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# RENAL AMYLOIDOSIS IN CHILDHOOD*
## An Overview of the Topic with 25 Years Experience

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**Amyloidosis is a heterogeneous group of diseases characterized by extracellular accumulation of an eosinophilic, hyalin and proteinaceous material containing mucopolysaccharide substance in various tissues and organs. Knowledge about the chemical structure of amyloid fibril proteins has led to the recognition of various forms of amyloidosis including Amyloid-A (AA), Amyloid-L (AL), hereditary, senile, dialysis-related, localized and cerebral amyloidosis. It is now recognized that all types of amyloid contain amyloid P (AP) component which is derived from the serum amyloid P component, a normal circulating glycoprotein and a member of the pentraxin family. A recent classification proposed by WHO-IUIS (Nomenclature Subcommittee) is based on the chemical nature of amyloid fibris rather than their clinical and pathologic features. The kidneys are frequently involved, and renal failure is the major cause of death.**

**Childhood renal amyloidosis is almost always secondary (reactive, AA type) and usually associated with chronic inflammatory, infectious and heredofamilial diseases. In developed countries, rheumatoid arthritis is the most common cause of renal amyloidosis, while in developing countries patients with familial Mediterranean fever (FMF) (untreated) and chronic suppurative infections constitute a large proportion of renal amyloidosis cases. No specific therapy is currently available for amyloidosis. Once renal amyloidosis develops, progress to end-stage renal failure is almost inevitable within 2-13 years. The aim of treatment is to give effective supportive therapy and to control the underlying diseases by colchicine, alkylating agents and appropriate antibiotics. The prognosis of patients with end-stage renal failure can be improved by maintenance dialysis and renal transplantation. The growing knowledge about the pathogenesis and chemical nature of amyloid fibris may open up further avenues for the discovery of specific therapeutic modalities against amyloidosis.** *Key words: renal amyloidosis, childhood, AA amyloidosis, WHO classification, pathogenesis.*

Amyloidosis is a multisystemic disease characterized by deposition of an extracellular eosinophilic substance in various organs[1, 2]. It may be localized or systemically distributed throughout the body, leading to organ damage and failure, and serious morbidity. Although the etiopathogenesis remains unsettled, recent advances in determination of the chemical structure of amyloid proteins has resulted in recognition of various forms of amyloidosis includin Amyloid-A, Amyloid-L, hereditary, senile, dialysis-related, localized and cerebral amyloidosis[3]. In addition, it is now recognized that all types of amyloid contain

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amyloid P (AP) component which is derived from the serum amyloid P component, a normal circulating glycoprotein and a member of the pentraxin family[3,4].

The kidneys are frequently involved in amyloidosis, and renal failure is the major cause of death. Cases of childhood renal amyloidosis are usually secondary to chronic inflammatory and infective disorders and familial conditions[1,2-5]. The incidence of renal amyloidosis as a cause of nephrotic syndrome has been estimated at about four percent in childhood, while its incidence varies from three to 12 percent in renal biopsies[2,5].

In an earlier study from our center (referral) of 170 children with biopsy-proven nephrotic syndrome, 33 cases (19%) were reported to have renal amyloidosis[6]. Additionally, the disease constitutes 11.5 percent of biopsy-requiring pediatric nephrological diseases in our center. The geographic predisposition of our country to familial Mediterranean fever (FMF) and the frequency of consanguineous marriages make renal amyloidosis a common nephrologic problem in childhood in Turkey.

*Nomenclature and Classification*

Many attempts have been made to classify amyloidosis. Most classifications have been based on the clinicopathological features. However, the methods for isolating and purifying amyloid fibrils and for identifying the chemical nature of the fibril proteins and their precursors have greatly developed, and amyloidosis is now classified on this basis. The most recent is the classification proposed by WHO-IUIS* Nomenclature Sub-committee in 1993 (Table I)[7]. The distinction between systemic and localized (organ or tissue-limited) amyloidosis has been avoided unlike in previous classifications, since some amyloid deposits which are thought to be localized might represent a predilection site of systemic amyloidosis.

