International Journal of Pediatrics and Adolescent Medicine 6 (2019) 146–150

HOSTED BY

Contents lists available at ScienceDirect

International Journal of Pediatrics and Adolescent Medicine

journal homepage: http://www.elsevier.com/locate/ijpam

Full length article

Clinical significance of IgM deposition in pediatric minimal change disease

Duaa M. Al Romaili [a], Turki O. Al-Hussain [b], Hazem S. Awad [a], Sermin A. Saadeh [a], Ibrahim A. Al-Hassoun [a], Turki A. Al-Shareef [a, *]

[a] Department of Pediatric Nephrology, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia
[b] Department of Pathology and Laboratory Medicine- Anatomic Pathology, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

ARTICLE INFO

Article history:
Received 21 March 2019
Received in revised form
19 July 2019
Accepted 3 September 2019
Available online 12 September 2019

Keywords:
Nephrotic syndrome
Minimal change disease
IgM
IgM nephropathy

ABSTRACT

Background: Idiopathic nephrotic syndrome (INS) is a common pediatric disease. Minimal change disease (MCD) is the most common histopathological subtype and usually has good prognosis. However, in less common presentations, INS may have an unusual course that makes renal biopsy a necessity to identify its etiology. Immunoglobulin M (IgM) occasionally deposits in the mesangium and can be seen under immunofluorescence (IF). The role of IgM is controversial in MCD. It is likely associated with less favorable outcomes for MCD. This study aims to investigate the clinical significance of mesangial IgM deposits on the outcome of MCD in a pediatric population.

Methods: In this retrospective cohort study, we obtained native kidney biopsy samples from 192 children who were diagnosed with MCD from 2003 to 2014. The samples were divided into groups according to the histopathological deposition of IgM in biopsies under IF. The group for which biopsies showed IgM was labeled as IgM + IF (n = 77), and the group for which biopsies were without IgM was labeled as IgM- IF (n = 115). We reviewed hypertension, hematuria, and estimated glomerular filtration rate (eGFR) at the time of presentation to our institute; response to steroid therapy (remission, dependence, frequent relapses, and resistance) and response after adjuvant immunosuppressive therapy (complete remission, partial remission, frequent relapses, and no response) when indicated; development of chronic kidney disease (CKD) and end-stage renal disease during the course of the disease (ESRD).

Results: Our results showed that mesangial IgM deposition in MCD showed significant statistical association with hypertension at the time of presentation ($P = .05$). There was statistically significant association between the presence of IgM deposition and the development of steroid dependence ($P = .05$) and CKD during the course of the disease ($P = .05$).

Conclusions: Our study showed that IgM deposition in MCD showed statistical association with hypertension by the time the patient presented to our institute, development of steroid dependence, and CKD. IgM may play a role in MCD. However, we recommend a prospective study to verify the role of IgM in MCD outcomes.

© 2019 Publishing services provided by Elsevier B.V. on behalf of King Faisal Specialist Hospital & Research Centre (General Organization), Saudi Arabia. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Idiopathic nephrotic syndrome (INS) is a primary glomerular disorder characterized by heavy proteinuria, hypoalbuminemia, and generalized body edema with no underlying etiology [1]. INS is a common disease in the pediatric population. The outcome of the disease depends on many factors including the histopathological subtype of INS. INS includes many histopathological subtypes including minimal change disease (MCD), which is common in INS. There are also focal segmental glomerulosclerosis (FSGS) (poor

* Corresponding author. Section of Pediatric Nephrology, Department of Pediatrics, King Faisal Specialist Hospital and Research Center, P.O. Box 3357 MBC: 58, Riyadh, 11211, Saudi Arabia.

E-mail addresses: dalromaili@kfshrc.edu.sa (D.M. Al Romaili), turkihussain@kfshrc.edu.sa (T.O. Al-Hussain), awadh2008@hotmail.com (H.S. Awad), ssermin@kfshrc.edu.sa (S.A. Saadeh), ihassoun@kfshrc.edu.sa (I.A. Al-Hassoun), tshareef@kfshrc.edu.sa (T.A. Al-Shareef).

