International Journal of Current Advanced Research
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: SJIF: 5.995
Available Online at www.journalijcar.org
Volume 6; Issue 11; November 2017; Page No. 7699-7705
DOI: http://dx.doi.org/10.24327/ijcar.2017.7705.1208

Research Article

STUDY OF ADULT MINIMAL CHANGE DISEASE WITH SPECIAL EMPHASIS ON ELECTRON MICROSCOPY

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A R T I C L E I N F O

Article History:
Received 16th August, 2017
Received in revised form 25th September, 2017
Accepted 3rd October, 2017
Published online 28th November, 2017

Key words:
Nephrotic Syndrome, Foot Processes Effacement, Immunofluroscence

A B S T R A C T

Minimal change disease (MCD) is defined when nephrotic syndrome occurs without any glomerular lesions on light microscopy, negative staining on immunofluorescence microscopy, and foot process effacement but no electron dense deposits on electron microscopy. Corticosteroid-sensitive nephrotic syndrome is the term used to describe the disease occurring in children with nephrotic syndrome who respond to corticosteroids but who have not had a renal biopsy to provide the histologic proof of MCD. However, most adult patients with the nephrotic syndrome are biopsied. Attempt has been made to concentrate on electron microscopy appearances in minimal change disease in adults.

Aim is to analyse the clinical, biochemical profile of adult patients with primary NS due to minimal change disease and to study the course of the minimal change disease and to study the response to therapy and outcome of minimal change disease.

The present study evaluated 30 patients diagnosed to have adult minimal change disease admitted to Gandhi Hospital, secunderabad, during the period of December 2013 to December 2015. Patients admitted with edema were evaluated with 24 hrs urinary protein, serum albumin and lipid profile. If patient is found to have proteinuria, hypercholesterolemia and hypoalbuminemia, he/she was subjected to renal biopsy, and all biopsy proven MCD cases were include in the study group Minimal change disease was found to be common in <30 yrs age group. Major clinical manifestation is oedema.Majority of cases are steroid responsive and frequent relapses are not uncommon among adults. Microscopic hematuria, hypertension and acute kidney injury are more common in adults. Hypertension is not uncommon in adult MCD. Duration of response to steroid is longer among adult MCD In steroid resistant cases, mild mesangial hypercellularity along with foot process effacement is most common in electron microscopy finding.

INTRODUCTION

Minimal change disease (MCD) is defined when nephrotic syndrome occurs without any glomerular lesions on light microscopy, negative staining on immunofluorescence microscopy, and foot process effacement but no electron dense deposits on electron microscopy[1].

Minimal change disease (MCD) is the cause of nephrotic syndrome in about 90% of children younger than 10 years, about 50% to 70% of older children, and 10% to 15% of adults[6]. MCD is characterised by the absence of histologic glomerular abnormalities, other than ultrastructural evidence of epithelial cell foot process fusion, in a patient presenting with nephrotic syndrome who is typically corticosteroid responsive.

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Corticosteroid-sensitive nephrotic syndrome is the term used to describe the disease occurring in children with nephrotic syndrome who respond to corticosteroids but who have not had a renal biopsy to provide the histologic proof of MCD. The presence of nephrotic syndrome is important because similar histologic findings may be seen in patients with proteinuria in the absence of nephrotic syndrome. Such patients may have different conditions with different prognosis and requirements for management. Whereas MCD is classically associated with normal-appearing glomeruli and corticosteroid responsiveness, MCD appears to overlap with a variety of histologic variants that have a tendency to be less corticosteroid responsive. These conditions include focal segmental glomerulosclerosis (FSGS) and IgM nephropathy. It is possible that both MCD and FSGS have similar initial histologic appearances but that FSGS is less corticosteroid responsive and hence develops secondary sclerosing lesions over time. Whether this represents a continuum of the same disease in which some subjects are corticosteroid sensitive and

others are not or whether they represent two distinct etiologies remains debated.

