CORPUS PUBLISHERS

Global Journal of Pediatrics (GJP)

Volume 1, Issue 2, 2021

Article Information

Received date : March 05, 2021

Published date: April 20, 2021

*Corresponding author

Borysova T, Assistant of Professor of the Department of Pediatrics, Dnipro State Medical University, Ukraine

Key Words

Juvenile idiopathic arthritis; Children, Secondary amyloidosis; Glomerulonephritis

Abbreviations

JIA: Juvenile Idiopathic Arthritis; IL-1: Interleukin-1; TNF- α: Tumor Necrosis Factor-Alpha; MPGN: Mesangio proliferative Glomerulonephritis; GN: Glomerulonephritis

Review Article

Renal Lesions of Juvenile Idiopathic Arthritis in Children: A Literature Review

Borysova T[1*], Samsonenko S[2], Badogina L[3] and Makoviichuk O[4]

[1]*Head of the department of Pediatrics, Dnipro State Medical University, Ukraine*

[2]*Assistant of Professor of the department of Pediatrics, Dnipro State Medical University, Ukraine*

[3]*Associate Professor of the department of Pediatrics, Dnipro State Medical University, Ukraine*

[4]*Assistant of Professor of the department of Propaedeutics of children's diseases, Dnipro State Medical University, Ukraine.*

Abstract

The literature review presents current data on the frequency, mechanisms of development, clinical manifestations, diagnosis and treatment of renal AA-amyloidosis and describes different forms of glomerulonephritis (GN) in children with juvenile idiopathic arthritis (JIA). The frequency of AA renal amyloidosis in JIA in children ranges from 0.8% to 2%, in adults with JIA duration of 28.3 years - 8.9%. In recent years, against the background of immunobiological therapy, the incidence of AA-amyloidosis of the kidneys in adults has decreased to 2%. AA-amyloidosis of the kidneys most often develops in children with the systemic form, in adults - with systemic and polyarticular forms of JIA. The first symptom of AA-amyloidosis of the kidneys is isolated proteinuria, which transforms into nephrotic syndrome. The peculiarity of the nephrotic syndrome is the absence of hypercholesterolemia in most cases, combined in some patients with arterial hypertension, hematuria, and impaired renal function. The available literature presents clinical cases of renal GN in children with JIA, viz: ANCA-associated GN, mesangioproliferative GN, including IgA- and IgM-nephropathy, membranous nephropathy, focal-segmental glomerulosclerosis, minimal change disease, extracapillary GN. Most publications are devoted to ANCA-associated HN, which developed in patients with a torpid course and a high degree of activity of polyarticular and systemic forms of JIA. The peculiarity of ANCA-associated HN was the presence of hypercreatininemia and, in almost half of cases, the development of terminal renal failure, despite the ongoing immunosuppressive therapy. The main method confirming the diagnosis of AA-amyloidosis and renal HN is the intravital renal morphological study. The use of immunobiological drugs in renal AA-amyloidosis and HN in children with JIA has therapeutic efficacy.