Peer review under responsibility of King Faisal Specialist Hospital & Research Centre (General Organization), Saudi Arabia.

https://doi.org/10.1016/j.ijpam.2019.09.001
2352-6467/© 2019 Publishing services provided by Elsevier B.V. on behalf of King Faisal Specialist Hospital & Research Centre (General Organization), Saudi Arabia. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

long-term prognosis in most of the cases) and other subtypes [2,3]. Most children with steroid-sensitive INS have MCD, while those who show steroid-resistant INS have FSGS [4]. The International Study of Kidney Disease in Children (ISKDC) and the Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN) have studied this since the 1960s, as well as many others. Their work has established the ground for the clinical management of SSNS and SRNS in pediatrics. As MCD is the most common subtype, the current standard of care in dealing with a new-onset INS involves assuming MCD histopathology and beginning treatment with steroids at the time of presentation without a biopsy [2]. However, resistance or frequent relapses occur in certain cases of INS with steroid dependence; here, a renal biopsy is indicated to identify the histopathological etiology [2,5].

Immunoglobulin M (IgM) is a serum antibody with a basic structure. It is biochemically the largest antibody in the human circulatory system and serves as an initial activator for the complement cascade [6]. IgM is a large molecule and hence cannot easily diffuse; it is commonly found in organs of the interstitium. In many cases of complicated INS, the histopathological findings of native kidney biopsy (NKB) samples showed MCD with IgM deposition mainly under immunofluorescence and sometimes electron microscopy [1,7]. Many studies have suggested that IgM might be a predictor of kidney function deterioration in the course of MCD. This speculation led to a relatively newly described clinicopathological entity of MCD, named as IgM nephropathy (IgMN) [6].

IgMN has no universally acceptable definition but is described as an idiopathic immune complex-mediated glomerulopathy manifested with heavy proteinuria and visible diffuse granular IgM deposits under IF [5,7]. It ranges from considering any positivity in the staining as significant, even if it is trace, while others put the threshold at +2. The disease occurs more frequently in children than in adults, and the pathophysiology is controversial with unclear pathophysiological background. Some investigators considered IgMN to be a transitional state between MCD and FSGS [5,6,8]. In this report, we examined the clinical significance of IgM under IF in MCD by assessing the initial presentation to our center with hypertension (HTN) and hematuria, the level of estimated glomerular filtration rate (eGFR), response to steroid treatment, response to adjuvant immunosuppressive therapy, progression to chronic kidney disease (CKD), and end-stage renal disease (ESRD) during the course of the disease.

2. Subjects and methods

2.1. Ethical considerations

This study was performed in King Faisal Specialist Hospital and Research Center (KFSHRC), Riyadh-Saudi Arabia. Data were collected from patients' charts, and for this purpose, the Integrated Clinical Information System (ICIS) was used in the institution. The study complied with the principles outlined by the Research Administration and Compliance Office (RAC) and conformed to its ethical conduct (RAC no. 2141144).

2.2. Patients and study design

In this retrospective study, we reviewed 403 renal biopsy reports of children with nephrotic syndrome, whose biopsies were performed and reported in King Faisal Specialist Hospital and Research Center (KFSHRC) from January 2003 to December 2014; 192 cases were labeled as pediatric MCD (Fig. 1).

a) Inclusion criteria:

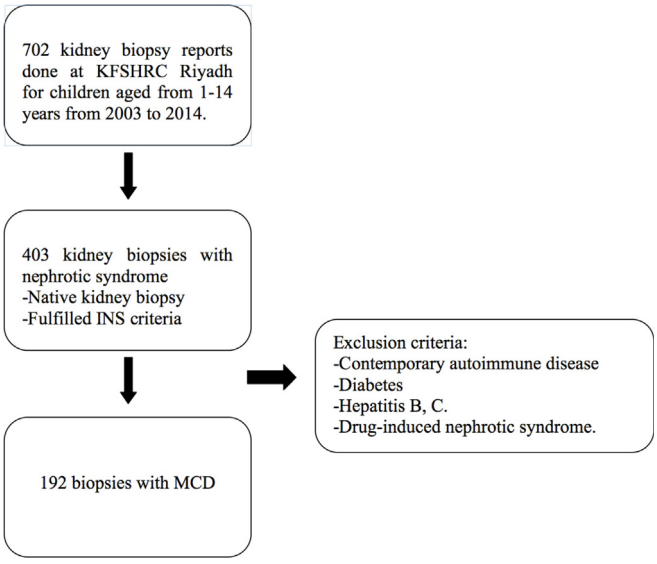

Fig. 1. Case selection. (1. Khalifa M. Improving Emergency Room Performance by Reducing Patients' Length of Stay. Stud Health Technol Inform. 2015; 213:41–4. Epub 2015/07/15. PubMed PMID: 26152948.)