Most children with the nephrotic syndrome are not biopsied; instead, they are typically treated empirically with steroids. However, most adult patients with the nephrotic syndrome are biopsied. Attempt has been made to concentrate on electron microscopy appearances in minimal change disease in adults.

Aim of the Study

1. To analyse the clinical, biochemical profile of adult patients with primary NS due to minimal change disease.
2. To study the course of the minimal change disease.
3. To study the response to therapy and outcome of minimal change disease.
4. To perform electron microscopic study for steroid resistant cases.

MATERIALS AND METHODS

The present study evaluated 30 patients diagnosed to have adult minimal change disease admitted to Gandhi Hospital, secunderabad, during the period of December 2013 to December 2015.

Inclusion Criteria

Minimum 18 yrs old.

Exclusion Criteria

- Patients with secondary glomerular disease.
- Those who were not able to understand the characteristics and implications of the study.

Parameters under the Study

- Blood urea, Sr. creatinine
- Ultrasound abdomen
- Serum Proteins, Albumin, 24hrs urinary proteins, spot protein creatinine ratio, CUE, lipid profile, Serum Creatinine and Renal Biopsy – Light Microscopy, Immuno Fluorescence and Electron Microscopy in the case of steroid resistant cases.

METHODS

This is a prospective observational study which was approved by hospital ethics committee. Patients admitted with edema were evaluated with 24 hrs urinary protein, serum albumin and lipid profile. If patient is found to have proteinuria, hypercholesterolemia and hypoalbuminemia, he/she was subjected to renal biopsy, and all biopsy proven MCD cases were include in the study group.

The following definitions were used while collecting the data:

MCD: Nephrotic syndrome with no glomerular lesions by light microscopy, no staining on immunofluorescence microscopy.

Complete remission (CR): Reduction of proteinuria to 0.3 g/day or 300 mg/g urine creatinine, serum albumin >35 g/L(3.5 g/dL).

Partial remission (PR): Reduction of proteinuria to 0.3–3.5 g/day(300–3500 mg/gurinecreatinine).

Relapse: proteinuria >3.5 g/day or >3500 mg/g (4350 mg/ mmol) urine creatinine after CR has been obtained.

Frequently relapsing NS (FRNS): Four or more relapses within1year.

Steroid-dependentNS(SDNS): Two relapses during or within 2 weeks of completing steroid therapy.

Steroid resistant NS (SRNS): Failure to achieve remission despite at least 16 weeks of prednisolone.

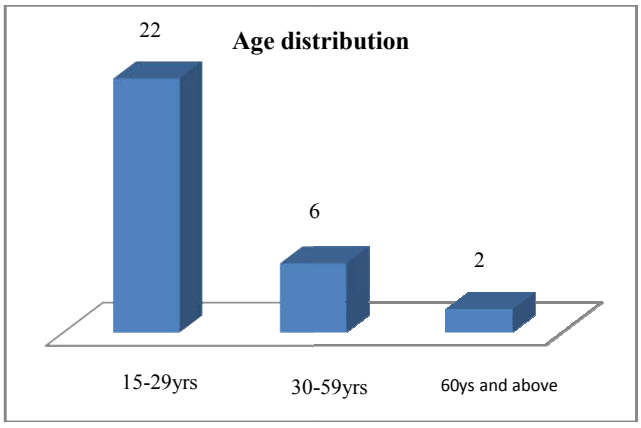
Acute kidney injury (AKI): Rise in serum creatinine by 0.3 mg/dL over the baseline or urine output<0.5 mL/kg/h for 6 h.

A single pathologist reported all of the histopathology for light microscopy and immunoflourescence. Electron microscopy done for steroid resistant cases. General principles of the treatment as per KDIGO guidelines remained the same over the study duration. Initial treatment given was daily prednisolone 1 mg/kg for 4–16 weeks followed by tapering over the next 6 months. Relapses were treated in a similar manner. Oral cyclophosphamide (CYP) 1.5–2mg/kg was used in Frequent Relapsing Nephrotic Syndrome, Steroid Dependent Nephrotic Syndrome with steroid intolerance and in Steroid Resistant Nephrotic Syndrome CNI's (tacrolimus) was used. Statistical analysis was performed using the software Statistical Package for the Social Sciences **(**SPSS) version 16.0. Continuous variables were expressed as mean and standard deviation (SD). Variables that were evaluated for possible association with the remission included serum albumin, cholesterol, 24-h urine proteins.