Introduction

The topicality of the problem of juvenile idiopathic arthritis (JIA) in childhood is determined by its high incidence [1-3]. The progressive course of the disease in children and reduced performance in adulthood is an important unfavorable socio-economic result of the disease [4]. Juvenile idiopathic arthritis is characterized by the development of erosive and destructive arthritis in children under 16 years of age, manifested by joint deformities and contractures, muscle atrophy, and in some patients a variety of extra articular lesions [5]. In the literature, lesions of the cardiovascular system, eyes, and lungs are most often described [6-8]. At the same time, renal damage in children with JIA is an understudied problem. It should be noted that, according to the literature, renal changes may develop regardless of the duration of JIA and determine the prognosis for these patients [9]. The structure of renal pathology is represented by secondary amyloidosis, glomerulonephritis, and tubulo-interstitial nephritis [10]. The most unfavourable renal lesion in JIA is secondary renal amyloidosis (AA-amyloidosis) [11, 12]. To date, the main mechanism of AA-amyloidosis development has been established, which consists in a constant or periodic increase in the concentration of serum amyloid A (SAA) [13]. The main site of SAA synthesis is the liver. In the blood of healthy people, SAA is usually present at low levels (20-50 μg/ml). Like C-reactive protein, it increases 1000-fold during the first 24 hours in response to inflammation of any etiology, and then returns to normal levels [14]. To realize the amyloidogenic potential of SAA, not only the inflammatory process in the body must be affected, but also its duration [15]. It has been established that proinflammatory cytokines: interleukin-1 (IL-1), IL-6, tumor necrosis factor-alpha (TNF-α), IL-2, IL-11 and others influence SAA synthesis [16 - 18]. This is confirmed by the work of the authors, who looked at the ratio of SAA concentration in the blood and levels of proinflammatory cytokines IL-1β and IL-6 in children with different forms of JIA. It was noted that increased blood levels of IL-1β, IL-6 and SAA have a direct correlation, indicating the role of proinflammatory cytokines in maintaining the chronic inflammatory process and stimulation of amyloidogenesis in children with JIA [18]. It is noteworthy that the use of glucocorticoids, which have an anti-inflammatory effect, does not reduce the synthesis of SAA, but rather increases it, because when interacting with IL-1 and TNF-α, they increase their ability to stimulate the synthesis of SAA in the liver. Therefore, the use of glucocorticoids is a risk factor for the development of AA-amyloidosis [19]. An increase in the SAA concentration in the blood cannot be considered as the only explanation for the development of AA amyloidosis, because not every patient with JIA develops amyloidosis [20]. It should be noted that four SAA genes (SAA 1, SAA 2, SAA 3, SAA 4) located on the short arm of chromosome 11 have been described. The main ones in the development of AA-amyloidosis are SAA1 and SAA2 [21]. Five isotypes are distinguished in the SAA1 gene, of which SAA1.1 and SAA1.5 are ascribed the greatest amyloidogenicity [22]. There are reports on the role of the genetic factor in the predisposition to the development of AA amyloidosis. For example, a clinical case of a child with renal AA amyloidosis against the background of JIA and carriage of the heterozygous G196W mutation in MEFV was described. The disease was characterized by high activity and the development of AA renal amyloidosis two years after the debut of JIA [23]. Because of a violation of the ratio of SAA surface molecular charges, its instability and aggregation into an amyloid fibril occurs, which is deposited in the extracellular spaces of the kidneys, gastrointestinal tract [24]. In kidneys, amyloid is found in the walls of bringing and taking out arterioles, capillary loops and glomerular mesangium, basal membranes of tubules and stroma. As the process progresses, the glomeruli are completely replaced by amyloid with the formation of glomerulosclerosis and the development of the clinical picture of AA-amyloidosis [14]. The incidence of AA renal amyloidosis in JIA is represented by several studies. For example, *David J. et al.* [25] in 1993 reported 1-2% of cases of AA renal amyloidosis in childhood, *Duarte A.C. et al.* [26] in 2005 -0.8% of particular importance is the result of follow-up of patients with JIA. In one study, 246 patients aged 19-78 years were analyzed. AA-amyloidosis of the kidneys was established in 8.9% of patients. The duration of JIA before the development of AA amyloidosis was 28.3 years.

The authors determined the frequency of AA-amyloidosis development depending on the form of JIA. This complication most frequently developed in systemic (19.2%) and polyarticular types of JIA (with rheumatoid factor negative - 9.8%, positive - 2.7%). AA-amyloidosis was significantly less common in the widespread oligoarticular form of JIA (3.6%), enthesitis-associated (3.1%), and psoriatic (6.7%) arthritis. None of the cases of oligoarticular persistent JIA showed signs of AA-amyloidosis [27]. The study of *Lane T. et al.* [24], conducted at the National Amyloidosis Center, located in the UK. Retrospectively evaluated the dynamics of AA renal amyloidosis incidence over 24 years. Data from 625 patients in three groups were studied: 1990-1997; 1998-2006; and 2007-2014. The mean age of patients with AA-amyloidosis increased from 46 years (1990-1997) to 56 years (2007-2014). A comparison of renal AA-amyloidosis rates in patients with JIA between 1990 and 2014 revealed a distinct decrease in the incidence of this renal complication from 25% to 2% ($p<0.001$). The authors attributed the findings to advances in JIA therapy, namely the use of immunobiological agents [24]. The clinical characteristics of AA renal amyloidosis in children with JIA are characterized by the presence of asymptomatic isolated proteinuria or nephrotic syndrome [28]. In the available literature, we found a description of 24 clinical cases of AA renal amyloidosis in children with JIA in 14 publications. Data on the analysis of the clinical characteristics of these patients are presented in Table 1.

Patients ranged in age from 6 to 17 years, with a mean age of 11.2 years. AA-amyloidosis was slightly more common in children older than 10 years (14 of 24 cases). AA-amyloidosis of the kidneys predominantly developed in boys than in girls (21 to 3). Almost all patients (23 children) had a systemic form of JIA. The duration of JIA before the development of clinical signs of AA renal amyloidosis ranged from 2 to 15 years (mean, 7.1 years). In all patients, the first symptoms of renal amyloidosis development were proteinuria of varying severity from 0.5 g/day to 33 g/day. However, the genesis of proteinuria in patients was not clarified until nephrotic syndrome developed. In children with JIA, urine screening is a very important method in the early diagnosis of AA renal amyloidosis [39]. Nephrotic syndrome was characterized by marked edema in 16 cases, significant proteinuria and hypoalbuminemia in all patients. The peculiarity of nephrotic syndrome was the absence of hypercholesterolemia in the majority of children (20 children). In addition, nephrotic syndrome was combined with arterial hypertension in six children, hematuria in four, and macrohematuria in one case (Table 1). Two patients had elevated blood creatinine levels, and one of them was diagnosed with stage IV chronic kidney disease. Both these cases ended lethally within a short period of time [29, 30]. Severe reduction of diuresis has been described in one patient, which also ended lethally [32]. In adults, nephrotic syndrome in AA amyloidosis is characterized by a steadily progressive course and a rapid decline in renal function [40]. To clarify the genesis of

Table 1: Clinical characteristics of children with AA kidney amyloidosis against the background of JIA.