- Cases of nephrotic syndrome that fulfilled the criteria of INS definition (Table 1) [5,6,8,10].
- NKB samples.
- Patients with MCD whose biopsies were performed at any age between 1 and 14 years.

b) Exclusion criteria:

- Cases of contemporary autoimmune disease, rheumatoid arthritis, hyper-complementemia, hyper-IgA syndrome, and diabetes mellitus.
- Concurrent or past history of hepatitis B or C.
- Drug-induced nephrotic syndrome.

Patients with these categories were excluded, as they have pathophysiologies, treatments, and prognostic values different from those of MCD.

We categorized the sample based on the histopathological type and categorized the IF intensity of IgM into two groups: The group for which biopsies showed IgM depositions under IF was labeled as IgM + IF, and the group for which biopsies were without IgM was labeled as IgM-IF. The subjects in both groups were evaluated by the presence of HTN, presence of hematuria, and the median eGFR at the time of first presentation to our institute. We also evaluated steroid response by the development of steroid-dependence or -resistance and frequent relapses or remission after steroid therapy. We also assessed the response to further adjuvant immunosuppressive therapy (complete remission, partial remission, frequent relapse, and no response), percentage of progression to chronic kidney disease (CKD), and end-stage renal disease (ESRD). The follow-up time was estimated as the time period in years from the time of biopsy to the last encounter in our center or until the patient reached 14 years.

2.3. Definitions

The definitions used in this study are summarized in Table 1.

2.4. Statistical analysis

Statistical analyses were performed using Statistical Package for

Table 1
Study definitions.

Classification	Definition
Nephrotic syndrome	Edema, uPCR ≥2000 mg/g (≥200 mg/mmol), or ≥300 mg/dl or 3 + protein on urine dipstick, hypoalbuminemia ≤2.5 mg/l (≤25 g/l)
Minimal change disease (MCD)	Absence of glomerular changes or minimal mesangial hyper-cellularity with no tubular atrophy, interstitial fibrosis, or glomerular segmental lesions or sclerosis
Hypertension	Blood pressure equal to or more than the 95th percentile for age, gender, and height measured on three different occasions
Microscopic hematuria	Presence of more than five RBCs per high-power field (40× magnifications) from collected sediment of 10–15 mL of centrifuged fresh urine
Estimated glomerular filtration rate (eGFR)	Schwartz equation with a bedside calculation of 0.413*(height in cm/serum creatinine in mg/dl)
Minimal change disease with presence of IgM under IF (IgM + IF)	MCD with IgM under IF with an intensity of ≥1+
Minimal change disease with no IgM under IF (IgM-IF)	MCD Intensity of IgM under IF with an intensity of trace or 0
Chronic kidney disease (CKD)	eGFR of less than 60 mL/min/1.73 m^2 for greater than three months with implications for health
End-stage renal disease (ESRD)	eGFR of less than 15 mL/min/1.73 m^2 while native kidneys could no longer sustain homeostasis due to irreversible decline in kidney function, eventually requiring dialysis
Response to steroid therapy	
Complete remission	uPCR <200 mg/g (<20 mg/mmol) or <1 + of protein on urine dipstick for 3 consecutive days
Steroid dependence	Two consecutive relapses during corticosteroid therapy or within 14 days of ceasing therapy
Frequent relapses	Two or more relapses within 6 months of initial response or four or more relapses in any 12-month period
Steroid resistance/no remission	Failure to achieve complete remission after 8 weeks of corticosteroid therapy
Response to adjuvant immunosuppressive	
Complete remission	Resolution of proteinuria, i.e., urine total protein-to-creatinine ratio ≤0.20 mg/mg) within 3 months of immunosuppressive therapy initiation
Partial remission	Decrease in edema clinically and stabilization of serum albumin to more than 2.5 g/dL with continued proteinuria
frequent relapses	Complete response to adjuvant immunosuppressive therapy; still has relapse more than 4 times per year
No response	No change in proteinuria despite additional adjuvant immunosuppressive therapy Decrease in edema clinically and stabilization of serum albumin to more than 2.5 g/dL with continued proteinuria

uPCR urine protein-to-creatinine ratio.

the Social Sciences (SPSS) version 22.0 software 2014. Age, eGFR, follow-up duration in years, and duration of adjuvant therapy in years were expressed in median. Other demographic data were reported in percentages. Analyses of categorical and continuous variables were performed using the chi-square test and Mann-Whitney *U* test, respectively. A *P* value of .05 or less was considered the threshold for statistical significance.

