** – white blood cells.

Tab. 1. Comparative analysis of clinical and biological parameters between the pre-pandemic group (two years before the announcement of the SARS-CoV-2 pandemic state in Poland) and the during-pandemic group (two years after the announcement of the SARS-CoV-2 pandemic state) with the t-Student test and Mann–Whitney test

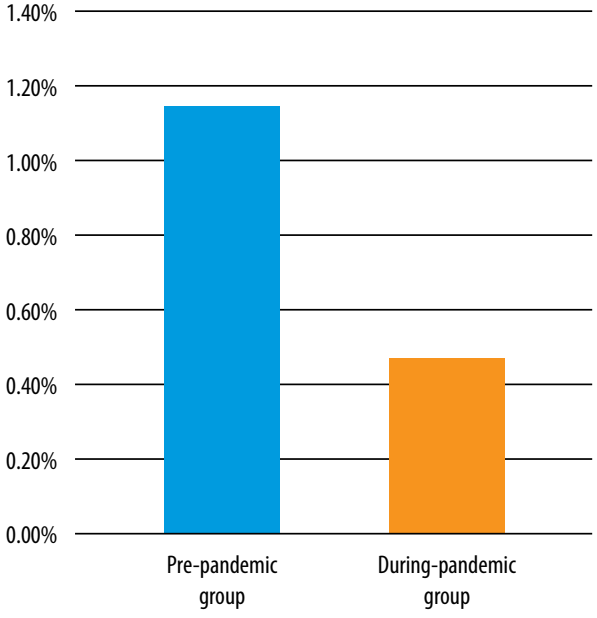

Fig. 2. Comparison of the incidence of IgAV-related hospitalisations in relation to the overall number of hospitalisations before and during the pandemic (p < *0.05)*

RESULTS

A total of 174 patients diagnosed with IgAV were admitted to the hospital between 20 March 2018 and 20 March 2022. Out of these, 117 were admitted before 20 March 2020 and 57 after that day. The mean age, hospitalisation time, weight, height, and laboratory results of the patients from both groups are demonstrated in Tab. 1. The highlighted values were statistically significant ($p < 0.05$).

The duration of hospitalisation was slightly longer during the pandemic (8.05 ± 8.40 days) compared to the pre-pandemic group (6.58 ± 6.16 days), although the difference did not reach statistical significance ($p = 0.194$). The number of patients admitted with IgAV in the pre-pandemic period in comparison to all admissions (117 out of 10,228) was significantly higher than during the pandemic (57 out of 12,035) ($p < 0.05$) (Fig. 2).

The mean age was significantly lower ($p = 0.01$) during the pandemic (5.51 ± 3.10 years) than pre-pandemically (6.98 ± 3.67 years) (Fig. 3).

It was found that the incidence of IgAV with renal involvement was higher during the pandemic (15.8%) than in the pre-pandemic period (11.1%). However, the observed difference did not reach statistical significance ($p = 0.381$), suggesting no significant difference in the incidence of IgAVN between the periods studied.

The chi-square test of independence was conducted to examine the association between the incidence of haematuria in patients and the duration of pandemic. The association between these variables was statistically insignificant, $\chi^2(1, n = 170) = 0.037$, $p = 0.85$.

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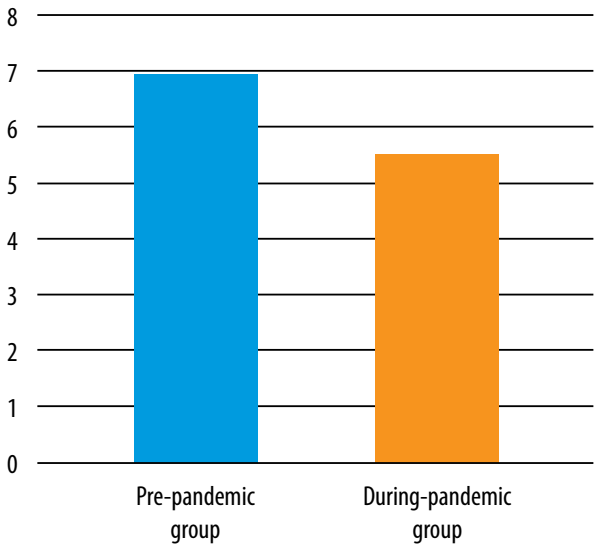