*Pathogenesis*

The amyloid deposit is composed of amyloid fibrils which are rigid, linear, non-branching, 7.5-10 nm wide and of indefinite length. They are insoluble and resistant to proteolytic digestion. These properties are partly related to "β-pleated sheet" conformation revealed by x-ray crystallography[1] (Fig. 1). Although very little is known about the factors involved in the formation and deposition of amyloid fibrils, it is clear that the presence of a protein precursor is necessary. The precursors could be either locally produced or circulating substances which are mainly abnormal in structure or concentration or both. Proteolytic cleavage of the precursor is also important in fibril formation since the subunit of a given fibril is usually a lower molecular weight fragment of the precursor. After cleavage, the fragment can aggregate itself and/or interact with the other fragments, leading

* International Union of immunological Societies.

to polymerization and fibril formation. However, there is now evidence that some intact undegraded variant transthyretin and β-2 macroglobulin molecules can also form fibrils in familial amyloid polyneuropathy and dialysis-related amyloidosis, respectively[3]. It seems clear that the presence of a precursor is necessary; however, the factors which determine the deposition of the amyloid in some individuals but not others, and its distribution throughout the body, are still unknown.

Table I: Neomenclature and Classification of Amyloid and Amyloidosis (WHO-IUIS Neomenclature Sub-Committee 1993)

| Amyloid protein[a,b] | Protein Precursor | Protein Type or Variant | Clinical Diagnosis |
|---|---|---|---|
| AA | ApoSAA | | Reactive (secondary) amyloidosis<br>Familial Mediterranean Fever<br>Familial amyloid nephropathy with urticaria and deafness (Muckle-Wells syndrome) |
| AL | κ, λ, e.g.,κIII | Aκ, Aλ, e.g., AκIII | Idiopathic (primary) amyloidosis, associated with myeloma or macroglobulinemia |
| AH | IgG 1 (γ1) | Aγ1 | |
| ATTR | Transthyretin | e.g., Met 30[c] | Familial amyloid polyneuropathy, (Portuguese) |
| | | e.g., Met 111 | Familial amyloid cardiopathy, (Danish) |
| | | TTR or Ile 122 | Systemic senile amyloidosis |
| AApoAI | ApoAI | Arg 26 | Familial amyloid polyneuropathy, Iowa |
| AGel | Gelsolin | Asn 187[d] | Familial amyloidosis, Finnish |
| Acys | Cystatin C | Gln 68 | Hereditary cerebral hemorrhage with amyloidosis, Icelandic |
| Aβ | β protein precursor e.g., βPP 695[e] | Gln 618 | Alzheimer's disease<br>Down syndrome<br>Hereditary cerebral hemorrhage with amyloidosis, Dutch |
| Aβ2M | β2-microglobulin | | Associated with chronic dialysis |
| AScr | Scrapie protein precursor 33-35[f] cellular form | Scrapie protein 27-30 | Creutzfeldt-Jacob disease, etc.. |
| | | e.g., Leu 102 | Gertsmann-Straüssler-Scheinker syndrome |
| Acal | (Pro) calcitonin | (pro) calcitonin | In medullary carcinoma of the thyroid |
| AANF | Atrial natriuretic factor | | Isolated atrial amyloid |
| AIAPP | Islet amyloid polypeptide | | In islet cells of Langerhans Diabetes type II, insulinoma |
| AIns[g] | Insulin | | Islet amyloid in the degu (a rodent) |
| AApoII[g] | ApoAII (murine) | Gln5 | Amyloid in senescence, accelerated mice |

[a] Non-fibrillar proteins, e.g., protein AP (amyloid P component), excluded.

[b] Abbreviations: AA, amyoid A protein; SAA, serum amyloid A protein; apo, apolipoprotein; L, immunoglobulin light chain; H, immunoglobulin heavy chain.

[c] ATTR Met 30 when used in text.

[d] Aminoacid position in the mature precursor protein. The position in the amyloid fibril protein is given in parentheses.

[e] Number of amino acid residues.

[f] Molecular mass (kilodaltons).

[g] Not found in humans.