3. Results

From 2003 to 2014, 192 children were diagnosed with MCD based on renal biopsy. The biopsy samples were taken for the following indications: steroid dependence (43%), frequent relapse (23.3%), steroid resistance (31.7%), age equal to or more than 12 years (4/192) (2%), and elevated serum creatinine at the time of presentation to our institute (2%). Seventy-seven biopsies (40%) were IgM + IF MCD, and 115 biopsies (60%) were IgM-IF MCD. The median time gap between the onset of the disease and the biopsy was 3.2 years for IgM + IF and 3.5 years for IgM-IF (p = .31). The sample included 122 females and 70 males. The median age was 3.1 years in the IgM + IF group and 3.9 years in the IgM-IF group ($P = .13$). HTN was present in 23.3% (18/77) of children with IgM + IF and 2.6% (3/115) of children with IgM-IF ($P = .05$). Microscopic hematuria was present in 1.3% (1/77) of children with IgM + IF and 1.7% (2/115) of children with IgM-IF. In contrast to HTN, the latter did not show statistical significance ($P = .27$). Between both groups, eGFR at the time of presentation showed no significant difference. The demographic data are shown in Table 2.

Steroid dependence developed in 45.5% (35/77) of IgM + IF and 41% (47/115) of IgM-IF. IgM + IF was significantly associated with the development of steroid dependence ($P = .05$) (Table 3). There were cases for which biopsies indicated age above 12 years old, and four cases showed remission after treatment with steroid (1 from the IgM + IF group and 3 from the IgM-IF group).

Adjuvant immunosuppressive therapy was started in cases that did not develop remission: 76 cases from the IgM + IF group and 112 cases from the IgM-IF group. The median duration for adjuvant immunosuppressive therapy between both groups was two years in IgM + IF and 1.9 years in IgM-IF. The duration of adjuvant immunosuppressive therapy did not differ between both groups

Table 2
Demographic data of the sample at the time of presentation to our institute.

Parameter	MCD 192 (100%)	MCD IgM + IF 77 (40%)	MCD IgM-IF 115 (60%)	*P* value
Median age, in years	3.5	3.1	3.9	.13
Gender				
Male	70 (36.5%)	25 (32.5%)	45 (39.1%)	.15
Female	122 (63.5%)	52 (67.5%)	70 (60.9%)	
Hypertension	21 (10.9%)	18 (23.3%)	3 (2.6%)	.05[a]
Hematuria	3 (1.6%)	1 (1.3%)	2 (1.7%)	.27
Median eGFR[b]	94	91.5	98	.63

MCD: Minimal change disease.
MCD IgM + IF: Minimal change disease with IgM under immunofluorescence.
MCD IgM-IF: Minimal change disease with no IgM under immunofluorescence.
eGFR: Estimated glomerular filtration rate.
[a] Significant association.
[b] Measured in mL/min/1.73 m^2

Table 3
Steroid response during steroid therapy.

Parameter	IgM + IF n = 77	IgM-IF n = 115	*P* value
Median follow-up in years	4	5.2	0.13
Steroid Response			
Dependence	35 (45.5%)	47 (41%)	0.05
Resistance	26 (33.7%)	35 (30.4%)	–
Frequent relapses	15 (19.5%)	30 (26%)	–
Remission	1 (1.3%)	3 (2.6%)	–

[a]: Significant association.
-: Not significant.

($P = .32$). IgM deposition was not associated with any difference in the outcomes after adjuvant therapy in either group (Table 4).

During the course of the disease, CKD developed in 10.4% (8/77) in IgM + IF and 1.7% (2/115) in IgM-IF ($P = .05$). ESRD did not differ between the two groups (Table 5).

