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Immunoglobulin A Vasculitis Nephritis in Children: Experience from a Tertiary Care Hospital, Bangladesh

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Abstract

Background and Aim: Immunoglobulin A vasculitis (IgAV), formerly known as Henoch-Schönlein purpura (HSP), is the most common vasculitis in children with multiorgan involvement. Renal involvement is one of the important causes of morbidity and mortality. The objective of this study was to evaluate the frequency, clinical profile, and outcome of IgA vasculitis nephritis (IgAVN) in children.

Methods: This prospective cross-sectional study was conducted in Dr. M R Khan Children Hospital & Institute of Child Health, Dhaka, over a period of 5 years from January 2015 to December 2019. Data were collected using a structured questionnaire form and analyzed by the SPSS software version 20.0.

Results: A total of 57 cases of IgA vasculitis were admitted of whom 16 (28%) had renal involvement. The mean age was 7.7 years. Regarding renal involvement, the majority of the patients (56.25%) had isolated hematuria. All nephritis patients (100%) had purpura and 75% of the patients had severe abdominal pain. The mean hematocrit and the mean platelet count were significantly higher in the nephritis group compared to patients without nephritis (41.49±4.47 vs. 39.98±5.16, p-value <0.005 and 485.51±58.29 vs. 293.89±65.15, p-value <0.001, respectively). The level of complement C3 was significantly lower in the nephritis group compared to patients without nephritis (0.85±0.4 vs. 1.5±0.3, p-value <0.01). The majority (68.75%) of the patients recovered and 18.75% were in remission with immunosuppressant. None of the cases progressed to ESRD.

Conclusion: Severe abdominal pain, high platelet counts, high hematocrit levels, and low C3 concentrations are common findings in nephritis. Nephritis resolve spontaneously in most cases but severe nephritis requires treatment with immunosuppressive drugs for remission.

Keywords: Immunoglobulin A vasculitis; Nephritis; Vasculitis; Child.

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Introduction

Immunoglobulin A vasculitis (IgA vasculitis), formerly known as Henoch-Schönlein purpura (HSP), is the most common small vessel vasculitis in children clinically manifesting as a sudden appearance of palpable non-thrombocytopenic purpura, usually on the extensor surface of limbs, along with abdominal pain, arthritis, and nephritis (1, 2). The term "Henoch–Schönlein purpura" was coined by two researchers, Johann Schönlein and his student Eduard Henoch, who made an in-depth analysis of this disease for the first time. According to the new nomenclature established during the International Chapel Hill Consensus Conference in 2012 (CHCC2012), the disease is now known as immunoglobulin A vasculitis (IgAV). The consensus to change the previous name (HSP) to IgAV was supported by the pathophysiological features of this disease whereby abnormal immunoglobulin A (IgA) is deposited in vessel walls.

HSP nephritis is thus named immunoglobulin A vasculitis nephritis (IgAVN) (3). The annual incidence of IgA vasculitis is 10-20 in 100,000 and 90% of the patients are below 10 years of age (4). This multisystem disorder mainly affects the skin, joints, gastrointestinal tract, and kidneys but other

organs are also sometimes involved. Although most of the IgA vasculitis symptoms are self-limiting, nephritis may cause significant morbidity and mortality (5).

Approximately 40%-50% of the young patients with IgA vasculitis develop nephritis within 4-6 weeks of the initial presentation (4, 6). The manifestations of IgA vasculitis nephritis (IgAVN) are variable including microscopic hematuria, gross hematuria, proteinuria, rapidly progressive renal impairment, and end-stage renal disease (ESRD) (7). About 1-17% of IgAVN cases progress to renal failure or end-stage renal disease (ESRD) (8). Children presenting with IgA vasculitis should undergo urinalysis and blood pressure measurement to evaluate renal involvement. Patients with isolated hematuria do not usually develop end-stage renal disease but a patient who has proteinuria and hematuria features a 15% risk and a patient who presents with nephrotic nephritic has a 50% risk of developing ESRD (9, 10). Early detection of nephritis is crucial to prevent nephritis associated complications. The risk factors related to renal involvement in IgA vasculitis are not well established but some studies showed that epidemiological, clinical, and a number of immunological findings had predictive roles (11).

Relatively sparse data is available on pediatric IgAV nephritis in Bangladesh. Hence, this prospective cross-sectional study was conducted to analyze the frequency, characteristics, and clinical outcome of IgA vasculitis nephritis in children.

Methods

This prospective cross-sectional study was conducted in Dr. M R Khan Children Hospital & Institute of Child Health, Dhaka over 5 years from January 2015 to December 2019.