RESULTS

Age Distribution

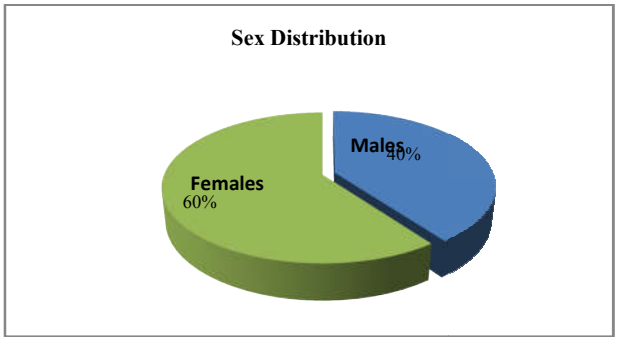
Age group(yrs)	No	Percentage
18-29	22	73.4%
30-59	06	20%
≥60	02	6.6%
Total	30	100%



Most of the patient in this study are in the age group of 18 yrs to 29 yrs consist 22 yrs (73.4%). 30 yrs to 59 yrs age group consist 6 patients (20%), more than 60 yrs age group consist 2 patients.

Sex Distribution

Sex	No	Percentage
Males	12	40%
Females	18	60%
Total	30	100%

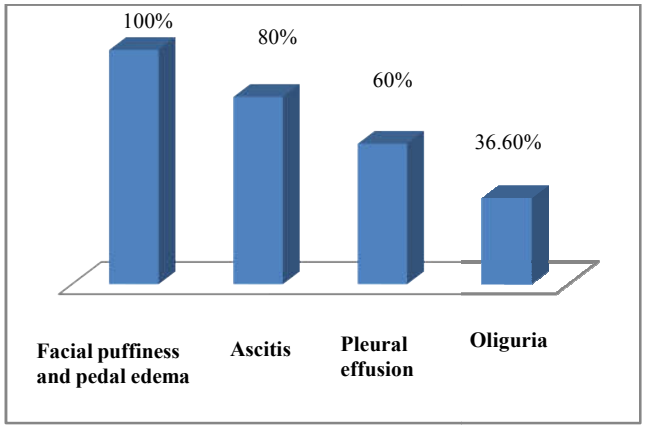


In this study, out of 30 cases 12 are male 18 cases are females.

Clinical Features at Presentation

	Clinical features	Incidence	%(Percentage)
1	Facial puffiness and pedal edema	30	100%
2	Ascitis	24	80%
3	Pleural effusion	17	60%
4	Oliguria	11	36.6%

Clinical Features at Presentation

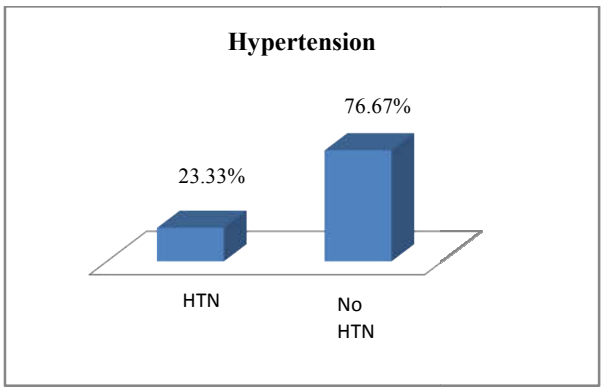


In this study, all patients present with facial puffiness and pedal edema, out of these patients ascitis found in 80% (24pts) of cases.

