Introduction

Nephrotic syndrome (NS), a clinical condition characterized by immense proteinuria, hypoproteinemia, and hypercholesterolemia, is a leading cause of edema due to renal disease. In childhood, the overall prevalence of NS is ~2-5 cases in 100,000 children [1-3]. Minimal change disease (MCD), a benign form with no histological lesions on renal biopsy, is the most common underlying pathology in children aged between 3 months and 16 years [4]. Focal segmental glomerulosclerosis (FSGS), membranoproliferative glomerulonephritis (MPGN), and lupus membranous nephropathy (LN) are the other common lesions [1, 4]. Histopathologic lesions seen in the adolescent population differ from those typically seen in young children or mature adults [5].

Materials and Methods

In this retrospective study, we evaluated the medical records of patients with adolescent-onset NS who received treatment at the Department of Pediatrics, SVPPGIP & SCB Medical College, Cuttack, Orissa, India, between January 2010 and January 2017. Patients with congenital, infantile, childhood-onset, and secondary causes of NS were excluded. All children were treated as per the Indian Society of Pediatric Nephrology (ISPN) protocol.

Results

The data of 48 adolescents were analyzed. The median age at onset of disease was 12 years (range: 10-14 years), and 68.75% (33/48) of the patients were males. Steroid-dependent NS (SDNS, 43.7%, 21/48) was the most common clinical course followed by frequently relapsing NS (FRNS, 29.1%, 14/48). Prednisolone with tacrolimus (37.5%, 18/48) and mycophenolate mofetil (35.4%, 17/48) were the most commonly used treatments. Biopsy results showed that minimal change disease (MCD) was the most common histopathological subtype (37.5%, 18/48) closely followed by focal segmental glomerulosclerosis (FSGS, 31.2%, 15/48). Most of the cases responded to a combination of prednisolone with either MMF, cyclophosphamide, or tacrolimus (23%).

Conclusions

The most common underlying cause of adolescent-onset nephrotic syndrome as assessed histopathologically is MCD, closely followed by FSGS with most of the cases responding to a combination of prednisolone with either mycophenolate mofetil, cyclophosphamide or tacrolimus.

Keywords: Adolescent-onset nephrotic syndrome; Minimal change disease; Focal segmental glomerulosclerosis; Steroid; Histopathology.
In adolescents, two-thirds of patients aged 10-20 years have pathologies other than MCD [1]. Corticosteroid therapy is the standard treatment along with diuretics, anti-hypertensives, cyclosporine, and mycophenolate mofetil (MMF) in children with NS, and response to steroids is well documented in this age group [6]. Since adolescent-onset NS patients are less likely to have MCD compared with younger children, guidelines suggest a biopsy-tailored treatment rather than initiating treatment with glucocorticoids for assessing response in this population, [7, 8] as the majority of studies have demonstrated that adolescent-onset NS is steroid resistant [9, 10]. Histological variability has been evidenced with adolescent-onset NS where the FSGS variety is also very common [9, 10]. Overall, there is a paucity of data regarding the renal histopathological findings and clinical treatment response in the adolescent-onset NS population. The current retrospective study was designed to analyze the histological spectrum and clinical course of adolescent-onset NS in India.

Materials and Methods

Patients of either sex presenting with adolescent-onset NS (age: 10 to 14 years) who received treatment with or without steroids as part of their clinical care at the Department of Pediatrics, Sardar Vallabhbhai Patel PG Institute of Pediatrics (SVPPGIP) and Sri Ram Chandra Bhanja (SCB) Medical College, Cuttack, Orissa, India between January 2010 and January 2017 were included in the analysis.

This study retrospectively evaluated the medical records of adolescent-onset NS patients to analyze the histological spectrum and clinical course. The data of the patients who were treated for adolescent-onset NS were analyzed. Patients with congenital, infantile, childhood-onset, older children without renal biopsy, and secondary causes of NS were excluded from the study. All children were treated as per the Indian Society of Pediatric Nephrology (ISPN) protocol [11]. The study endpoints included renal histopathological profile, clinical course, and response to treatment.

Results

Patients Characteristics and Demographics

Data of 48 patients with adolescent-onset NS who received treatment between January 2010 and January 2017 were analyzed. Figure 1 shows the patients’ characteristics.

Histopathological Spectrum

The results showed that MCD (37.5%, 18/48) was the commonest histopathological subtype closely followed by FSGS (31.2%, 15/48) (Figure 2). There were 10 cases of IgA nephropathy, 2 case of membranous nephropathy (MN), 1 case of C3 glomerulopathy (C3GN), 1 case of IgM nephropathy (IgMN), and 1 case of

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Parameters</th>
<th>N=48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>11.90 (1.40)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>12 (10-14)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>33 (68.75 %)</td>
</tr>
<tr>
<td>Female</td>
<td>15 (31.25%)</td>
</tr>
<tr>
<td>Indication, n (%)</td>
<td></td>
</tr>
<tr>
<td>SDNS</td>
<td>21 (43.7%)</td>
</tr>
<tr>
<td>FRNS</td>
<td>14 (29.1%)</td>
</tr>
<tr>
<td>Others*</td>
<td>13 (27.0%)</td>
</tr>
</tbody>
</table>

*Other indications include Henoch-Schönlein purpura nephritis (n=1), IgA nephropathy (n=3), infrequent relapse nephrotic syndrome + hypertension (n=2), nephrotic syndrome + acute kidney injury (n=2), nephro-nephritic (n=1), nephrotic syndrome (n=1), steroid resistant nephrotic syndrome (n=3), thalassemia + nephrotic syndrome (n=2)
Histopathological and Treatment Profile of Adolescent-Onset Nephrotic Syndrome– Pradhan SK et al

membranoproliferative glomerulonephritis (MPGN). Among 48 adolescents with NS, 21 (43.75 %) had SDNS and 3 (6.25 %) had SRNS. Among those with SDNS, 6 had FSGS and 7 had MCD, and in patients with SRNS, 2 had MCD and 1 had FSGS.

