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Pathology of idiopathic nephrotic syndrome in children: are the adolescents different from young children?

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Abstract

Background. There is no specific data on the pathological lesions underlying idiopathic nephrotic syndrome (INS) in adolescents in Pakistan. Moreover, it is not known whether the pathological lesions in adolescents differ significantly from young children with INS in our setup.

Materials and methods. A retrospective analysis was carried out on all patients with INS with onset ≤18 years of age. They were split into two groups: patients with onset of INS ≤12 years (young children group) and patients with onset ≥13 through 18 years of age (adolescent group). Renal biopsies were evaluated by light microscopy, immunofluorescence and electron microscopy. The histopathological lesions on renal biopsies were analyzed and compared between the two groups.

Results. The adolescents comprised 173 (32.1%) patients, and there were 365 young children (67.8%). The mean age of adolescents at the time of onset of INS was 12.15 ± 1.5 years and there were 113 boys (65.3%) and 60 girls (34.6%). The mean age of young children was 7.26 ± 3.24 years and there were 231 boys (63.2%) and 134 girls (36.7%). Focal segmental glomerulosclerosis was the most common histopathological lesion in adolescents (36.4%) followed by minimal change disease (MCD) (28.9%).
Adolescent-onset INS had a significantly higher frequency of membranous glomerulonephritis and membranoproliferative glomerulonephritis (MPGN) (P < 0.05) and significantly lower frequency of MCD (P < 0.05) than early childhood-onset INS.

Conclusions. Our data indicate that the pathological lesions in adolescent INS are different from younger children and resemble more closely those seen in adults. Our findings are concordant with the few previously published studies on this subject.

Keywords: adolescents; focal segmental glomerulosclerosis; minimal change disease; nephrotic syndrome; pathological lesions

Introduction

Adolescents have generally been included in the children category in the published renal biopsy surveys of glomerulopathies underlying idiopathic nephrotic syndrome (INS) [1–4]. However, during the past few years, a few investigators have observed significant differences in the clinical and histopathological features of adolescent-onset INS as compared to early childhood INS [4–10]. This has obvious implications for the biopsy indications and the treatment options for this subset of patients. There is still lack of international consensus guidelines on the biopsy indications and the treatment protocols in this age group [10–12]. We have previously reported on the spectrum of histopathological lesions underlying INS in children, but we did not specifically address the differences in the lesions observed in young children as compared with adolescents in that study [13]. Until now, there is no information on the pattern of histopathological lesions in adolescent-onset INS in Pakistan.

We undertook this study to determine the histopathological lesions underlying INS in adolescents in our center and to compare these with the lesions in early childhood INS. We also aimed to compare our findings with the previously published studies on adolescent-onset INS from different parts of the world.

Patients and methods

A retrospective analysis was carried out on all patients with INS, with onset ≤18 years of age, referred to Pediatric Nephrology Unit of Sindh Institute of Urology and Transplantation (SIUT) from July 1995 to July 2008. We divided all patients into two age groups: adolescent group (onset of INS ≥13 through 18 years) and early childhood group (onset of INS <12 years). Standard definition of nephrotic syndrome (NS) was used for inclusion in the study [1, 2, 13]. Patients with secondary causes for NS were excluded. All patients were assessed clinically, followed by laboratory investigations and renal biopsy. Following clinical, laboratory and histopathological features were noted: age at onset, sex, duration from presentation to the biopsy, blood pressure, 24-h urinary protein, serum albumin, serum blood urea nitrogen, serum creatinine, microscopic or macroscopic hematuria and final histopathological diagnosis. The biopsy indications in both groups of patients are shown in Table 1. After obtaining informed consent, 114 (65.8%) adolescents underwent kidney biopsy prior to any attempt at treatment, while 59 (34.1%) received standard therapy with steroids as per International Study of Kidney Disease in Children (ISKDC) guidelines, before they underwent renal biopsy. All children in the early childhood INS group were initially treated with steroids, and biopsies were carried out only in those who were steroid dependent or resistant and planned for immunosuppressive therapy. Briefly, the children were treated with 2.0 mg prednisone/kg body weight per day for six weeks, followed by single dose of 1.5 mg/kg body weight prednisone on alternate days for six additional weeks, which was then gradually discontinued over 3 months. Remission was defined as the absence of proteinuria (complete) or reduction of proteinuria to nonnephrotic levels without edema (partial). The clinical response to prednisone therapy was classified as follows: steroid sensitive—complete or partial remission of proteinuria during the steroid therapy persisting for at least 12 weeks after therapy; steroid dependent—two relapses of proteinuria within 14 days after stopping or during alternate day steroid therapy; resistant—no remission of proteinuria during four consecutive weeks of daily therapy.