The study was approved by the Ethics Committee of the Institute. This study was done on 57 patients with a diagnosis of HSP according to the 2010 EULAR/PRINTO/PRES (12) criteria including palpable purpura plus one of the following: abdominal pain, IgA deposits in biopsy, arthritis/arthralgia, nephropathy, age < 16 years. Informed written consent was obtained from all patients. Patients with other vasculitis like SLE, JIA, preexisting renal disease, and those who did not give consent were excluded from the study. Detailed clinical and laboratory evaluations (urine RME, spot protein/creatinine ratio, or 24-hour urine total protein) were done to ascertain renal involvement. Data were collected using a structured questionnaire and analyzed by SPSS version 20.0. Quantitative data are expressed as the mean ± standard deviation and categorical data are presented as frequency. Independent sample t-test was used to compare quantitative variables, p-values of less than 0.05 (at 95% CI) were considered statistically significant.

IgA vasculitis nephritis was categorized into isolated hematuria (either microscopic or gross), significant proteinuria, nephrotic syndrome, nephritic syndrome, and nephrotic nephritic syndrome. Renal biopsy was classified according to the ISKDC classification. Patients with IgA vasculitis and/or renal involvement were managed as per hospital protocol. Renal follow-up finished after 36 months upon the resolution of urinary abnormalities. The follow-up was initially monthly for six months, then every 3 months for 1 year, and then every 6 months for 18 months. Follow-up continued if urinary abnormalities persisted or CKD ensued. Long-term outcomes were classified as- (a) normal (no hypertension and normal physical examination, urine, and renal function); (b) remission (proteinuria decreased to <0.3g/day/1.73m^2 following immunosuppressive therapy, normal renal function, normal urine R/M/E, and normal physical examination) (c) minor urinary abnormalities (normal physical examination with microscopic hematuria or mild proteinuria); (d), active renal disease (hypertension, significant or heavy proteinuria, or eGFR <90mL/min/1.73m^2; (e) and end-stage renal disease or death (2).

Operational definitions

Minimum proteinuria was defined as urinary protein >1+ (30 mg/dL) using a dipstick test. Nephrotic range proteinuria was defined as 24-hour urinary protein >3.5 gm/1.73m^2/day or a spot urine protein/creatinine ratio> 0.2gm/mmol with or without edema and hypoalbuminemia. Significant proteinuria was defined as a spot protein/creatinine ratio >0.02 gm/mmol (2).

Microscopic hematuria was defined as red blood corpuscle (RBC) >5 /µL in a fresh uncentrifuged urine specimen.

Gross hematuria was defined as a visible red urine sample with correlating microscopic findings of erythrocytes in a urine test.

Nephritic syndrome: Hematuria in association with at least one of the following: raised serum urea and creatinine, hypertension, oliguria.

Nephritic nephrotic: Features of nephritic syndrome plus a nephrotic range proteinuria.
Hypertension was defined as multiple measurements of the blood pressure above the 95th percentile for age, height, and gender (13).
The ISKDC (International Study of Kidney Disease in Children) classification of biopsy findings in IgAV nephritis.

Results

Of 57 patients with immunoglobulin A vasculitis, 16 (28%) were found to have nephritis, of whom 9 (57.1 %) were male and 7(42.9 %) were female with a male to female ratio of 1.3:1.

The present study showed that 50% of the patients (n=8) with IgA vasculitis nephritis were in the age group 5-10 years, 37.5% (n=6) were in the age range 10-15 years, and only 12.5% (n=2) were below 5 years of age. The mean age of the nephritis patients was 7.7 ±2.6 years (range: 3.5-15 years).
Regarding renal involvement, the majority of the patients (n=9, 56.25 %) had isolated hematuria, 2 (12.5%) had hematuria plus mild proteinuria, 2 (12.5%) had nephritic syndrome, 1 (6.25%) had nephrotic nephritic syndrome, 1 (6.25%) had significant proteinuria, and one (6.25%) had nephrotic syndrome (Table 1).

Table 1: Types of renal involvement in IgA vasculitis children (n=16)

Types of renal involvement	Frequency (%)
Isolated hematuria	9 (56.25)
Hematuria +Mild proteinuria	2 (12.5)
Nephrotic syndrome	1 (6.25)
Nephritic syndrome	2 (12.5)
Nephritic Nephrotic syndrome	1(6.25)
Significant proteinuria	1 (6.25)
Total	16 (100)

As for clinical features, all IgA vasculitis nephritis patients (n=16, 100%) had the characteristic rash and palpable purpura, 11 patient (68.5%) had abdominal complaints, 9 had hematuria, 6 (37.5%) had joint involvement, 4 (25%) had oliguria and edema, and 3(18.75%) had hypertension (Table 2).