Author	Age (in years)/ sex	Form of JIA	Duration of JIA (in years)	Clinical signs of AA renal amyloidosis						
				Nephrotic Syndrome						Increased blood creatinine
				Severe swelling	High proteinuria	Hypoalbu-minemia	Hypercholes-terinemia	Arterial hypertension	Hematuria	
Hamdan J et al, 1986 [29]	6/b	S	4	+	+	+	-	-	+	+
	7/b	S	2	+	+	+	-	-	-	-
	11/b	P	10	+	+	+	-	-	-	-
	7/b	S	4	-	+	+	-	-	-	-
	17/b	S	15	-	+	+	-	-	+	-
	16/b	P	13	+	+	+	-	-	+	-
	11/b	S	6	-	+	+	-	-	+	-
	6/b	S	4	-	+	+	-	-	-	-
Lévy M. et al.1987 [30]	14/g	S	3	+	+	+	-	-	-	+
Kavukçu S. et al. 1995 [31]	11/b	S	10	+	+	+	+	+	-	-
Sukalo A.V. et al 2002 [32]	10/g	S	8	+	+	+	+	+	-	-
Duarte C. et al. 2006 [26]	9/g	S	6	+	+	+	-	-	-	-
Sharma A. et al. 2006 [33]	10/b	S	2	+	+	+	-	-	-	-
Akhtar N. et al. 2008 [34]	16/b	S	5	+	+	+	-	+	-	-
De La Torre et al. 2011 [35]	14/b	S	12	+	+	+	+	-	-	-
Cantarini L. et al. 2012 [23]	9/g	S	4	-	+	+	-	-	-	-
Saha A. et al. 2013 [36]	12/b	S	4	+	+	+	+	+	-	-
	15/b	S	12	-	+	+	-	-	-	-
Topaloglu R. et al. 2015 [37]	10/b	S	2	-	+	+	-	-	-	-
Maleknejad M. et al. 2015 [38]	7/b	S	6	+	+	+	-.	+	-	-
Kwiatkowska M. et al. 2015 [11]	16/b	S	14	+	+	+	-	-	-	-
	14/b	S	8	+	+	+	+	-	-	-
Saha A. et al. 2017 [39]	13/b	S	10	-	+	+	+	-	-	-
Gupta A. et al. 2019 [16]	10/b	S	6	+	+	+	-	+	-	-

Note: g - girl; b - boy; "+" - presence of the sign; "-" - absence of the sign, S- systemic form of JIA; P- polyarticular form of JIA.

nephrotic syndrome, all children underwent intravital morphological examination of the kidneys, which allowed diagnosing AA-amyloidosis in them. In renal biopsy specimens stained with Congo red, in polarized light, amyloid changes the red color staining to apple-green glow, which is found in the glomeruli and the medullary layer of the kidneys [41]. A number of authors emphasized the low informative value of rectal biopsy for AA renal amyloidosis diagnosis [11, 30]. To assess the risk of AA-amyloidosis of the kidneys, it is preferable to determine the SAA level in blood. This was shown in a study by *Stepanova A.A.* [42], who revealed an increase in this index to 286.3±27.2 mg/l in children with JIA. However, it should be noted that only 48% of patients had isolated proteinuria from 0.1 to 0.4 g/m2/day, and in none of the cases, nephrotic syndrome was formed. Based on the data obtained, the author concluded that there is a risk of AA renal amyloidosis in JIA in children. The therapeutic insertion tactics of patients with renal AA-amyloidosis are currently actively discussed in the literature. There are several reports on the management of the nephrotic syndrome in AA-amyloidosis of the kidneys with the use of immunobiological drugs [11, 16, 35, 37]. The positive effect of recombinant humanized monoclonal antibody to human IL-6 receptor (tocilizumab) was described in three clinical cases in children with AA-amyloidosis of the kidneys against the background of JIA [11, 16, 35]. The results of using a recombinant form of human IL-1 receptor antagonist (anakinra) in two patients with renal AA-amyloidosis developed against the background of JIA are presented [37]. In the children, there was a reduction in proteinuria from 980 mg/day to 45 mg/day. At the same time, a control renal biopsy after two and four years showed no regression of AA-amyloidosis. In the available literature, we found a description of 21 clinical cases of various variants of glomerulonephritis (GN) in children with JRA, namely: ANCA-associated glomerulonephritis (ANCA-GN), mesangioproliferative glomerulonephritis (MPGN), including IgA- and IgM-nephropathy, membrane nephropathy (MN), focal segmental glomerulosclerosis (FSGS), extracapillary GN, minimal change disease (MCD). The greatest number of publications is devoted to ANCA-GN in children with JIA. The clinical characteristics of these patients are presented in (Table 1).