Differences in biopsy indications across different subgroups of nephrotic children were multifactorial. In a few cases of adolescents, early consent was not available for undertaking renal biopsy and empirical steroid treatment was given. In others, clinical or laboratory abnormalities suggestive of non-nephrotic change disease (MCD) pathology were present at the time of presentation. However, the most important factor was a change in the biopsy policy over the study period. During the first 10 years of study, all children, including adolescents with INS, were seen by adult nephrologists, a conservative approach to renal biopsy was employed and the biopsy numbers were small, averaging 24/year. In 2005, a separate pediatric nephrology unit was established and a dedicated team of pediatric nephrologists was inducted. A more liberal biopsy approach was adopted and the number of renal biopsies increased markedly, averaging 105/year [14]. During this later period, the majority of adolescents were subjected to renal biopsy prior to starting treatment.

The histopathological lesions of patients with adolescent-onset INS were determined and compared with the younger children with INS onset ≤12 years, over the same study period as per objective of our study.

Pathologic study

Renal biopsies were evaluated by light microscopy (LM), immunofluorescence (IF) and electron microscopy (EM) as described in detail in our previous study [13]. Briefly, two cores of renal biopsy were obtained in each case. One core was fixed in 10% buffered neutral formalin and processed for LM. The other core was divided into two pieces for IF and EM study.

LM study

Briefly, for LM, routinely 10 serial sections are cut and stained with hematoxylin and eosin, Mason’s trichrome, periodic acid-Schiff and silver methenamine stain, as described previously [13]. The biopsies were read by two experienced renal pathologists first independently and then jointly to arrive at the best possible consensus diagnosis.

IF study

Tissue for IF was snap frozen in liquid nitrogen and sections cut on cryotome. The sections were stained by fluorescein isothiocyanate-conjugated antisera specific for IgG, IgA, IgM, C3 and C1q (Dako, Glostrup, Denmark) according to established methodology [13]. The slides were then visualized and graded semiquantitatively as 0 to 3+, and distribution was described as membranous or mesangial in a granular or linear pattern.

EM study

Tissue samples for EM were processed according to established techniques [13]. Briefly, EM tissue was fixed in 2.5% glutaraldehyde, postfixed in 1% osmium tetroxide at 0.02 M Sorenson phosphate buffer at pH 7.4, processed for electron microscopy and embedded in Eponate resin. Ultra-thin sections were stained with uranyl acetate and lead citrate and examined under a transmission electron microscope.

Table 1. Biopsy indications in the young children and the adolescents presenting with INS

<table>
<thead>
<tr>
<th>Biopsy indications</th>
<th>Young children</th>
<th>Adolescents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid-dependent INS</td>
<td>220 (60.2%)</td>
<td>32 (54.2%)</td>
</tr>
<tr>
<td>Steroid-resistant INS</td>
<td>145 (39.7%)</td>
<td>27 (45.7%)</td>
</tr>
<tr>
<td>Adolescent-onset INS</td>
<td>NA</td>
<td>114</td>
</tr>
<tr>
<td>Total</td>
<td>365</td>
<td>173</td>
</tr>
</tbody>
</table>

*Percentages are given only for steroid-treated young children and adolescents. NA, not applicable.
thin sections (100 nm) were cut on Leica ultramicrotome. Sections were stained with uranyl acetate and lead citrate and examined with JEM 1200 EX II electron microscope (JEOL, Tokyo, Japan).