4. Discussion

Many studies reviewed the IgM deposits in INS. Some studies hypothesized on the pathophysiology of IgM in MCD but did not describe a clear cause. One hypothesis suggested that MCD with IgM could be a transitional uncommon stage between MCD and FSGS, called IgMN as mentioned earlier—this could explain the deterioration of MCD. Another hypothesis suggested that this could be a distinct form of the disease, named as primary IgMN [6]. Many studies have contrasted MCD with IgM depositions to IF-negative and have shown significant disagreement. Cohen et al. suggested that patients with IgM positivity in the mesangium had a weaker response to steroids [11]. Kanemoto et al. evaluated IgM significance on INS outcome in a study that included 105 patients (30 subjects who were positive for IgM deposition and 40 subjects who were negative for IgM deposition) regardless of the INS histopathological subtype [7]. The study suggested that the IgM deposits were associated with steroid-resistance ($P = .03$).

Habib et al. reported an insignificant relationship between IgM deposits and the initial response to steroids or final outcome [12]. Spreitzer et al. ran a retrospective study comparing the clinical characteristics of disease at presentation, clinical course, and renal outcome among IgM nephropathy, C1q nephropathy, and IF-negative MCD. The study found no statistically significant difference: children with IgM nephropathy, C1q nephropathy, and IF-negative MCD were clinically indistinguishable [13]. The role of glomerular IgM depositions remains controversial. Mubarak et al. hypothesized that IgM can be a cause for classical immune complex-mediated activation of the complement cascade in the glomerular mesangium causing damage and the pathophysiological response to the damage similar to other studies [6]. This theory is based on the fact of frequent presence of C1q and C4 deposits in addition to IgM deposits in glomerular mesangium in most of cases along with the absence of properdin and factor B. Interestingly, glomerular IgM depositions can be seen in a variety of systemic diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis, and Alport's syndrome that can present as nephrotic syndrome. We excluded subjects with these diagnoses from our study sample. Our study had a larger sample size, and we suspect our cohort is more representative because it covered the various clinical presentations of MCD. These patients required renal biopsy because of the abnormal response to steroid therapy: steroid-dependence, frequent relapse, and steroid-resistance with four other patients who initially presented with INS at the age of 12 years as well as older subjects requiring kidney biopsy.

Our study revealed that children with IgM + IF MCD showed more cases of HTN when presented to our center than children with IgM-IF MCD. However, this might be because most patients were referred after initial steroid therapy at primary hospitals with no available data about the duration of steroid therapy. We found statistical significance for IgM presence in MCD with the development of CKD, but data about other contributing causes were insufficient. A further prospective study is required with a larger sample size.

Table 4
Outcomes of MCD course after start of adjuvant immunosuppressive therapy.

Parameter	IgM + IF n = 76	IgM-IF n = 112	*P* value
Median duration of adjuvant therapy, in years	2	1.9	.32
Outcomes after adjuvant therapy			
Complete remission	59 (77.7%)	87 (77.6%)	.28
Partial remission	12 (15.7%)	16 (14.3%)	–
Frequent relapse	4 (5.3%)	8 (7.2%)	–
No response	1 (1.3%)	1 (0.9%)	–

[a]: Significant association.
-: Not significant.

Table 5
Development of CKD and ESRD.

Parameter	IgM + IF n = 77	IgM-IF n = 115	*P* value
CKD	8 (10.4%)	2 (1.7%)	.05[a]
ESRD	1 (1.3%)	1 (0.9%)	.21

CKD: Chronic kidney disease.
ESRD: End-stage renal disease.
[a]: Significant association.

5. Conclusion

Mesangial IgM deposition is associated with HTN at the time of presentation. Mesangial IgM depositions showed statistical association with the development of CKD. However, a prospective study is required to verify the role of IgM depositions in MCD outcome.

Support

This study was not supported by any research grants or funds.

Conflicts of interest

The presentation of the information that the authors are involved with promotes quality and improvement in health care and will not promote any specific business interest. The authors have declared that there is no conflict of interest.

Ethical considerations

This is a retrospective study that will use existing information, and no additional blood test or any other procedure was performed for the purpose of the study.

The following ethical considerations were taken care of:

1) All data needed for research already exist and are obtained through routine clinical care.
2) All data will be stored in Pediatric Research Unit, accessed only by the Principal
   Investigator and the assigned Clinical Research Coordinators and Co investigator.
3) The entire information of the patient will be kept strictly confidential. Each patient will be given a study number, and all

patient data will be entered into the designated data sheet (EXCEL) without any patient identifiers.
4) Waiver of informed consent is submitted with justification.
5) The Declaration of Helsinki and GCP guidelines will be followed.