As shown in Table 2 girls predominated among patients with ANCA-GN. The children were mostly of school age, with two children of early childhood. Polyarticular and systemic forms of JIA were equally frequent, with a persistently high degree of disease activity being a peculiarity of their course. The duration of ANCA-GN onset from the debut of JIA varied from 1 to 6 years. The main clinical manifestations of ANCA-GN were isolated minimal proteinuria, in four cases combined with hematuria, and elevated blood creatinine. In one child, hypercreatininemia was the only sign of ANCA-GN [43].

Researchers suggest high levels of proinflammatory cytokines and antibodies to neutrophil cytoplasm (ANCA) to be the cause of ANCA-GN in children with JIA [46-48]. It should be noted that the results of ANCA screening in children with JIA showed an increase in its level in 35-45% of cases [49, 50]. The study of *Speckmaier M. et al.* [51] found that even in the absence of clinical signs of GN, the increase in ANCA titer in children with JIA was three times more frequent than that of antinuclear antibodies. Pulse therapy with prednisolone in combination with various immunosuppressants (cyclophosphamide, azathioprine, methotrexate, mycophenalate mofetil) was attempted in clinical cases of ANCA-GN in children with JIA presented over 15 years ago. This treatment proved to be ineffective, since the formation of terminal renal failure was observed *Belot A et al.* [46] noted successful treatment of ANCA-GN in a child with JIA with an interleukin-1 receptor antagonist (the drug Anakinra). Thus, for timely diagnosis of ANCA-HN in children with a high degree of activity of systemic or polyarticular form of JIA, despite the ongoing baseline therapy, the inclusion of ANCA, proteinuria and serum creatinine levels in the complex of examination is indicated. Mesangioproliferative glomerulonephritis has been demonstrated in four patients with JIA in the available literature [52 - 55]. The forms of JIA were different: systemic (2), polyarticular (1) and oligo articular (1). Signs of MPGN were observed during the first three years of JIA, and in one case, they preceded the onset of joint syndrome by 4 years [54]. The clinical symptoms of MPGN in JIA were represented by the classical nephrotic syndrome (NS) in one child [54], asymptomatic moderate proteinuria in three patients, and in two cases combined with hematuria. Immunofluorescence study of nephrobiopsy in two patients allowed diagnosing IgA- and IgM-nephropathy [54, 55]. Corticosteroids both as monotherapy and in combination with cytostatics (methotrexate) were used in treatment of three patients with IgM-nephropathy [52, 53], the inhibitor of tumor necrosis factor α (i-TNFα) - Infliximab - was additionally included in the patient with IgM-nephropathy [54]. In IgA-nephropathy, monotherapy with an angiotensin-converting enzyme inhibitor was used [55]. Remission of MPGN was achieved in all presented clinical cases [50 - 55]. The authors define the importance of interleukin-6 (IL-6) both in the pathogenesis of JIA and MPGN [56 - 59]. Local activation of classical and trans-signal IL-6 pathways has been shown to be involved in autoimmune and inflammatory kidney diseases [60]. Pro-inflammatory cytokine IL-6 has been shown to be involved in pathological disorders of mesangium, increasing its proliferation and sclerosis [61]. In addition, mesangial cells can also secrete IL-6 and activate inflammatory cells, which play an important role in immune and metabolic damage of the kidney [62]. Membranous nephropathy (MN) has been described in three school-age children with polyarticular and systemic JIA [63-65]. The onset of MN was observed within one year of the debut of JIA and was manifested by asymptomatic proteinuria of varying degrees. In addition, two patients had elevated blood cholesterol levels [63, 65]. The functional state of the kidneys was not impaired. Researchers attribute the occurrence of MN in JIA to the use of such drugs as D-penicillamine [64], buccillamine (Japanese analogue of D-penicillamine) [63]. A positive therapeutic effect was achieved in two children by withdrawal of the causative drug that induced the development of MN. A special clinical case is that of a child with a systemic form of JIA who developed MN because of intravenous immunoglobulin and, 3.5 years later, extracapillary GN. Despite immunosuppressive therapy in this case, terminal renal failure developed [65]. Focal-segmental glomerulosclerosis was described in three patients, including two children with polyarticular and one with oligoarticular (1) form of JIA [30, 66, 67]. The duration of FSGS from the debut of JIA ranged from 4 months to 3 years. Clinically, FSGS in one patient manifested as classical NS [67], and in the other 2 cases - as moderate proteinuria [30, 66]. In one child, proteinuria was combined with hematuria and arterial hypertension [66]. All patients with FSGS were prescribed pulse therapy with prednisolone in combination with azathioprine, but no positive treatment effect was achieved in any case. The outcome of the disease is the development of terminal renal failure [30, 66, 67]. The minimal changes disease is presented in the observation of *Lévy M. et al.* [30] in a 15-year-old child. The debut of MCD was observed 2 years after the onset of the polyarticular form of JIA. The main clinical manifestation of MCD was the classic nephrotic syndrome, a hormone-sensitive variant with persistent remission. The authors did not explain the mechanism of MCD development in this patient of interest

Table 2: Clinical cases of ANCA-GN in children with JIA according to the literature.