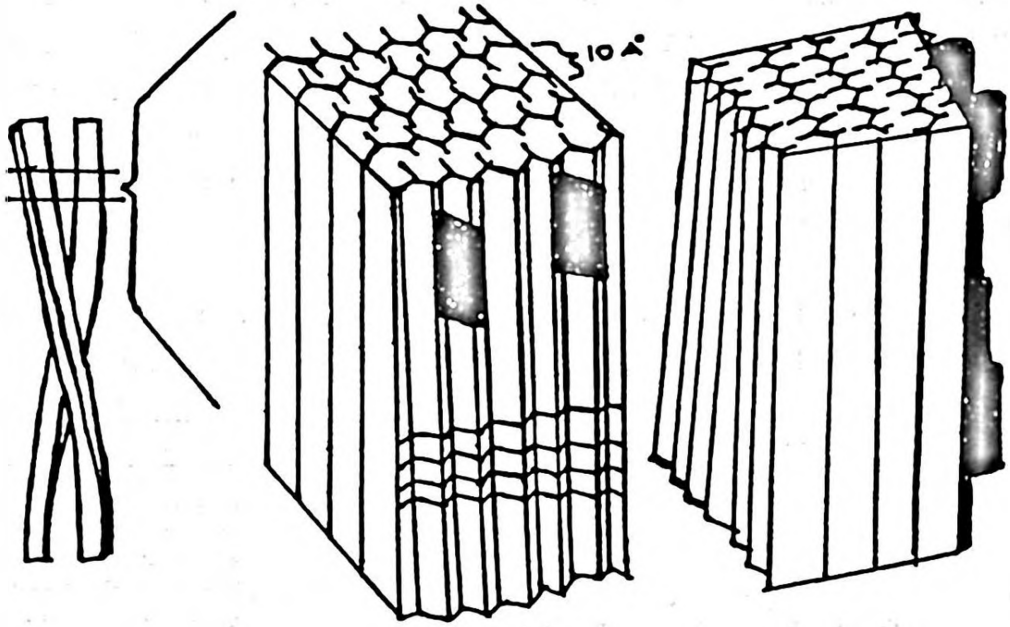



Fig. 1: "β-pleated sheet" structure of AA and AL fibrils. (The black areas represents the places where the molecules of Congo red dye bind to amyloid fibrils).

Amyloid-L protein (AL) is the major component of amyloid fibrils in multiple myeloma, macroglobulinemia and idiopathic (primary) amyloidosis. The AL proteins consist of polypeptide chains derived from immunoglobulins. The amino acid sequence of these chains has been found in some cases to be identical with the variable region of circulating light chains from the same patients. The constant region of the light chain at the C-terminal end is usually deficient, suggesting a cleavage mechanism (Fig. 2). Certain Bence-Jones proteins which were found in the primary type of amyloidosis can form fibrils in vitro showing all the morphologic and staining characteristics of amyloid[1,3].

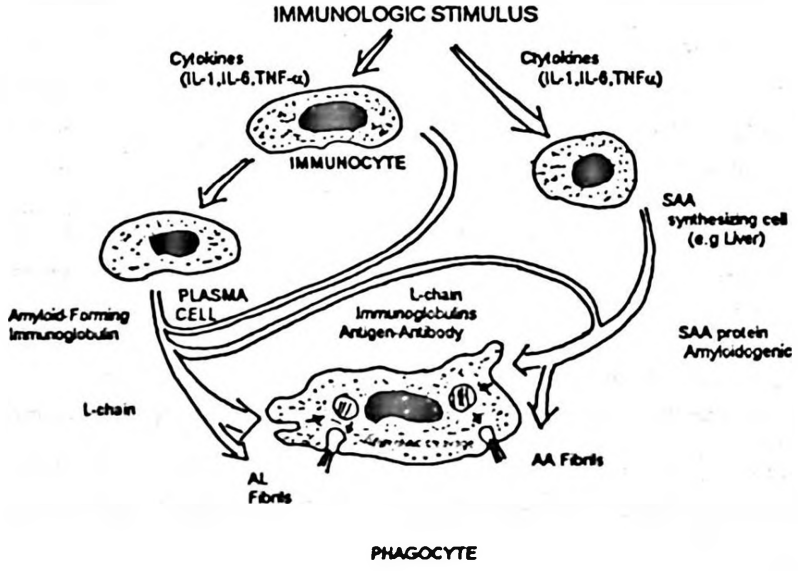



Fig. 2: Schematic representation of amyloidogenesis.

Amyloid-A protein (AA) is found in secondary (reactive) amyloidosis, familial Mediterranean fever and familial amyloid nephropathy with urticaria and deafness (Muckle-Wells' syndrome). It is likely derived from serum amyloid A (SAA), an acute-phase protein synthesized and secreted by the liver in response to interleukin-1 (IL-1), IL-6 and tumor necrosis factor (TNF). In a few individuals, the cells of the mononuclear phagocyte system are thought to be partially responsible for cleavage of SAA to form a fragment of 8500 kDa which makes amyloid deposits in several organs and systems (Figs. 2, 3). From the murine models it is known that SAA is polymorphic, and only gene products of SAA 2 are amyloidogenic[3, 4]. On the other hand, susceptibility to AA amyloidosis may be related to amyloid enhancing factor (AEF), which accelerates deposition of the amyloid. AEF is likely a product of immunologically competent spleen cells, but its chemical structure is unknown.