Pleural effusion found in 60% (17 pts) of cases.
Oliguria is presenting complaint in 11 pts (36.6%).
History of allergic rhinitis, atopy noted in 4 cases.

Hypertension

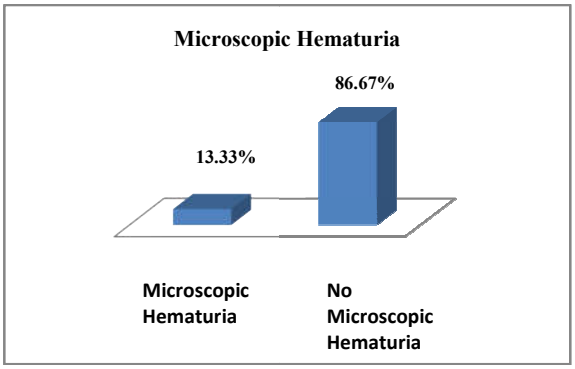
Hypertension	7
No hypertension	23



In this study, out of 30 patinets, 7 patients (23.3%) found to be hypertensive at the time of presentation.

Microscopic Hematuria

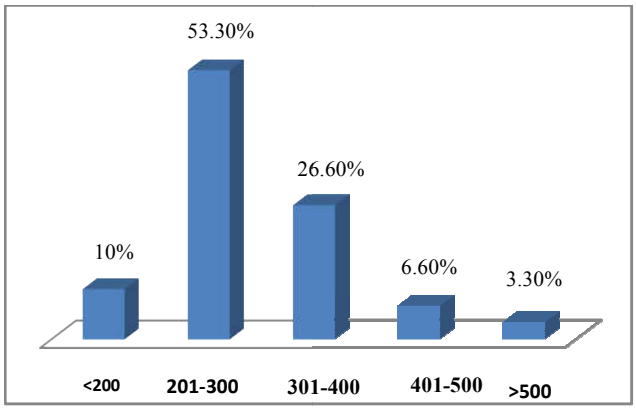
Microscopic hematuria	4
No microscpoic hematuria	26



In present study, 4 out of 30 pts (13.33%) show microscopic hematuria at the time of presentation.

Distribution of S.Cholesterol

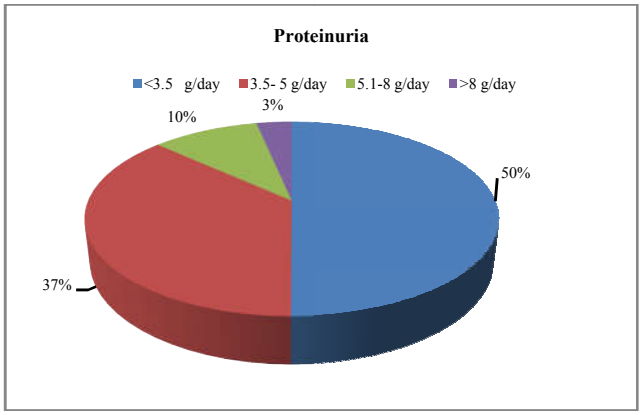
S.Cholesterol	No	Percentage
<200mg/dl	3	10%
201-300mg/dl	16	53.3%
301-400mg/dl	8	26.6%
401-500mg/dl	2	6.6
>500mg/dl	1	3.3



In present study, hypercholesterolemia is seen in 90% (27 pts) of the patients at the time of presentation. In this people, the elevated cholesterol levels are mostly in the region of 201-300 (53.3%), 301-400 (26.6%).

Distribution of 24hr proteinuria

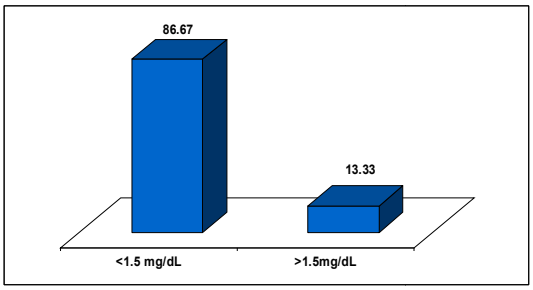
Proteinuria	No	Percentage
<3.5 g/day	15	50%
3.5- 5 g/day	11	36.6%
5.1-8 g/day	3	10%
>8 g/day	1	3.3%



In present study, most of the patients present with proteinuria (50%) of <3.5gr/d. Most of these patients show serum albumin level <2g/dL.
>8g/d of proteinuria seen in only 3.3% of study patients.