Author	Age (years)/ sex	Form of JIA	Duration of the onset of GN from the debut of JIA (in years)	Clinical manifestations of GN					ANCA	Exodus
				Swelling	AH	↑ blood creatinine	proteinuria	hematuria		
Dhib M., et al, 1996 [43]	12/g	P	5	-	-	+	-	-	+	Terminal renal failure. Renal replacement therapy.
	10/g	P	-	-	-	-	+	+	+	Recovery
Washizawa K., et al, 1998 [44]	12/g	S	3	-	-	-	+	+	+	No info
Hwang Y.S., et al, 2005 [45]	15/b	P	3	-	-	+	+	+	+	Recovery
Belot A. et al., 2012 [46]	0,9/g	S	1	-	-	+	+	-	+	Lethal
	4/g	S	6	-	-	+	+	-	+	Terminal renal failure. Renal replacement therapy.
	1,3/b	S	4	-	-	+	+	+	+	Remission

Note: g-girl; b-boy; S- systemic form of JIA; P- polyarticular form of JIA; AH- arterial hypertension; "+" - presence of the sign; "-" - absence of the sign.

are clinical cases of NS, which preceded, over several years, the appearance of signs of JIA in two young children [68, 69]. Researchers explain the pathogenetic link between NS and JIA as follows. Both conditions are associated with T-lymphocyte dysfunction, excessive production of circulating factors, and abnormal cytokine expression [70]. Genetic predisposition and association with HLA-DR antigens from major histocompatibility complex type II are also important [71, 72]. One child was diagnosed with JIA after 4 years and another - after 8 years, and there was a recurrence of NS [68, 69]. In one case, oligoarticular variant of JIA was diagnosed [68], in the other - enteric-associated [69]. A positive effect of glucocorticoid and cytostatic therapy was noted in one patient [68]. In the second child, the standard therapy for diagnosed MCD was replaced with Etanercept because of its ineffectiveness, and its use resulted in a positive therapeutic effect and remission for both JIA and NS [69]. At the same time, it should be noted that there is a case of extracapillary or "semilunar" GN described in the literature as a side effect of Etanercept in a 15-year-old child with psoriatic JIA [73]. The main clinical manifestations of this GN were the appearance of arterial hypertension, impaired renal function, moderate proteinuria and hematuria. Against the background of pulse therapy with methylprednisolone and withdrawal of the drug "Etanercept", positive dynamics in the form of normalization of kidney function was noted after 1 month [73].

Conclusion

1) The incidence of AA renal amyloidosis in JIA in children ranges from 0.8% to 2%; in adults with a JIA duration of 28.3 years, it is 8.9%. In recent years, against the background of immunobiological therapy, the incidence in adults has decreased to 2%.

2) Renal amyloidosis AA most often develops in children with the systemic form of JIA. In children with polyarticular and systemic forms of JIA, the literature describes individual clinical cases of different forms of glomerulonephritis (GN). Most publications are devoted to ANCA-associated GN in patients with a torpid course and a high degree of JIA activity.

3) The first symptom of renal AA-amyloidosis in children with JIA is isolated proteinuria, which transforms into nephrotic syndrome. The peculiarity of ANCA-associated GN was the presence of hypercreatininemia and in almost half of cases the development of terminal renal failure, despite the ongoing immunosuppressive therapy. Single clinical cases of MPGN, MCD, FSGS, extracapillary GN in children with JIA were described more than 10 years ago, clinically manifested by proteinuria and rarely nephrotic syndrome.

4) The use of immunobiological drugs in AA renal amyloidosis and renal GN in children with JIA has therapeutic efficacy.

5) Thus, all children with a high degree of activity of polyarticular and systemic forms of JIA for timely diagnosis of renal AA-amyloidosis and HN require monitoring of urine analysis, blood creatinine level.

References

1. Palman J, Shoop-Worrall S, Hyrich K, McDonagh JE (2018) Update on the epidemiology, risk factors and disease outcomes of Juvenile idiopathic arthritis. Best Pract Res Clin Rheumatol 32(2): 206-222.

2. Fellas A, Hawke F, Santos D, Coda A (2017) Prevalence, presentation and treatment of lower limb pathologies in juvenile idiopathic arthritis: A narrative review. J Paediatr Child Health 53(9): 836-840.

3. Abdwani R, Abdalla E, Al Abrawi S, Al Zakwani I (2015) Epidemiology of juvenile idiopathic arthritis in Oman. Pediatr Rheumatol Online J 13: 33.