Final diagnosis

This was retrieved from the original renal biopsy reports, which contain personal data, clinical information, laboratory findings, LM, IF and EM findings and final diagnosis.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) for Windows version 10.0 (SPSS, Chicago, IL). Descriptive statistics were used, such as mean ± SD for continuous variables such as age and numbers (percentages) to describe the proportion of categorical variables such as sex and the frequency of different pathological lesions. Chi-squared test was used to compare the frequency of different pathological lesions among the two groups. A P-value < 0.05 was considered significant.

Results

The adolescent group was comprised of 173 (32.1%) patients and the young children group 365 (67.8%). The mean age of the adolescent group at the time of onset of INS was 15.12 ± 1.5 years and there were 113 boys (65.3%) and 60 girls (34.6%). The mean age of young children was 7.26 ± 3.24 years and there were 231 boys (63.2%) and 134 girls (36.7%). The median duration from presentation to renal biopsy in the young children group was 91.57 weeks (range: 16.86–520.14 weeks) and in adolescents 4.42 weeks (range: 0.57–114.29 weeks). The median duration in steroid-treated adolescents was 20.57 weeks (range: 15.14–114.29 weeks), while nontreated adolescents were biopsied at markedly shorter intervals, with a median duration of 1.7 weeks (0.57–9.86 weeks). Table 2 shows a comparison of some clinical and laboratory features among the young children and the two subgroups of adolescents.

As is evident from this table, there was no significant difference in these parameters among the three subgroups, except for the duration from the disease onset to renal biopsy. The latter reflects the differences in biopsy indications among the three groups of children. Table 3 shows a comparison of histopathological lesions among the two subgroups of adolescents: those who underwent renal biopsy after a course of steroids and those who underwent biopsy before any treatment.

Table 2. A comparison of some clinical and laboratory features among young children, subgroup of adolescents with pretreatment biopsy and adolescents with biopsy after steroid treatment

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Young children, (n = 365)</th>
<th>Adolescents with RB after steroid treatment, (n = 59)</th>
<th>Adolescents with pretreatment RB, (n = 114)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At presentation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S. Cr (mg/dL)</td>
<td>0.45 ± 0.21</td>
<td>0.7 ± 0.42</td>
<td>0.72 ± 0.55</td>
<td>NS</td>
</tr>
<tr>
<td>Serum albumin (g/L)</td>
<td>1.98 ± 0.75</td>
<td>2.5 ± 0.8</td>
<td>2.49 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>Hematuria, %</td>
<td>15</td>
<td>27.6</td>
<td>38.5</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>17.6</td>
<td>26.5</td>
<td>31.4</td>
<td>NS</td>
</tr>
<tr>
<td>Duration (weeks)b</td>
<td>91.57</td>
<td>20.57</td>
<td>1.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>S. Cr (mg/dL)</td>
<td>0.48 ± 0.27</td>
<td>0.8 ± 0.4</td>
<td>0.82 ± 0.43</td>
<td>NS</td>
</tr>
<tr>
<td>Hematuria, %</td>
<td>16.4</td>
<td>31.4</td>
<td>40.6</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>18.8</td>
<td>19.5</td>
<td>32.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

*aSCr, serum creatinine, NS, not significant, RB, renal biopsy.

*bDuration in weeks is given as median value from the onset of disease to renal biopsy.