Table 2. Clinical features of IgA vasculitis nephritis (n=16)

Clinical Features	Frequency (%)
Skin Rash (purpura)	16 (100)
Joint involvement /Arthritis	6 (37.5)
Gastrointestinal symptoms (abdominal pain, colitis, bowel obstruction or ischemia)	12 (75%)
Gross hematuria	9 (56)
Oliguria	4 (25)
Edema	4 (25)
HTN	3 (18.75)

According to Table 3, the mean hematocrit was significantly higher in nephritis group compared to patients without nephritis (41.49 ± 4.47 vs. 39.98 ± 5.16, p-value <0.005). The mean platelet count was higher in the nephritis group versus patients without nephritis (485.51 ± 58.29 vs. 293.89 ± 65.15, p-value <0.001), and the complement C3 level was significantly lower in the nephritis group than in patients without nephritis (0.85±0.4 vs. 1.5±0.3, p-value <0.01). There was no significant difference in the leucocyte count, BUN, serum creatinine, and serum IgA level between the study groups. As for histological grading, of four patients who underwent biopsy, one had grade III a, one had grade III b, one had grade IV a, and one had grade IV b (Table 4).

Table 3. Comparison of laboratory parameters between IgA vasculitis & IgA vasculitis nephritis

Parameters	Patient with IgA vasculitis nephritis (n=16)	Patient with IgA vasculitis without nephritis (n=41)	p-value
Hematocrit (%/L, mean ± SD)	41.49 ± 4.47	39.98 ± 5.16	0.005*
Leucocytes ($\times 10^9$/L, mean ± SD)	5.10 ± 4.25	5.13 ± 13.83	0.918 NS
Platelet($\times 10^9$/L, mean ± SD	485.51 ± 58.29	293.89 ± 65.15	<0.001*
BUN (Mean±SD)	5.61±3.3	4.81±3.2	0.412 NS
Mean serum creatinine (µmol/L, mean ± SD)	63.50 ± 24.85	60.17 ± 16.50	0.314 NS
C 3 g/L Mean ± SD	0.85±0.4	1.5±0.3	<0.01*
Serum IgA g/L mean ± SD	2.3 ±0.2	2.5 ± 0.2	0.141 NS

* Statistical test: independent sample t test (p-value < 0.05 was considered statistically significant).

Table 4. ISKDC histological classification of biopsy findings in IgAV nephritis (n=4)

ISKDC classification	Frequency (%)
Grade III a	1 (25%)
Grade III b	1 (25%)
Grade IVa	1(25%)
Grade IVb	1 (25%)
Total 4	4 (100%)

Table 5 presents the treatment given to IgAVN patients. The majority (n=10, 62.5%) did not need immunosuppressants and only supportive treatment was given; four patients (25%) received immunosuppression, i.e. induction by pulse methylprednisolone + IV pulse cyclophosphamide (CYC) followed by oral prednisolone +mycophenolate mofetil (MMF). One patient (6.25%) was only treated with oral prednisolone, and one patient (6.25%) received an angiotensin receptor blocker (ARB).

Table 5. Treatment given to IgAV nephritis patients (n=16)

Treatment	Frequency (%)
No Immunosuppressant	10 (62.5)
ARB	1 (6.25)
Only Steroid	1 (6.25)
Induction by IV pulse Methyl+ CyC Maintenance by Oral CS+ MMF	4 (25)
Total	16 (100)

Table 6 shows that the majority of the nephritis patients (n=11, 68.75%) recovered completely, three patients (18.75%) were in remission with immunosuppressant treatment, one patient had minor urinary abnormalities, and 1 patient had active renal disease. No case of ESRD or death was observed.

Table 6. Clinical outcome of IgA vasculitis nephritis after 3 years follow-up (n=16)

Outcome	Frequency (%)
Normal	11 (68.75)
On remission with immunosuppressant	3 (18.75)
Minor urinary abnormalities	1 (6.25)
Active renal disease	1 (6.25)
End stage renal disease	0
Death	0

Discussion

Immunoglobulin A vasculitis nephritis (IgAVN) is not an uncommon association in children presenting with immunoglobulin A vasculitis (IgAV). Moreover, IgAV nephritis may cause acute renal failure or rapidly progressing glomerulonephritis, chronic kidney disease, and end-stage renal disease (14).

In the present study, 16 out of 57 (28%) IgA vasculitis patients had nephritis, which was consistent with some reports in the literature (15-17).

This study found that males were more affected than females (1.3:1), which was similar to previous studies (M: F= 1.24:1) (2). The mean age of the patients was 7.7±2.6 years in the present study, which was in line with studies conducted by Feng et al and Schinzel et al that reported a mean age of 8.50 ± 2.91 years and 7.3 ±3.1 years, respectively (13, 17). The majority of children in this study had isolated hematuria (56.2%) followed by hematuria + proteinuria (12.5%). Moreover, 12.5% had nephritic syndrome, 6.25% had significant proteinuria, and 6.25% had nephrotic syndrome. Schinzel et al found similar results in their retrospective study and reported that 67% of children had hematuria, 14% had nephrotic syndrome, 8.9% had nephritic syndrome, and 8.9% had significant isolated proteinuria. The prevalence of nephrotic syndrome was almost two times higher in the study by Schnizel et al compared to the present study (14.9% vs. 6.2%), which may be due to the larger sample size and ethnicity (17). Another study also found that isolated hematuria was the most common renal manifestation in IgA vasculitis, which is similar to our findings (18, 19).