4. Bojko YaE (2014) Long-term effects of juvenile rheumatoid arthritis: observations of 70 patients. Ukrainian Rheumatological Journal 2: 67-72.

5. Okamoto N, Yokota S, Takei S (2019) Clinical practice guidance for juvenile idiopathic arthritis (JIA) 2018. Mod Rheumatol 29(1): 41-59.

6. Berezhnij VV, Marushko TV, Marushko YuV (2006) Features of the clinical course of rheumatoid arthritis in adolescents. Child health 1(1): 23-26.

7. Barišić Kutija M, Perić S, Knežević J, Juratovac Z, Vukojević N (2019) Complication and prognosis of juvenile idiopathic arthritis associated uveitis in the era of modern immunomodulatory treatment. Psychiatr Danub 31(1): 44-49.

8. Liu YC, Tu YL, Wu RC, Huang JL, Yao TC (2014) Life-threatening pneumonitis complicating low-dose methotrexate treatment for juvenile idiopathic arthritis in a child. Pediatr Emerg Care 30(6): 415-417.

9. Sihvonen S, Korpela M, Mustonen J, Laippala P, Pasternack A (2004) Renal disease as a predictor of increased mortality among patients with rheumatoid arthritis. Nephron Clin Pract 96(4): c107-c14.

10. Delplanque M, Pouchot J, Ducharme-Bénard S (2020) AA amyloidosis secondary to adult onset Still's disease: About 19 cases. Semin Arthritis Rheum 50(1): 156-165.

11. Kwiatkowska M, Jednacz E, Rutkowska Sak L (2015) Juvenile idiopathic arthritis complicated by amyloidosis with secondary nephrotic syndrome - effective treatment with tocilizumab. Reumatologia 53(3): 157-60.

12. Joss N, McLaughlin K, Simpson K, Boulton-Jones JM (2000) Presentation, survival and prognostic markers in AA amyloidosis. QJM 93(8): 535-542.

13. Cimaz R, Von Scheven A, Hofer M (2012) Systemic-onset juvenile idiopathic arthritis: the changing life of a rare disease. Swiss Med Wkly 142: 13582.

14. Sack GH (2018) Serum amyloid A - a review. Mol Med 24(1): 46.

15. Rameev VV, Kozlovskaya LV, Malinina EA, Serova AG, Kogarko IN,et al. (2009) Determination of circulating amyloid precursor proteins in the diagnosis and monitoring of systemic amyloidosis. Clinical Nephrology 2: 55-62.

16. Gupta A, Bagri NK, Tripathy SK, Barwad A, Phulware RH, et al. (2020) Successful use of tocilizumab in amyloidosis secondary to systemic juvenile idiopathic arthritis. Rheumatol Int 40(1): 153-159.

17. Papa R, Lachmann HJ (2018) Secondary AA Amyloidosis. Rheum Dis Clin North Am 44(4): 585-603.

18. Stepanova AA, Savenkova ND, Novik GA, Dement`eva EA, Gurina OP (2015) The diagnostic value of the concentration of cytokines IL-1β, IL-6, TNF-α and the protein precursor of amyloid SAA in the blood in patients with juvenile rheumatoid arthritis. Russian Journal of Perinatology and Pediatrics 5(60).

19. Cope AP, Aderka D, Doherty M (1992) Increased levels of soluble tumor necrosis factor receptors in the sera and synovial fluid of patients with rheumatic diseases. Arthritis Rheum 35(10): 1160-1169.

20. Sarkisova IA (2006) Rheumatoid arthritis as a leading cause of the development of secondary AA amyloidosis (Literature review). Nephrology and dialysis 1(8): 15-26.

21. Cunnane G (2001) Amyloid precursors and amyloidosis in inflammatory arthritis. Curr Opin Rheumatol 13(1): 67-73.

22. Yamada T, Okuda Y, Takasugi K, Itoh K, Igari J (2001) Relative serum amyloid A (SAA) values: the influence of SAA1 genotypes and corticosteroid treatment in Japanese patients with rheumatoid arthritis. Ann Rheum Dis 60(2): 124-127.

23. Cantarini L, Lucherini OM, Simonini G, Galeazzi M, Baldari CT, et al. (2012) Systemic-onset juvenile idiopathic arthritis complicated by early onset amyloidosis in a patient carrying a mutation in the MEFV gene. Rheumatol Int 32(2): 465-467.

24. Lane T, Pinney JH, Gilbertson JA (2017) Changing epidemiology of AA amyloidosis: clinical observations over 25 years at a single national referral centre. Amyloid 24(3): 162-166.

25. David J, Vouyiouka O, Ansell BM, Hall A, Woo P (1993) Amyloidosis in juvenile chronic arthritis: a morbidity and mortality study. Clin Exp Rheumatol 11(1): 85-90.

26. Duarte C, Gomes C, Correia AJ, Salgado M (2006) Renal amyloidosis: an uncommon complication of juvenile idiopathic arthritis. Clin Rheumatol 25(4): 548-549.