Distribution of S Creatinine

S Creatinine	No	Percentage
<1.5 mg/dL	26	86.67
>1.5mg/dL	4	13.33



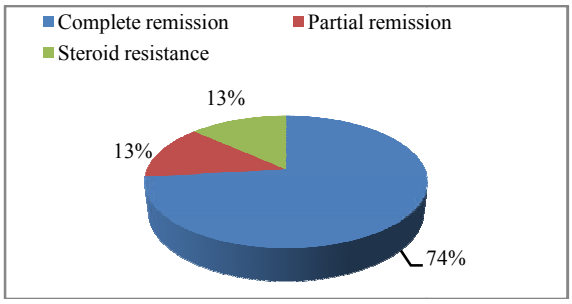
In present study patient present with elevated serum creatinine in 4 patients (13.3%).

These patients show tubular simplification (ATN) along with normal looking glomuruli (MCD) on light microscopy.

2 of these patients have taken herbal medication prior to hospitalisation.

Response to Daily Steroids

Complete remission	22	73.33%
Partial remission	4	13.33%
Steroid resistance	4	13.33%



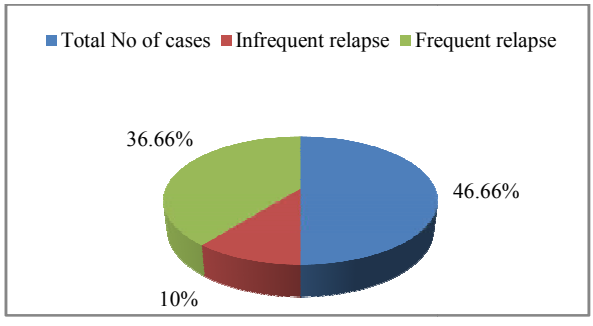
In present study, all patients were treated initially with steroids as per KDIGO guidelines.

Most of the patients (73.3%) show complete remission.
Partial remission seen in 4 patients (13.3%).

Steroid resistance seen in (13.3%). These patients are started on CNI's (Tacrolimus).

Relapse

Total No of cases	14	46.66%
Infrequent relapse	3	10%
Frequent relapse	11	36.66%



In present study relapse seen in 14 cases (46.6%) during study period.

Out of which 11 patients are freequent relapses (36.6%).

Time To Responce To Steroid Therapy

Time to remission	11 weeks (4 w -8 w)
Time to relapes	10 months (6 m-15 m)
Mean no of relapes	2.1

In this study time to responce to steroid therapy 11 weeks(4 w -8 w)
In this study time to relapes was 10 months (6 m-15 m)
In this study mean no of relapes were 2.4.

Alternative Therapy For Steroid Resistant Cases

No of cases treated with CNI(Tacrolimus)	4
Response to CNI	3 cases partially responded 1 case not respanded.

In this study steroid resistante case were 4 among them 3 patients were responded to CNI's and 1 patient not responded.