Acknowledgment

We sincerely thank Prof. Mohamed M. Shoukri (Department of Cell Biology) and Mr. Abdulmonem M. El-Dali (Department of Biostatistics) for their great assistance during data analysis. We also thanks Ms. Areej A. Al-Fattani (Department of Pediatrics) for clinical coordination and regulatory help.

The authors responsibilities were as follows: Dr. Turki A. Al-Shareef is the study supervisor and corresponding author. Dr. Duaa M. Al Romaili wrote the study proposal and manuscript and did data entry. Dr. Turki Al-Hussain collected histo-pathology data. Dr. Hazem S. Awad, Dr. Sermin A. Saadeh, and Dr. Ibrahim A. Al-Hassoun helped review the study. All authors read and approved the final manuscript; there were no conflicts of interest.

References

[1] Park SJ, Shin JI. Complications of nephrotic syndrome. Korean J Pediatr 2011;54(8):322–8. https://doi.org/10.3345/kjp.2011.54.8.322. Epub 2011/11/17, PubMed PMID: 22087198; PubMed Central PMCID: PMCPMC3212701.
[2] Wynn SR, Stickler GB, Burke EC. Long-term prognosis for children with nephrotic syndrome. Clin Pediatr (Phila). 1988;27(2):63–8. https://doi.org/10.1177/000992288802700201. Epub 1988/02/01, PubMed PMID: 3338230.
[3] Besbas N, Topaloglu R, Saatci O, Bakkaloglu A. Long-term follow-up in children with steroid-resistant nephrotic syndrome. Clin Pediatr (Phila). 1992;31(5):283–8. https://doi.org/10.1177/000992289203100504. Epub 1992/05/01, PubMed PMID: 1582094.
[4] Primary nephrotic syndrome in children: clinical significance of histopathologic variants of minimal change and of diffuse mesangial hypercellularity. A Report of the International Study of Kidney Disease in Children. Kidney Int 1981;20(6):765–71. Epub 1981/12/01. PubMed PMID: 7334749.
[5] Swartz SJ, Eldin KW, Hicks MJ, Feig DI. Minimal change disease with IgM+ immunofluorescence: a subtype of nephrotic syndrome. Pediatr Nephrol 2009;24(6):1187–92. https://doi.org/10.1007/s00467-009-1130-0. Epub 2009/02/17, PubMed PMID: 19219463.
[6] Mubarak M, Kazi JI. IgM nephropathy revisited. Nephro-Urol Mon 2012;4(4):603–8. https://doi.org/10.5812/numonthly.2805. Epub 2013/04/11, PubMed PMID: 23573499; PubMed Central PMCID: PMCPMC3614302.
[7] Kanemoto K, Ito H, Anzai M, Matsumura C, Kurayama H. Clinical significance of IgM and C1q deposition in the mesangium in pediatric idiopathic nephrotic syndrome. J Nephrol 2013;26(2):306–14. https://doi.org/10.5301/jn.5000133. Epub 2012/05/30, PubMed PMID: 22641570.
[8] Brugnano R, Del Sordo R, Covarelli C, Gnappi E, Pasquali S. IgM nephropathy: is it closer to minimal change disease or to focal segmental glomerulosclerosis? J Nephrol 2016;29(4):479–86. https://doi.org/10.1007/s40620-016-0269-6. Epub 2016/02/05, PubMed PMID: 26842624.
[10] Group IGOGW, Disease d. KDIGO clinical practice guideline for glomerulonephritis. Kidney Int 2012;2(s2).
[11] Cohen AH, Border WA, Glassock RJ. Nehprotic syndrome with glomerular mesangial IgM deposits. Lab Investig 1978;38(5):610–9. Epub 1978/05/01. PubMed PMID: 347169.
[12] Habib R, Girardin E, Gagnadoux MF, Hinglais N, Levy M, Broyer M. Immunopathological findings in idiopathic nephrosis: clinical significance of glomerular "immune deposits. Pediatr Nephrol 1988;2(4):402–8. Epub 1988/10/01. PubMed PMID: 3153051.
[13] Vintar Spreitzer M, Vizjak A, Ferluga D, Kenda RB, Kersnik Levart T. Do C1q or IgM nephropathies predict disease severity in children with minimal change nephrotic syndrome? Pediatr Nephrol 2014;29(1):67–74. https://doi.org/10.1007/s00467-013-2551-3. Epub 2013/07/16, PubMed PMID: 23852271.