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Comparative histological and clinical differences between children and adults in IgA nephropathy

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ABSTRACT

IgA nephropathy (IgAN), as an autoimmune-mediated kidney disease worldwide, is considered an important cause of end-stage renal disease in adults. The most important diagnostic method in the patients is the evaluation of the biopsy findings. To date, several studies have examined different histopathological findings in patients with IgAN with an attempt to find out the relationship between morphologic findings with outcome and disease progression. Although there have been limited reports of IgAN in children, the Oxford scoring system is currently the most widely used IgAN classification and is validated for use in children and adults. In this review, we examined the most frequently published pathological findings on IgAN with a focus on Oxford classification between adults and children and attempted to highlight the key differences. The main purpose of this study was to assess the prognosis of patients with IgAN in childhood and adulthood, with emphasis on pathological risk factors for disease progression. Our results indicated that acute glomerulonephritis in children was predominantly reported more than chronic lesions. In addition, mesangial and endocapillary lesions were more common in children than in adults. In contrast, glomerular sclerosis, tubular atrophy/interstitial fibrosis, and atherosclerotic lesions were more common in older individuals.

Implication for health policy/practice/research/medical education:
In children, IgAN often presents as an acute form of glomerulonephritis, typically lacking chronic damage detected in adults. This condition presents as the higher occurrence of glomerular proliferation and hypercellularity, inflammatory conditions, and acute kidney injury at the outset of the disease in children versus adult population. Additionally, the response to steroid treatment is significantly better in children than adults.

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Introduction

IgA nephropathy (IgAN) is one of the most common primary glomerular diseases in both children and adults worldwide (1,2). It is an important end-stage renal disease etiology in adults and children. In 1968, for the first time, IgAN was defined by Berger and Hing as an intracapillary/mesangial glomerular deposition of immunoglobulin A (IgA) (3,4). Although the etiology of IgAN is poorly understood, the role of cross-immune reactions following infections against abnormal glycosylated IgA1 hinge region, accompanied by deposition of the circulatory immune complex and tubulointerstitial damage causes reduced renal function (Figure 1A) (5). The incidence of IgAN in children is significantly higher (100 new cases per million per year) than in adults (30-45 new cases per million per year) (6,7). The estimation of the true incidence rate of IgAN is influenced by the timing of renal biopsy, the degree of proteinuria, and the severity of renal impairment (8,9). Evidence from large cohort studies of children and adults with IgAN has demonstrated significant differences in clinical presentation, pathological, and treatment responses across the adult and pediatric age groups (10,11). Previous studies have also documented that treatment with steroids can improve clinical outcomes in children better than in adults (12,13). The recent Kidney Disease Improving Global Guidelines (KDOGI) also recommends steroid therapy should be initiated in children with IgAN when the proteinuria is greater than 1.0 g/day, while its prescription should be reserved in adult patients only those at high risk of disease

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progression to end-stage kidney disease (ESKD) (14).

A retrospective study from Norway registered in the Norwegian Kidney Biopsy Registry (NKBR) and the Norwegian Renal Registry (NRR) from 1988 to 2021, found that IgAN was the second most common primary glomerulonephritis (15). Another cohort study (including 2299 adults and 140 children) of the UK National Registry of Rare Kidney Diseases (RaDaR) with a median 5.9 years' follow-up, reported approximately 50% of patient's progress to ESKD within 10-15 years of diagnosis (16). The main pathologic finding in affected children and adults is the presence of IgA as a main immunoglobulin in the glomerular area. Renal biopsy, an invasive diagnostic procedure, is usually performed either at the disease onset or following a period of observation (17).

Several studies mentioned the clinical presentations and renal function assessment or pathological parameters in predicting IgAN outcomes (14,18). Meanwhile, the recent study in 2023 validates using the Oxford classification with clinicopathological parameters as the outcome predictors. Therefore, the presence of abnormally elevated serum creatinine level along with pathological parameters, such as a higher degree of interstitial fibrosis/tubular atrophy, can demonstrate the progression to ESKD on the follow-up (19).