27. Packham JC, Hall MA (2002) Long-term follow-up of 246 adults with juvenile idiopathic arthritis: functional outcome. Rheumatology (Oxford) 41(12): 1428-1435.

28. Bilginer Y, Akpolat T, Ozen S (2011) Renal amyloidosis in children. Pediatr Nephrol 26(8): 1215-1227.

29. Hamdan J, Manasra K, Ilahi F (1986) Amyloidosis secondary to juvenile rheumatoid arthritis: a case report from Saudi Arabia. Ann Trop Paediatr 6(4): 279-282.

30. Lévy M, Prieur AM, Gubler MC (1987) Renal involvement in juvenile chronic arthritis: clinical and pathologic features. Am J Kidney Dis 9(2): 138-146.

31. Kavukçu S, Türkmen M, Saatçi O, Başdemir G, Gülay Z et al. (1995) Juvenile rheumatoid arthritis and renal amyloidosis (case report). Int Urol Nephrol 27(3): 251-256.

32. Sukalo AV, Kravczova GI, Kraeva SS (2002) Secondary renal amyloidosis in a 10 year old girl with juvenile rheumatoid arthritis. Belarusian Medical Journal 2: 122-124.

33. Sharma A, Gupta A, Mitra S, Nada R, Bhattad S, Singh S (2016) Systemic Juvenile Idiopathic Arthritis with Amyloidosis: An Uncommon Complication with a Favourable Outcome. Indian J Pediatr 83(5): 477-478.

34. Akhtar N, Kiran S, Hussain A, Suleman BA, Jaleel S (2009) Renal amyloidosis in juvenile rheumatoid arthritis. J Coll Physicians Surg Pak 19(2): 130-132.

35. De La Torre M, Arboleya L, Pozo S, Pinto J, Velasco J (2011) Rapid and sustained response to tocilizumab, anti-interleukin-6 receptor antibody, in a patient with nephrotic syndrome secondary to systemic juvenile idiopathic arthritis-related amyloidosis. NDT Plus 4(3): 178-180.

36. Saha A, Chopra Y, Theis JD, Vrana JA, Sethi S (2013) AA amyloidosis associated with systemic-onset juvenile idiopathic arthritis. Am J Kidney Dis 62(4): 834-838.

37. Topaloglu R, Batu ED, Orhan D, Ozen S, Besbas N (2016) Anti-interleukin 1 treatment in secondary amyloidosis associated with autoinflammatory diseases. Pediatr Nephrol 31(4): 633-640.

38. Maleknejad M, Moshari J, Azarfar A (2015) Renal Amyloidosis Due to Juvenile Rheumatoid Arthritis Occurring in Early Childhood. J Ped. Nephrology 3(2): 79-81.

39. Saha A, Pais P, Iyengar AA, Abraham AK (2017) Proteinuria in children with juvenile idiopathic arthritis: Making the case for early urinary screening. Saudi J Kidney Dis Transpl 28(6): 1408-1411.

40. Chevrel G, Jenvrin C, McGregor B, Miossec P (2001) Renal type AA amyloidosis associated with rheumatoid arthritis: a cohort study showing improved survival on treatment with pulse cyclophosphamide. Rheumatology (Oxford) 40(7): 821-825.

41. Jagusiak A, Rybarska J, Konieczny L (2019) Amyloids, Congo red and the apple-green effect. Acta Biochim Pol 66(1): 39-46.

42. Stepanova AA (2013) Amyloid precursor SAA-protein in the blood and kidney pathology in rheumatoid arthritis in children and adolescents: autoref. dis. PhD. Sankt–Peterburg P. 25.

43. Dhib M, Prieur AM, Courville S (1996) Crescentic glomerulonephritis in juvenile chronic arthritis. J Rheumatol 9: 1636-1640.

44. Washizawa K, Wakabayashi Y (1998) A case of juvenile rheumatoid arthritis with MPO-ANCA associated nephritis. Ryumachi. 38(1): 29-33.

45. Hwang YS, Rhie Y J, Ahn SY (2005) A Case of ANCA-associated Pauci-immune Crescentic Glomerulonephritis in Juvenile Rheumatoid Arthritis. Journal of the Korean Society of Pediatric Nephrology. 9(2): 231-236.

46. Belot A, Bader-Meunier B, Niaudet P (2012) ANCA-associated glomerulonephritis in systemic-onset juvenile idiopathic arthritis. Am J Kidney Dis 59(3):439-443.

47. Heeringa P, Huugen D, Tervaert JW (2005) Anti-neutrophil cytoplasmic autoantibodies and leukocyte-endothelial interactions: a sticky connection? Trends Immunol 26(11): 561-564.

48. Mustila A, Korpela M, Mustonen J (1997) Perinuclear antineutrophil cytoplasmic antibody in rheumatoid arthritis: a marker of severe disease with associated nephropathy. Arthritis Rheum 40(4): 710-717.