Table 3. A comparison of histopathological lesions among the two subgroups of adolescents: those who underwent renal biopsy after a course of steroids and those who underwent biopsy before any treatment

<table>
<thead>
<tr>
<th>Pathological lesions</th>
<th>Adolescents with biopsy after steroid treatment, n (%)</th>
<th>Adolescents with biopsy before steroid treatment, n (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCD and variants</td>
<td>18 (31)</td>
<td>32 (28)</td>
<td>NS</td>
</tr>
<tr>
<td>FSGS</td>
<td>28 (47.4)</td>
<td>35 (30.7)</td>
<td>NS</td>
</tr>
<tr>
<td>MGN</td>
<td>7 (11.8)</td>
<td>25 (21.9)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>MesPGN</td>
<td>1 (1.7)</td>
<td>8 (7)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>MPGN</td>
<td>3 (5)</td>
<td>10 (8.7)</td>
<td>NS</td>
</tr>
<tr>
<td>IgAN</td>
<td>1 (1.7)</td>
<td>2 (1.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Crescentic glomerulonephritis</td>
<td>0</td>
<td>2 (1.7)</td>
<td>NA</td>
</tr>
<tr>
<td>Postinfectious glomerulonephritis</td>
<td>1 (1.7)</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Total</td>
<td>59 (100)</td>
<td>114 (100)</td>
<td></td>
</tr>
</tbody>
</table>

*aIgAN, IgA nephropathy, NA, not applicable.
membranous glomerulonephritis (MGN) was significantly lower as compared with nonsteroid-treated adolescents. A comparison of histopathological lesions in all adolescents and young children groups is shown in Table 4. It is evident that FSGS is the most common histopathological lesion in the adolescent group (36.4%) followed by MCD (28.9%). Adolescent-onset INS has a significantly higher frequency of MGN and membranoproliferative glomerulonephritis (MPGN) (P<0.05) and lower frequency of MCD (P<0.05) than childhood-onset INS.

## Discussion

This study, the largest reported to date in the literature, provides information for the first time in this country about the spectrum of histopathological lesions underlying adolescent-onset INS. It is well known that the glomerular diseases vary according to age and ethnicity groups [8–10]. The ethnicity being homogenous in our cohort, we sought to determine the effect of age on the histopathological spectrum of glomerulopathies in patients ≤18 years presenting with INS. Apart from being the largest series to date, the study is also important in that it is the sixth publication throughout the world specifically addressing the pathological lesions in NS in an adolescent age group.

There are certain limitations in the study as well. Firstly, the biopsy indications are not similar in the two study groups. This is partly explained by the lack of international consensus guidelines on the biopsy indications for adolescents presenting with INS [10]. The differences in biopsy indications have obvious implications for the spectrum of pathological lesions observed on renal biopsies. However, we were lucky to have two subgroups among the adolescents with differences in biopsy indications, one of which may be thought of as an internal control for the entire group. A comparison of pathological lesions among the subgroups of adolescents shows that the overall predominance of non-MCD lesions in adolescents as compared to young children is maintained across both subgroups. There are, however, some differences with regard to some specific non-MCD lesions. Among these, a significantly higher prevalence of FSGS in the subgroup of adolescents who were treated with steroids prior to renal biopsy is noteworthy. The exact cause of this is not known but may partly be explained on the basis of selection bias of this lesion in steroid-treated adolescents caused by its relatively poor response to steroid therapy. Similarly, a lower prevalence of MGN among the steroid-treated adolescents may partly be explained by the fact that the majority of MGN cases had clinical or biochemical abnormalities at the time of presentation and were biopsied before any attempt at steroid treatment.

Secondly, the timing of renal biopsies was not homogeneous across all groups of children. The differences in the timing, more or less, reflect the differences in biopsy indications. The timing to renal biopsy was markedly short in the subgroup of adolescents, who were biopsied before any attempt at treatment. In contrast, the duration to renal biopsy was markedly longer in young children, who were treated with prolonged courses of steroids before subjecting them to renal biopsy.