**Treatment Response**
Most of the cases responded to a combination of prednisolone and MMF (23%). All the patients responded to the respective treatment regimens as described in Figure 3.

**Figure 3.** Treatment regimens
Other treatments include prednisolone (n=1), prednisolone + angiotensin-converting enzyme inhibitor (n=3), prednisolone + azathioprine (n=1), prednisolone + cyclosporine (n=2).

**Discussion**
There is scanty literature on adolescent-onset NS with variable results. The treatment outcomes and long-term prognosis in NS majorly depend on the underlying histopathological characteristics. Some investigators have studied adolescent-onset NS in a few countries like Romania [9], Iran [3], Pakistan (Sindh) [10], and India [7]; however, little information is available about India. Hence, this retrospective study was conducted to understand the histological pattern and treatment response of adolescents-onset NS in India.

The mean age of the patients in our study was 11.9±1.4 years, which was similar to the Romanian study (13.6±2.18 years) and Sindh study (15.1±2.13 years). The male to female ratio in our study was 2.2:1, similar to Sindh study (2.1:1) while the Romania study had a ratio of 1:1. The presentation of male to female ratio is similar to that generally observed in children with NS [8, 10, 12]. There are no data on differences in gender predilection to NS in children; in children younger than eight years at onset, the male/female ratio varies from 2:1 to 3:2. In older children, adolescents and adults, the male/female ratio is approximately equal [3].

Only the cases that underwent biopsy under the guidelines mentioned in the ISPN protocol were analyzed in this study. This study was conducted in the eastern India, and demonstrated that after biopsy, MCD was the most common histopathologic type (37.5%) closely followed by FSGS (31.25%). In another Indian study by Gulati et al. in adolescents, the most common histopathologic type was FSGS (46.3%) followed by MPGN (12-18 years of age) [7]. Zsusanna et al. in Romania showed that the most common histological type in adolescents was FSGS (50%) followed by MPGN (33%) [9]. A Sindh based study by Shakeel et al. also demonstrated that FSGS (80%) was the most common histological type [10]. Compared to previous reports in adolescent patients, our study results for histopathologic evaluations are slightly different.

Previous reports in adolescent patients have shown that MCD, FSGS, and MPGN are the major subtypes, which is similar to the histopathological findings of our study where MCD and FSGS were the most common subtypes; however, MPGN was not very common in our population.

Glucocorticoids remain the standard treatment for children with NS [6]. Treatment guidelines suggest a biopsy-tailored treatment in adolescents as the histological spectrum is generally different in this population compared with children [7, 8]. Furthermore, resistance to steroid drugs has been observed in adolescent-onset NS, which could be contributed to the histological variability in this population [9, 10]. Our study showed that adolescents also respond to steroid drugs. The most common histological type in our study was MCD and the most common clinical course was SDNS. A combination of prednisolone with MMF, tacrolimus, or cyclophosphamide showed the
maximum response. These findings were similar to the studies conducted in Sindh and Romania where steroid sensitive patients showed the highest response [9, 10]. Although this study showed that the most common underlying cause of SDNS beginning in adolescence is MCD, this finding needs to be confirmed with multicenter studies across India to acquire a more accurate picture.

Conclusions
This retrospective study conducted in Cuttack, India showed that histopathologically, MCD was the most common subtype followed by FSGS in adolescent-onset nephrotic syndrome with most of the cases responding to a combination of prednisolone with either mycophenolatemofetil, cyclophosphamide, or tacrolimus. These results need to be confirmed in larger studies across multiple cities or centers.

Acknowledgement
We would like to thank Mr. Shreekant Sharma (Lambda Therapeutic Research Ltd.), Drs. Mujtaba Khan and Jaykumar Sejpal (Intas Pharmaceuticals Ltd.) for support in developing the concept/medical writing, additional editorial support and follow-up with the journal/publisher, and Dr. Venugopal Madhusudhana (Lambda Therapeutic Research) for additional editorial assistance.

Previous Presentation: Poster on the data of this article was presented at the 13th Asian Congress of Pediatric Nephrology in conjunction with the 39th Malaysian Pediatric Association Annual Congress, 5-7th October 2017 Kuala Lumpur, Malaysia.

Authors Contributions
SKS and SKP take responsibility for the content of the manuscript, including the data and analysis. SKS, SKP, SB and AK contributed to the acquisition of data, review of the manuscript and final approval.

Conflict of Interest
The authors declare no conflicts of interest.

Financial Support
The manuscript development support was provided by Intas Pharmaceuticals Ltd.