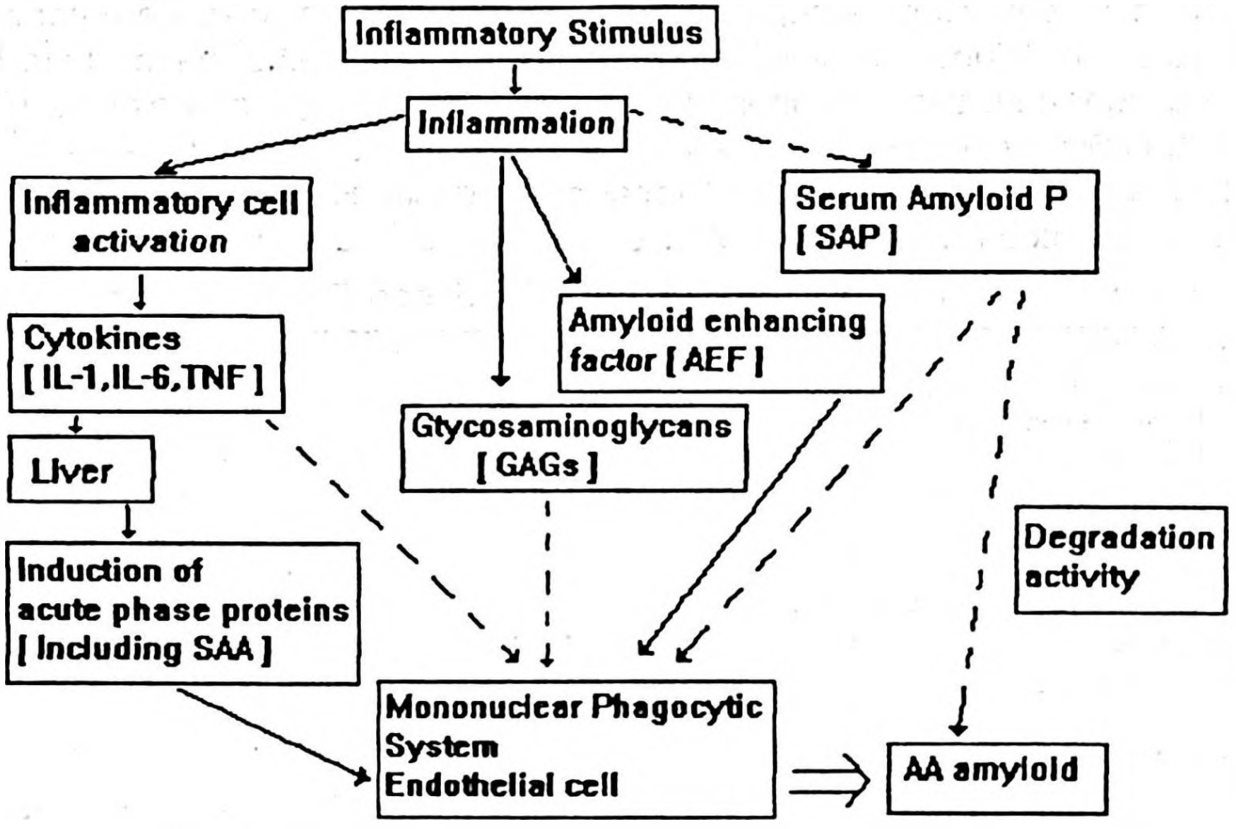



Fig. 3: Pathogenesis of reactive (AA type) amyloidosis.