Akute Kidney Injury In Mcd

No of AKI	4 case
Time to recover	4.6 weeks
Biopsy showing ATN	4 case

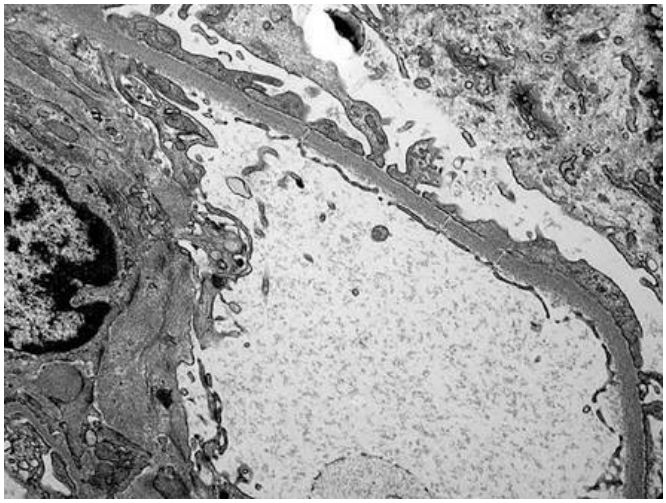
4 patients develped AKI in this study.
Average time to recovery was 4.6 weeks
On biopsy all of them showed ATN
All 4 patient were recovered.
Non of them required HD.

Electron Microscopic Findings In Steroid Resistant Cases

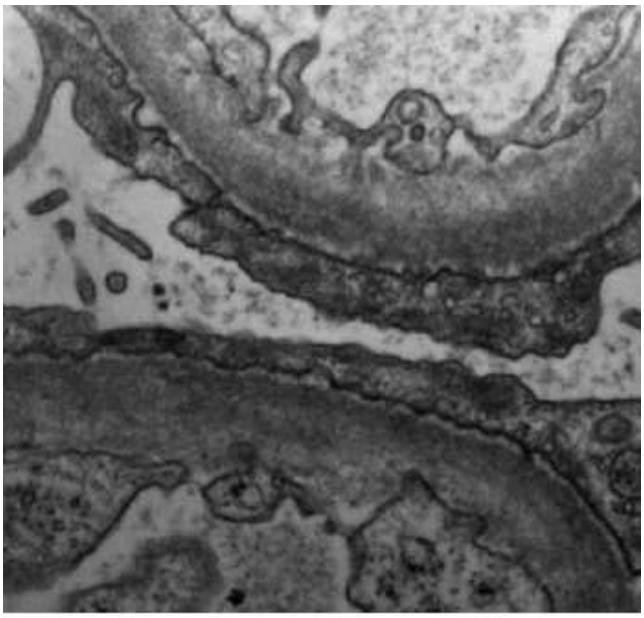
Electron microscopic findings	No. of patients
Mild mesangial proliferation with podocyte foot process effacement	3
Focal segmental glumorulo sclerosis with Podocyte foot process effacement.	1

Three patients were electron microscopy pictures of glomeruli showing Mild mesangial proliferation with podocyte foot process effacement.

Patient No. 4

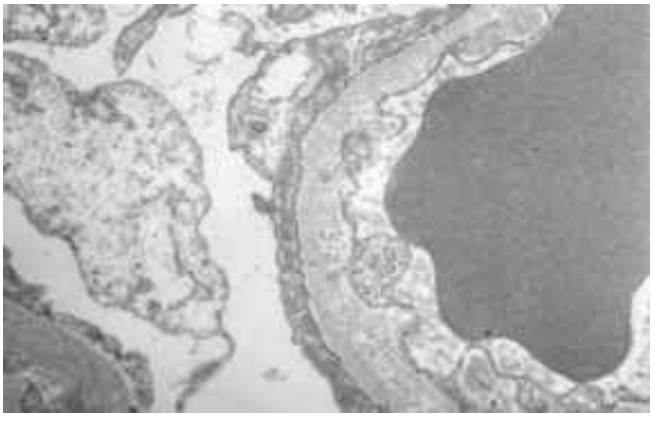


Patient No 27



Patient No 30

Electron microscope picture of glomuroli showing Focal segmental glumorulo sclerosis with Podocyte foot process effacement



Patient No 11

In steroid resistant cases (4 cases), electronic microscopic study was done, 3 patients showing mild mesangial hypercellularty along with diffuse podocyte foot process effacement.

1 case showing Focal segmental glumorulo sclerosis with Podocyte foot process effacement.