Based on a multicenter prospective cohort of 1060 children with IgAN, age, estimated glomerular filtration rate (eGFR), proteinuria, mean arterial blood pressure, use of renin-angiotensin system blocker at biopsy, race/ethnicity, use of immunosuppression before biopsy, and Oxford pathological scores were chosen as predictors in the models (20). Similarly, a study on 883 patients with IgAN, showed the benefit of assessing trajectory hematuria and proteinuria by using urine dipstick in high-risk patients' diagnosis (21). These promising investigations along with other recently published data emphasize substitute diagnostic and prognosis determination by using non-invasive methods based on the IgAN pathogenesis. For example, current studies showed the benefits of urine galactose deficient IgA1 and urinary Cd4 as outcome predictor biomarkers (22,23).

Subsequently, new data has emerged questioning the diagnostic validity of performing renal biopsy performance in children with minimal proteinuria and hematuria, suggesting the lack of correlation between clinical presentations and histological findings and thus, there would be no benefits of performing kidney biopsy in this sub-group of pediatric patients (24).

Although proteinuria, hematuria, and IgA deposits pathologically are seen in both children and adults with IgAN, there are different clinical and pathological manifestations regarding the management of IgAN between pediatric and adult patients (11).

Here we provide a review of the literature articles to compare as assess the different pathologic findings and morphological risk factors based on the Oxford system (MEST-C) criteria between children and adults with IgAN.

Search strategy

For this review, we conducted a comprehensive search across multiple databases, including PubMed, Web of Science, EBSCO, Scopus, Google Scholar, Directory of Open Access Journals (DOAJ) and Embase. The search utilized a variety of keywords, including; IgA nephropathy, autoimmune-mediated kidney, biopsy findings, histopathological findings, clinical outcomes, and disease progression. Additionally, we incorporated related terms to ensure a thorough exploration of the literature and enhance the inclusiveness of relevant studies.

The search aimed to capture a broad spectrum of research pertaining to IgAN in both pediatric and adult populations, emphasizing the diverse pathological aspects and outcomes associated with this autoimmune renal condition.

Mesangial cells

Several studies showed that mesangial cellularity and cellular crescent are present in a higher extent in children than in adults. According to the Oxford classification, mesangial hypercellularity (M) is divided into two groups; M0 (≤50% of glomeruli with this feature) or M1 (>50% of glomeruli with mesangial hypercellularity), (Figure 1B(I)). It has been reported that the initial onset of IgAN marked by mesangial hypercellularity in children, whereas in adults, there is expansion of the glomerular mesangial matrix too. Fibrinogen deposition in adults may play a role in matrix expansion (25). Additionally, mesangial cellularity was more strongly correlated with proteinuria and was considered as a more robust feature in outcome prediction in children than in adults (26,27). A recent investigation showed that persistent mesangial hypercellularity could ultimately cause irreversible glomerulosclerosis, posing a leading risk for disease progression in children. The function of the kidneys is impacted by the destruction of capillary loops caused by compression, as well as the release of numerous cytokines and extracellular matrix by mesangial cells (28-30). In this regard, a previous study revealed the correlation between mesangial hypercellularity with greater presence of anemia, dyslipidemia, and reduced renal function (28). The most characteristic IgA deposits in children with IgAN have been described as hypercellularity mesangial cells. Additionally, mesangial hypercellularity was mostly diffuse in children and is focally segmental in adults. Moreover, following IgAN progression, mesangial cellularity decreases and matrix and fibrosis increase (31,32).

Endocapillary cells

Biopsies from children showed significant endocapillary hypercellularity compared to biopsies from adults, even

in younger children than adolescents. Endocapillary hypercellularity (E) and segmental glomerulosclerosis (S) are binary parameters; were classified as points 0 (absent) and 1 (present) in the Oxford classification (Figure 1B(II)). A large study on five continents indicated the prominent endocapillary and extracapsular proliferation in pediatrics, versus vascular changes which were more common in adults (16). Besides, endocapillary hypercellularity might contributed to the progression and formation of sclerotic lesions in children (21). Conversely, Coppo et al revealed that endocapillary, and extra-capillary hypercellularity were not significant in children and adults with a history of hematuria. Their study also showed that the effect of this lesion on proteinuria was similar in adults and children (17). Furthermore, the cohort study on 54 pediatrics with IgAN biopsied from 1982 to 2010 revealed that endocapillary hypercellularity was the only independent predictor in children (33). While some previous studies showed that endocapillary hypercellularity has not been definitively established as an independent predictive factor in both adults and children, recent studies indicated that patients with endocapillary hypercellularity are at a higher risk of more rapid disease progression (5,34). Moreover, Studies in both adults and children showed that endocapillary hypercellularity decreased on a second biopsy after immunosuppressive therapy (11).