Fig. 3. Comparison of mean age for the patient groups: pre-pandemic (6.98 ± 3.67 years) and during-pandemic (5.51 ± 3.10 years) (p < *0.05)*

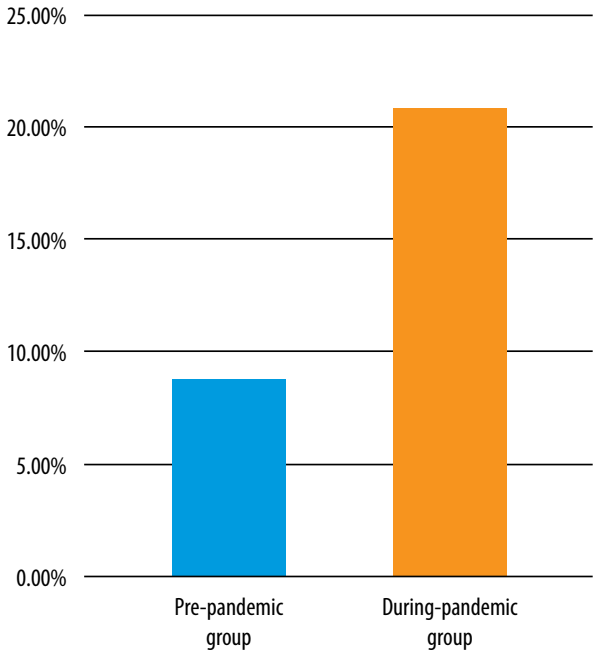

Fig. 4. Comparison of food allergy incidence in the pre-pandemic patient group (8.8%) and in the during-pandemic patient group (20.8%) (p < *0.05)*

Data analysis showed no statistically significant difference in the frequency of abdominal symptoms associated with IgAV between the compared groups before and during the pandemic. The frequency of these symptoms remained at a similar level, with 41% before and 41.8% during the pandemic. The incidence of food allergy among patients diagnosed with IgAV was found to be significantly higher ($p = 0.03$) during the pandemic (20.8%) compared to the pre-pandemic period (8.8%) (Fig. 4).

No statistically significant differences were observed in other investigated factors including the laboratory results of patients [except for the difference in IgG levels that were higher in the pre-pandemic group (1,124.34 ± 334.0 mg/dL vs. 945.52 ± 249.47 mg/dL during the pandemic, $p = 0.01$)]. Only three out of 57 patients admitted to the hospital during the pandemic tested positive for the SARS-CoV-2 infection. None had received the COVID-19 vaccine.

DISCUSSION

Our study found a notable decrease in hospital admissions for IgA vasculitis during the COVID-19 pandemic. The implementation of lockdowns, coupled with the widespread adoption of systematic mask-wearing, might have contributed to a reduction in the occurrence of IgAV cases caused by other pathogens[12]. Notably, the outcomes of our investigation align with two other studies, both indicating a reduction in IgAV incidence among the paediatric population during the COVID-19 pandemic[13,14]. It is essential to acknowledge that our study was conducted at a highly specialised centre that provides care for a large group of patients with IgAV and IgAVN. However, the findings still reflect the experience of only one clinic. Nevertheless, additional research is recommended, involving a nationally representative cohort, mirroring the approach taken in a French study by Kaya Akca et al.[13].

The decrease in overall IgAV hospitalisations might be associated with the cautious approach of parents toward potential SARS-CoV-2 exposure in healthcare settings during the pandemic. Consequently, hospital care was predominantly sought by parents of children presenting more serious IgAV symptoms. Conversely, parents of children with milder manifestations may have opted for home-based care or sought medical advice through telemedicine services. Further research and a comprehensive analysis are necessary to validate and improve the understanding of the implications of such patterns on disease presentation and management. The lower average age of patients during the pandemic may be attributed to the fact that parents of younger children were more inclined to agree to hospitalisation due to concerns about their health, despite the risks associated with the epidemiological threat, as they tend to show stronger empathic concern for their child's suffering and are more likely to seek quick diagnosis, treatment, and reassurance[15].