DISCUSSION

The present study evaluated 30 patients diagnosed to have adult minimal change disease admitted to Gandhi Hospital, Secunderabad, during the period of December 2013 to December 2015 fulfilling the inclusion and exclusion criteria.

Mean age in this study was 29.5±10.86yrs. Minimum age in this study was 18yrs and maximum being 62 yrs. Maximum number of patients in this study were in 18-29 yrs age group, followed by 30-59yrs. From renal biopsy registry data from south India done by U Das *et al*[2], and N. Balakrishnan *et al*[3] MCD was seen in <30yrs age group. Similarly, in a study by Goyal V *et al*[4] MCD was common in the age groups of 16-29yrs. In Chinese data[5], MCD was common among the patients aged 14-24 yrs. In a study by Keskar *et al*[6], mean age at presentation is 30 yrs. Present study has similar results.

Most of the patients in this study were females. Out of 30 cases 12 were males (40%) and 18 were females (60%) with M:F-1:1.5 which is similar to a study by Waldmann *et al*[54]. But, in renal biopsy registry data by N Balakrishnan *et al*[51] in CMC Vellore and other study by Keskar *et al*[55] males outnumbered females.

In the present study, all paitents (100%) presented with facial puffiness and pedal edema. 80% of patients had ascitis and 40% had pleural effusion. This was noted especially in patients with severe hypoalbuminemia. This is similar to previous study done by Glassock *et al*[56] showing a correlation between the degree of ascitis or pleural effusion and hypoalbuminemia. In the present study 7(23.33%) patients had hypertension at presentation, which is less when compared to a study by Waldmann *et al*[54](42.9%) and a study by Afsoon Emami Naini *et al*[57] (32.5%).

In the present study 4(13.33%) patients had hematuria at presentation which is similar to a study by Afsoon Emami Naini *et al*[57] (12%), Keskar *et al*[55] and Gruppe HE *et al*[58] (13.5%). But, Waldmann *et al*[54] demonstrated microscopic hematuria in 28.9% patients.

In the present study, 90% of the patients had hypercholesterolemia at presentation. Hypercholesterolemia was seen maximum(53.3%) in the range of 200-300mg/dl. In a study by Radhakrishnan *et al*[26], 87% had >200mg/dl, 53% had 300mg/dl and 25% had 400mg/dl .The results were similar in this study.

Mean proteinuria in the present study is 3.77±1.46 g/d, whereas in the study by Waldmann *et al*[54], it was 9.93±0.71 g/d. 50% of patients had subnephrotic range proteinuria and remaining 50% had nephrotic range proteinuria.

AKI complicated the nephrotic syndrome at presentation in 4 cases (13.33%) which is similar to a study by Waldmann *et al*[6] (17.9%), whereas in a study by Keskar *et al*[7] 6.55% cases had AKI. Complete remission was achieved in 22(73.33%) patients, partial remission was achieved in 4(13.33%) patients with daily steroids. 4(13.33%) patients were steroid resistant, who were started on tacrolimus. In a study by Waldmann *et al*[6], complete remission was achieved in 70.25% patients and partial remission in 4.85% patients. 27% Patients were steroid resistant.

In the present study, 11(36.66%) patients had frequent relapses and 3(10%) patients had infrequent relapses. In a study by Waldmann *et al*[6], 71.1% cases had relapses.

Overall results of the present study were comparable to previous studies. In steroid resistant cases (4 cases), electronic microscopic study was done, 3 patients showing mild mesangial hypercellularty along with diffuse podocyte foot process effacement.1 case showing Focal segmental glumorulo sclerosis with Podocyte foot process effacement in electronic microscopic study. In waldmann *et al* study 6 cases showing Focal segmental glumorulo sclerosis in electronic microscopic study out of 11 steroid resistant cases.