Overall, results from our study are in good agreement with all previously reported studies on pathological lesions in adolescent INS. MCD constituted 28.9% of INS in this age group, while non-MCD lesions accounted for 71% of cases. In the young children group, non-MCD lesions were less than MCD (48.8 versus 51.2%). A similar preponderance of non-MCD lesions has been noted in all studies reporting on the pathological lesions underlying INS in adolescents except in the study by Takada et al. [5] from Japan. A closer scrutiny of these studies shows that the reported predominance of non-MCD lesions in adolescents has increased remarkably during the recent past as compared with the earlier periods. The first study to report on increased prevalence of non-MCD lesions included only 25 adolescents out of 413 children (6%) and in which non-MCD lesions constituted 60% of cases of INS [4]. Subsequent studies on the pathology of adolescent INS by Hogg et al. [6] and Baqi et al. [7] found markedly higher rates of non-MCD lesions, seen in 69 and 80% cases, respectively. In fact, both these studies concluded that the pathological lesions in adolescents resemble those observed in recent studies of adult nephrotics, as has also been observed in our study [15–17].

When specific lesions are considered, there are some differences depending on the era of study, ethnicity of the study population, geographic location, biopsy policies and other factors. FSGS was the most common lesion in our adolescents, found in 36.4% of cases. This is markedly higher than the prevalence observed by Hogg et al. [6] (18.5%), but lower as compared with the prevalence reported by Baqi et al. [7] (52%). The study by Hogg et al. [6] was conducted in the early 90s when reports of increasing incidence of FSGS appeared for the first time in the literature, especially among black adults [13, 15].
contrast, the study by Baqi et al. [7] was reported during late 90s and included a vast preponderance of African-American adolescents. Regionally, FSGS was reported in 46.3% of Indian adolescents [10], which is slightly higher as compared with our finding. The prevalence of FSGS has markedly increased during the recent past in both children and adults throughout the world [13, 16, 17]. There was no significant difference in the prevalence of FSGS in prebiopsy treated and all adolescents subgroups in our study.

MCD was the next common lesion in our study, found in 28.9% of cases. Early reports in children by ISKDC and single-center studies showed a preponderance of this disease in children [1–3]. However, all the studies specifically addressing the adolescent age group found a lower prevalence of MCD except the study by Takada et al. [5] in which MCD was found in 52% of cases [6–10]. However, the latter investigators also observed a decreasing incidence of this lesion as compared with MGN and proliferative lesions in the adolescents [5]. In the report of the Southwest Pediatric Nephrology Study Group (SPNSG) of 65 patients [6], 31% had MCD, and Baqi et al. [7] also reported a low incidence of MCD (20%) in an adolescent population.

Membranous (MGN) constituted 18.5% of cases of INS in adolescents in our study. This is significantly higher as compared with the young childhood group and approaches the rate seen in our adults with INS [17]. We observed a significantly higher frequency of MPGN (7.5%) among adolescents compared with younger children (1.1%). In the study of Hogg et al. [6], the frequency of MPGN was 12%, while Baqi et al. [7] observed the prevalence of MPGN to be 7%, which is close to our finding. No significant difference among the study groups was found in the prevalence of mesangial proliferative glomerulonephritis (MesPGN).

Although there is excellent concordance between the various reports of pathological lesions in adolescents with INS, it is worth mentioning here that there are a number of potential biases inherent in the case selection in most of these studies, especially those of retrospective nature. In order to minimize the potential bias in favor of more severe lesions in prebiopsy-treated patients who underwent biopsy as compared with nontreated patients, we compared the lesions among the two subgroups of adolescents (pretreatment biopsy group and all adolescents). We found a more or less similar spectrum of pathological lesions in both the subgroups, confirming that there is little difference of treatment or the nature of biopsy indications on the spectrum of pathological lesions in adolescent patients. Similar results were also obtained by the SPNSG [5].

There are no clear guidelines regarding biopsy indications in the adolescent age group patients who present with NS, and only one study has addressed this problem [10]. Nephrologists throughout the world are divided on this issue. Some give a trial of steroids before undertaking biopsy, while others routinely obtain pretreatment biopsy [7, 11]. We used both the above approaches in our patients and the results indicate there is no significant difference in the pathological lesions in both treated and nontreated adolescents, as discussed previously.

In conclusion, we have found that the pathological spectrum of glomerulopathies in adolescents with INS is markedly different from younger children and is more comparable to that seen in adults.

Conflict of interest statement. None declared.

References


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