The absence of statistically significant differences in the incidence of IgAVN and the length of hospitalisation, as well as the lack of significant differences in clinical and biological parameters between the two groups (with the exception of the difference in IgG levels, which is associated with the average age of patients in both groups[16]), indicates that the COVID-19 pandemic did not have a significant impact on the clinical course of the disease in the patient population studied. Considering the fact that due to the epidemiological threat, one would expect to see mainly IgAV cases with

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a worse prognosis admitted to the hospital (renal involvement being one of the most significant negative prognostic factors[7]), our findings may be somewhat surprising. Thus, further research is needed to advance the understanding of the determinants of the risk of severe IgAV (with renal involvement, among others) in the context of the pandemic.

It is hard to explain why patients with food allergies were more common during the pandemic than in the pre-pandemic period. The rise in food allergies in children during the pandemic might stem from altered diets, reduced or increased exposure to diverse allergens, as well as increased health awareness leading to more diagnoses.

The possibility to assess correlations between the COVID-19 infection and the presence and severity of IgAV is limited, as only three patients during the pandemic tested positive for SARS-CoV-2. Nevertheless, the possibility that more patients might have been infected cannot be ruled out, since children were very often asymptomatic transmitters[17]. Children's response to the virus differs from that of adults, as some children may exhibit COVID-19 symptoms and produce antibodies targeted against SARS-CoV-2, despite consistently testing negative for the virus through the standard reverse transcription polymerase chain reaction (RT-PCR) test[18]. In a particular study, it was observed that three children belonging to the same family developed antibodies against SARS-CoV-2. Two of these children exhibited mild symptoms associated with COVID-19. However, despite undergoing 11 consecutive RT-PCR tests over a span of 28 days while living with their parents, who had tested positive for the virus, none of the children tested positive on the RT-PCR tests[19]. Even though only three children tested positive for COVID-19 during their hospitalisation, the possibility of a previous undetected COVID-19 infection contributing to the development of IgAV cannot be excluded.

Various case reports in the medical literature suggest that the SARS-CoV-2 infection served as a triggering factor for IgAV[20–23], akin to occurrences observed with other infections. On the other hand, the systemic review from 2021, based on 13 cases reporting IgAV and IgAVN associated with the COVID-19 infection, concluded that there is a paucity of scientific evidence on the pathogenesis of such link. Nevertheless, the relationship between those two pathologies is acknowledged[24]. This highlights the multifaceted nature of IgAV aetiology and warrants further exploration of potential associations between viral infections, including SARS-CoV-2, and the development or exacerbation of IgAV.

Another triggering factor for IgA vasculitis (IgAV) can be the vaccination against COVID-19. A study of 330 cases (of which 84 were children) shows that COVID-19 vaccines are associated with a mild but significant excess of IgAV reports, although not greater than that observed with other vaccines[25].

In Poland, the first COVID-19 vaccinations for children began on 7 June 2021. None of the patients in our study was vaccinated against COVID-19. Therefore, further research is necessary to understand the implications of COVID-19 vaccination on IgAV in children.

CONCLUSION

The COVID-19 pandemic led to a decrease in the number of hospitalisations due to IgAV but did not affect the clinical course of the disease or the incidence of nephropathy during its course.

In the context of the resurgence of COVID-19 infections (especially in the autumn-winter period), it is important to consider COVID-19 as one of the potential factors contributing to IgAV.

Further studies, involving a larger group of patients, will be essential for better understanding this relationship and developing effective management strategies for IgAV in the context of the continuously evolving nature of the pandemic.

Conflict of interest

There are no conflicts of interest.

Funding/Support and role of the sponsor

1WI/1/M/MG/N/21.

Author contribution

Original concept of study: KP, TU, JU, MMW. Collection, recording and/or compilation of data: KP, TU, JU, EP, MJ. Analysis and interpretation of data: KP, TU, MMW. Writing of manuscript: KP, TU, JU, EP. Critical review of manuscript: KP, TU, MMW. Final approval of manuscript: KP, TU, JU, MMW.

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