	Variable	Waldman et al	Keskar et al	Present study
1	Age at onset	45.1±1.6	30.46 ± 13.43	29.5±10.86
2	Gender(M/F)	1:1.5	1.2:1	1:1.5
3	S Creatinine (mg/dl)	1.39±0.13	-	1.3±0.78
4	S Albumin (g/dl)	2.21±0.08	2 ± 0.7	1.9±0.98
5	Urine protein (g/d)	9.93±0.71	5.33 ± 3.75	3.77±1.46
6	S Cholesterol (mg/dl)	420.8±16	380±135	293.26±100.76
7	Hypertension (%)	42.9%	6.55%	23.33%
8	AKI(%)	17.8%	6.55%	13.33%
9	Hematuria(%)	28.9%	13.11%	13.33%

Time To Responce To Steroid Therapy

Study	Waldmann *et al*	Keskar *et al*	Present study
Time to remission	13 weeks	5.33weeks(2-16 w)	11 weeks(4-8w)
Time to relapse	21.6weeks	12.2 months	10 months(6-15m)
Mean no of relapses	2.9		2.4

In this study time to response to steroids (11 weeks) comparable to waldmann *et al* study (13 weeks) but longer than keskar at al study (5.33 weeks).

In this study time to relapse was 10 months (6m-15m) which is comparable to other studies (waldmann *et al* study 21.6 weeks, in keskar *et al* study 12.2 months)

In this study nean no of relapses (2.4) comparable to waldmann *et al* study

Alternative Therapy For Steroid Resistant Cases

Study	Waldmann *et al*	Keskar *et al*	Present study
No of patients treated with CNI who were steroid resistant.	2	1	4
Response to CNI(Tacrolimus)	1patient(50%) partial remission	No response to Tacrolimus	3 patients (75%) partial remission. 1patient not responded

In this study steroid resistant cases were 4 among them 3 patients were responded to CNI's (Tacrolimus).and 1 patient not responded.

In keskar *et al* study 1 patient treated with Tacrolimus but no response. In waldmann *et al* study 2 patient were given CNI's (Tacrolimus).1 patient responded 1 patient not responded.

Akute Kidney Injury In Mcd

Study	Waldmann *et al*	Keskar *et al*	Present study
No of AKI cases	24(22.8%)	14(22.95%)	4(13.33%)
Time recover	6.4 weeks		4.6 weeks
Biopsy showing ATN	14 cases		4 cases
No of patients recovered		14 (100%)	4 (100%)

In this study 4 out of 30 patients (13.33%) developed AKI (waldmann *et al* study -22.8%, keskar *et al* study -22.95%).

Time to recover in this study was comparable to waldmann *et al* study (present study – 4.6 weeks, waldmann *et al* study 6.4 weeks).

In this study all 4 patients under went renal biopsy which showed ATN (in present study 100% in waldmann *et al* study 63% showed ATN). All patients in present study recovered on conservative management comparable to keskar *et al* study. None of them required HD

CONCLUSIONS

1. Minimal change disease was found to be common in <30 yrs age group.
2. Major clinical manifestation is oedema.
3. Majority of cases are steroid responsive and frequent relapses are not uncommon among adults.
4. Microscopic hematuria, hypertension and acute kidney injury are more common in adults.
5. Hypertension is not uncommon in adult MCD.
6. Steroid resistant cases are more common among adult MCD patients.
7. Duration of response to steroid is longer among adult MCD
8. In steroid resistant cases, mild mesangial hypercellularity along with foot process effacement is most common in electron microscopy finding.
9. AKI occur in significant no of adult MCD patients, majority of them recovered.

Limitations

1. Small study population.
2. This is nonrandomized and is largely a referral- based population. Therefore, it may not be representative of all adult patients with MCD.
3. Electron microscopy study done in steroid resistant cases only, not in all cases.
4. Short duration of follow-up.

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How to cite this article:

Hari Prasad P *et al* (2017) 'Study of Adult Minimal Change Disease with Special Emphasis on Electron Microscopy', *International Journal of Current Advanced Research,* 06(11), pp. 7699-7705.
DOI: http://dx.doi.org/10.24327/ijcar.2017.7705.1208

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