In the present study, common clinical features of IgA VN were palpable purpura (100%) followed by gastrointestinal symptoms (75%), hematuria (56%), and arthritis (37.5%). Edema and hypertension are less common presentations in 25% and 18.7% of the patients, respectively. Zhu et al conducted a study in Chinese children with IgAV and found that all patients (100%) with nephritis had cutaneous manifestations. Intestinal manifestations were seen in 70.1%, arthritis was present in 61.1%, and hypertension was found in 17.9% of the patients, which is consistent with our study (17, 20). Abdominal pain and hematuria are the most common findings in IgAV nephritis patient according to some reviews and meta-analyses (21-23).

Regarding laboratory parameters, the mean hematocrit was significantly higher in the nephritis group than in patients without nephritis (41.49 ± 4.47 vs. 39.98 ± 5.16, p-value <0.005). The mean platelet count was also higher in the nephritis group compared to patients without nephritis (485.51 ± 58.29 vs. 293.89 ± 65.15, p-value <0.001). The complement C3 level was significantly lower in the nephritis group versus patients without nephritis (0.85±0.4 vs. 1.5±0.3, p-value <0.01). These findings are consistent with the results of a meta-analysis that found thrombocytosis, a low C3 level, an elevated ASO titer, and leukocytosis were risk factors for nephritis (24). However, according to the present study, the leukocyte count was not significantly different between patients with and without nephritis, which could be due to the small sample sizeThe mechanism of thrombocytosis, leukocytosis, and low C3 in IgAV nephritis patients is tissue injury induced by inflammatory agents secreted by neutrophils triggered by an inflammation-induced factor (25).

The present study found that BUN, serum creatinine, and IgA levels were not significantly different between IgA vasculitis patients with and

without nephritis, which was similar to the results of a cohort study (26).

Four patients underwent renal biopsy and the findings were grade IIIa (25%), grade III b (25%), grade IVa (25%), and grade IV b (25%) according to ISKDC. Nickarver et al conducted a retrospective analysis of biopsy findings of 17 patients. Most of the patients were in ISKDC grade II and III. In the present study, 50% of the patients were in grade III and the remaining 50% were in grade IV, but this finding is not conclusive due to the small sample size (n=4) (27).

The majority of the patients with nephritis (62.5%) responded well to supportive treatment. Four patients who had severe nephritis (25%) received immunosuppression. One (6.25%) patient was only treated with oral prednisolone and one patient (6.25%) received an angiotensin receptor blocker (ARB). Although many drugs have shown promising results, the standard treatment for IgA VN is still not clear (16). We used immunosuppressive therapy, i.e. intravenous pulse methylprednisolone and intravenous cyclophosphamide followed by oral prednisolone and mycophenolate mofetil, which is consistent with many systemic reviews, KDIGO2018, and SHARE recommendation. Oral prednisolone is often recommended as a first-line treatment and use of ARB or ACE inhibitor is advised for patients with persistent proteinuria > 3 months (28-32). We used ARB in one patient with persistent proteinuria and the outcome was favorable. Zaffanello et al published a review and showed many reports of treatment with prednisolone, methylprednisolone, cyclophosphamide, azathioprine, cyclosporine, dipyridamole, warfarin, and plasma exchange (33). Some studies have shown promising results for rituximab in IgAV nephritis (34, 35).

In this study, the majority of the patients (n=11, 68.75%) recovered completely, three patients (18.75%) were in remission with immunosuppressive therapy, one patient had minor urinary abnormalities, and one patient had active renal disease. None of the patient developed ESRD or died during the study period. In a retrospective study by Feng et al., IgA VN patients were treated with steroids and mycophenolate mofetil. After a follow-up of 6 months to 5 years, 70.37% had complete remission, two patients showed active renal disease, and none of the cases progressed to ESRD, which is consistent with our finding (13).

Limitations of our study were single-center study and small sample size.

Conclusion

Severe abdominal pain, a high platelet count and hematocrit level, and a low C3 level are common findings in nephritis. Nephritis resolves spontaneously in most cases but some patients with severe nephritis need immunosuppressive drugs for remission.

Conflict of Interest

The author declares no conflicts of interest.

Financial Support

Not declared.

Ethics

This prospective cross-sectional study was conducted in Dr. M R Khan Children Hospital & Institute of Child Health, Dhaka over 5 years from January 2015 to December 2019. The study was approved by the Ethics Committee of the Institute.

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