49. Mulder L, Rossum M, Horst G (1997) Antineutrophil cytoplasmic antibodies in juvenile chronic arthritis. J Rheumatol 24(3): 568-575.

50. Bakkaloglu A, Ozen S, Saatci U (1999) Antineutrophil cytoplasmic antibodies in juvenile chronic arthritis. Clin Rheumatol 18(4): 304-307.

51. Speckmaier M, Röther E, Terreri T (1996) Prevalence of anti-neutrophil cytoplasmic antibodies (ANCA) in juvenile chronic arthritis. Clin Exp Rheumatol 14(2): 211-216.

52. Gedalia A, Mendez EA, Craver R (2001) Renal involvement in juvenile rheumatoid arthritis: report of two cases. Clin Rheumatol 20(2): 153-156.

53. Bandin F, Merhenberger M, Modesto A (2008) Steroid-responsive nephrotic syndrome in a child with juvenile idiopathic arthritis. Pediatr Nephrol 23(4): 651-654.

54. Voyer LE, Alvarado C, Cuttica RJ (2013) Nephrotic syndrome due to immunoglobulin M mesangial glomerulonephritis preceding juvenile idiopathic arthritis. Iran J Kidney Dis 7(3): 231-234.

55. Matsukura H, Igarashi N, Kazama T (2014) Concurrent occurrence of juvenile reactive arthritis and IgA nephropathy. Clin Nephrol 81(5): 379-380.

56. Kallen KJ (2002) The role of transsignalling via the agonistic soluble IL-6 receptor in human diseases. Biochim Biophys Acta 1592(3): 323-343.

57. Peake NJ, Khawaja K, Myers A (2006) Interleukin-6 signalling in juvenile idiopathic arthritis is limited by proteolytically cleaved soluble interleukin-6 receptor. Rheumatology (Oxford) 45(12): 1485-1489.

58. Tanaka T, Narazaki M, Kishimoto T (2018) Interleukin (IL-6) Immunotherapy. Cold Spring Harb Perspect Biol 10(8): a028456.

59. Akioka S. Interleukin-6 in juvenile idiopathic arthritis. Mod Rheumatol 29(2): 275-286.

60. Gohda T, Makita Y, Shike T (2001) Dilazep hydrochloride, an antiplatelet drug, inhibits lipopolysaccharide-induced mouse mesangial cell IL-6 secretion and proliferation. Kidney Blood Press Res 24(1): 33-38.

61. Su H, Lei CT, Zhang C (2017) Interleukin-6 Signaling Pathway and Its Role in Kidney Disease: An Update. Front Immunol

62. Lu H, Zhou J (2008) HBV X gene transfection upregulates IL-1beta and IL-6 gene expression and induces rat glomerular mesangial cell proliferation. J Huazhong Univ Sci Technolog Med Sci 28(3): 247-250.

63. Kawasaki Y, Suzuki J, Sike T (2000) Bucillamine-induced nephropathy in a child with juvenile rheumatoid arthritis and Kartagener's syndrome. Pediatrics international: official journal of the Japan Pediatric Society 42(3): 316-318.

64. Suzuki K, Tanaka H, Ito E (2004) Therapy-related membranous nephropathy in juvenile idiopathic arthritis with Turner syndrome. Pediatr Int 46(3): 377-379.

65. Foster BJ, Duffy CM, Sharma AK (1998) Systemic juvenile rheumatoid arthritis complicated by two different renal lesions. Pediatr Nephrol 12(2): 113-116.

66. Gedalia A, Mendez EA, Craver R (2001) Renal involvement in juvenile rheumatoid arthritis: report of two cases. Clin Rheumatol 20(2): 153-156.

67. Varma S (2010) Juvenile rheumatoid arthritis with focal segmental glomerulosclerosis: a rare association. Pediatr Nephrol 25: 2189-2190.

68. Kari JA, Bamashmous H, Mahan JD (2002) Steroid-sensitive nephrotic syndrome and juvenile idiopathic arthritis. Pediatr Nephrol 17(11): 975-976.

69. Ito S, Tsutsumi A, Harada T (2010) Long-term remission of nephrotic syndrome with etanercept for concomitant juvenile idiopathic arthritis. Pediatr Nephrol 25(10): 2175-2177.

70. Kim SH, Park SJ, Han KH (2016) Pathogenesis of minimal change nephrotic syndrome: an immunological concept. Korean J Pediatr 59(5): 205-211.

71. Otero GA, Esteban J, Salgado J (1991) Chronic juvenile arthritis and minimal change glomerulonephritis (MCGN), the same pathogenic basis?. Anales de Medicina Interna 8(8): 413-414.

72. Shi D, Zhang Y, Liu D (2021) Analysis of the clinical characteristics of arthritis with renal disease caused by a NPHS2 gene mutation. Clin Rheumatol

73. Mene P, Franeta AJ, Conti G (2010) Extracapillary glomerulonephritis during etanercept treatment for juvenile psoriatic arthritis. Clinical and Experimental Rheumatology 18: 91-93.