Glomerulosclerosis

Chronic scarring lesions, including segmental glomerulosclerosis and partial and visceral adhesion of Bowmen's capsules in at least a glomerulus, were reported in 76% of biopsies of children and adults in Oxford classifications in the study by Roberts et al (35). This lesion attributes to the several mechanisms, such as podocyte damage due to mediators produced by mesangial cells, podocyte maladaptation following hemodynamic changes, and scarring due to segmental endocapillary inflammatory lesion with necrosis (Figure 1B(III)) (36). Renal dysfunction and increased proteinuria were associated with podocyte hypertrophy and tubular pole sclerosis (tip lesion), and segmental sclerosis (37). However, cohort studies revealed that, the only variables that could be predicted were tubulointerstitial fibrosis/atrophy and glomerulosclerosis (34,38). In the recent study on 153 pediatrics diagnosed with IgAN, the chance of achieving complete remission was significantly reduced in those with a higher age of disease onset and the presence of segmental glomerulosclerosis lesions in pathological findings (39).

In several comparisons, children had fewer pathologic findings, with milder presentations than adults; so far, they had greater mesangial and endocapillary hypercellularity, and less segmental glomerulosclerosis and tubulointerstitial damage than adults (40,41). In addition, Haas et al conducted a pathological study to compare 99 children and 125 adults diagnosed with IgAN. They showed that focal or diffuse proliferative lesions had significantly different 10-year renal survival rates (80% in children versus 35% in adults) (42).

Tubular and interstitial lesions

The final stage in IgAN illustrated the interaction between the immune complex and mesangial components, particularly the mesangial IgA transferrin receptor (CD71), the type 4 collagen, and the integrins. In the initial stages, these interactions cause local inflammation and mesangial proliferation, and if they persist, the release of pro-fibrotic mediators induces fibrosis (Figure 1B(IV)) (5).

To date, less progression to chronicity has been demonstrated in children than in adults, resulting in a lower pathological percentage of tubular injury and fibrosis reported in children (31).

In the MEST-C system, tubular atrophy and interstitial fibrosis (T) are categorized based on the percentage of cortical fibrosis involved; T0 (0% to 25%), T1 (26% to 50%), and T2 (more than 50% of the interstitial space involved) (37).

Until now, tubular atrophy and interstitial fibrosis as an independent outcome indicator in children have not been well established (43). However, a renal biopsy study on 1243 pediatric Chinese IgAN patients revealed that S and T lesions were useful and independent long-term prognostic factors rather than M and E variables (43).

Crescent formation

Macrophage infiltration in the urinary space across with basement disturbance causes crescent production. However, early treatment with immunosuppressants, especially in children, can resolve small crescents (5). Nevertheless, crescents could eventually lead to glomerular fibrosis. Several studies have emphasized the decreased renal survival rate in both adults and children with crescent formation (44,45). Nonetheless, early diagnosis in children and initiation of immunosuppressive treatment can lead to regression of crescents and an increase in the survival rate. According to the Oxford classification, crescent formation is divided into three groups C0 (no crescents), C1 (crescents in at least 1 but <25% of glomeruli), or C2 (crescents in at least 25% of glomeruli). However, this classification does not discriminate between inflammatory and fibrotic crescents (46). It has been demonstrated that in pediatrics, crescents mostly contain inflammatory cells and less fibrous organization than in adults (Figure 1B(V)). Additionally, glomerular macrophage infiltration, and sialoadhesin-activated macrophages were correlated with crescent and adhesion formation in both adults and children (25).

Crescent formation is more commonly reported in adults than children. Though, a Western study demonstrated that children accounted for 4.9% of

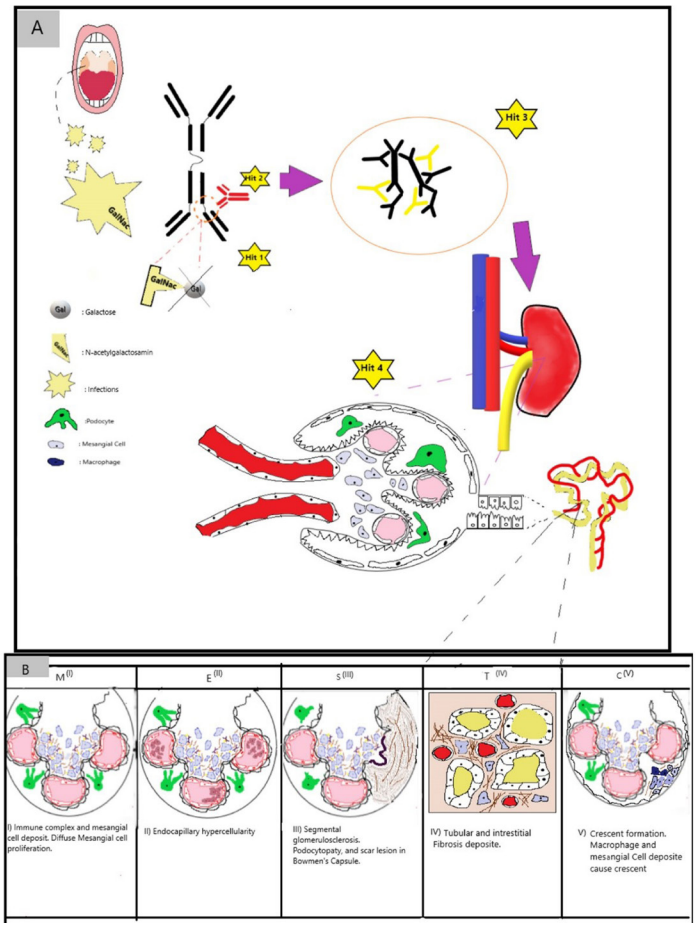

Figure 1. (A) IgA-nephropathy mechanisms, hit 1-2: Immune-cross reaction after infections against abnormal glycosylated IgA1 Hing region, hit 3: Immune-complex formation, hit 4: Immune complex deposited in glomeruli. (B) Different renal lesions with particular pathological findings.

crescentic glomerulonephritis cases (47). Furthermore, the most frequently reported leading cause of crescentic glomerulonephritis, with more than 50% of glomeruli involved with crescent, was immune complex-mediated glomerulonephritis and IgAN (48). Additionally, crescent formation was more common in children than in adults in a prospective study that included 206 adults and 59 children with IgAN with proteinuria over a median of 69 months (41).

Immunopathological findings

While there are more common immunopathological findings in both children and adults with IgAN, some studies showed differences in immunological distributions. In children, IgA deposits were more commonly detected in mesangial and capillary walls.

However, in adults, this distribution is limited to the mesangial area. The presence of IgA deposition in the capillary has been associated with a poor prognosis in children (49). Additionally, IgA deposition accompanied by C3, IgG, and/or IgM was reported with poor prognosis in these patients, despite not being included in Oxford criteria (50,51). Furthermore, it is being reported that C4d mesangial deposit may contribute to poor prognosis in children (48). Moreover, the large sample study, along with previous studies in adults, illustrated the relationship between the presence of >+1 C3 deposit and renal function deterioration in children (43).

Though the overall pattern remains consistent across age groups, the intensity and extent of IgA deposition may vary. Children with IgAN often exhibit more intense and widespread immunofluorescence staining, further emphasizing the heightened immune response observed in pediatric cases.

Conclusion

To summarize, IgAN manifests differently in children compared to adults, displaying unique histopathological characteristics that impact clinical outcomes. Unlike in adults, where it typically presents as chronic glomerulonephritis, IgAN manifests as an acute form of the disease in children. In pediatric IgAN, proteinuria appears to be linked to glomerular hypercellularity, whereas non-proliferative lesions seem to be associated with it in adult IgAN. Understanding these age-related variations is crucial for tailoring treatment strategies and predicting long-term outcomes for patients with IgAN.

Authors' contribution

Conceptualization: Samaneh Zandifar, Arefeh Zahmatkesh.

Validation: Arefeh Zahmatkesh.
Visualization: Samaneh Zandifar, Arefeh Zahmatkesh.
Supervision: Samaneh Zandifar, Arefeh Zahmatkesh.
Writing–original draft: Samaneh Zandifar, Arefeh Zahmatkesh
Writing–review and editing: Mohammad Ali Esmaeil pour, Azadeh Khayyat.

Conflicts of interest
The authors declare that they have no competing interests.

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Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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