Amyloid deposits have two additional constituents: sulphated glycoaminoglycans (GAGs) which are mainly heparin or heparansulphate, and amyloid P (AP) component. They are all present in all types of amyloid deposits. GAGs may be important in forming and maintaining β-pleated sheet structure. AP, which comprises 15 percent of the amyloid deposit, is identical and derived from a normal circulating plasma protein, a member of the pentraxin family SAP is also a normal constituent of the glomerular basement membrane and elastic fiber microfibrils throughout the body. The role of SAP in the pathogenesis of

amyloidogenesis is not known, but its function may be related to the binding reactions of amyloid with DNA, chromatin, GAGs and fibronectin and may contribute to the persistence of amyloid deposits by protecting them against proteolytic digestion[3, 8]

*Clinical and Laboratory Features*

Amyloidosis is rare in childhood. Primary amyloidosis-associated multiple myeloma or plasma cell dyscrasia has not been reported in children. It is uncommon before the age of 50, and the prominent clinical manifestations are cardiomyopathy, nephropathy, carpal-tunnel syndrome, hepatomegaly, subcutaneous nodules, hemorrhagic diathesis, macroglossia and peripheral autonomic neuropathy[1, 2].

Childhood amyloidosis is almost always secondary (AA type), and is usually associated with juvenile rheumatoid arthritis, chronic suppurative infections and familial Mediterranean fever (Table II)[2, 9-11]. Chronic infections such as tuberculosis, chronic pyelonephritis, empyema and brochiectasis are common causes of amyloidosis in developing countries. On the other hand, there has been a significant decrease in infectious causes of AA-type amyloidosis in the majority of Western countries where juvenile rheumatoid arthritis has been reported to be the most common cause of renal amyloidosis. However, this is not the case for our country and other Mediterranean and Middle Eastern countries.

Table II: The Predisposing Causes of Childhood Renal Amyloidosis.

| |
|---|
| A. Inflammatory |
| – Juvenile Rheumatoid Arthritis |
| – Reiter's syndrome |
| – Psoriatic arthritis |
| – Dermatomyositis |
| – Scleroderma |
| – Behçet's syndrome |
| – Inflammatory bowel disease |
| B. Infectious |
| – Tuberculosis |
| – Bronchiectasis |
| – Cystic fibrosis |
| – Chronic lung and pleural infections |
| – Chronic bone infections |
| – Chronic pyelonephritis |
| – Paraplegia |
| – Chronically infected burns |
| – Others (Mucormycosis, schistosomiasis etc.,) |
| C. Neoplastic |
| – Hodgkin's disease |
| – Renal carcinoma |
| – Others (Lymphomas, carcinomas of the gastrointestinal tract, etc.,) |
| D. Heredofamilial conditions |
| – Familial Mediterranean fever (FMF) |
| – The other familial autosomal dominant forms of amyloidosis |

In our center, we studied 174 children (the majority being referrals) with renal amyloidosis whose ages ranged from four to 18 years and found that familial Mediterranean fever (FMF) as an underlying disease accounted for the majority of the cases[10] (47.7%) (Table III). In 46 cases (26.4%), no underlying disease was determined. However, in this undetermined group, the development of AA-reactive type of amyloidosis could be explained as follows: Because of the geographic predisposition and the high rate of consanguineous marriages in our country, 46 cases of the undefined group as seen in Table III could be phenotype II patients

Table III: The Distribution of Associated Conditions in 174 Cases with Renal Amyloidosis

| Associated Condition | Number Cases | % |
|---|---|---|
| Familial Mediterranean fever (FMF) | 83 | 47.7 |
| Undefined* | 46 | 26.4 |
| Juvenile rheumatoid arthritis (JRA) | 15 | 8.6 |
| Tuberculosis | 9 | 5.1 |
| Chronic suppurative infections** | 5 | 3.0 |
| Unusual associations | | |
| – Hodgkin's lymphoma | 3 | 1.7 |
| – Bronchial asthma | 3 | 1.7 |
| – Henoch-Schönlein syndrome (HSS) | 3 | 1.7 |
| – Cirrhosis | 2 | 1.1 |
| – MPGN*** | 1 | 0.6 |
| – Rheumatic Heart Disease | 1 | 0.6 |
| – Alveolar Microlithiasis | 1 | 0.6 |
| – Myelofibrosbis | 1 | 0.6 |
| – Prader-Willi syndrome | 1 | 0.6 |

* Accepted as possible phenotype II FMF cases. Thus FMF probably accounted for 74.1% of the cases.

** Chronic pyelonephritis, lung abscess, empyema and bronchiectasis.

*** Membranoproliferative glomerulonephritis.

of FMF, in which renal amyloidosis precedes the classical signs and symptoms of FMF. Therefore, FMF probably accounted for nearly three-fourths (74.1%) of the cases with renal amyloidosis. As shown in Table IV, together with the above-mentioned series, we have experienced unusual associated cases in 18 patients out of 254 renal amyloidosis cases over a period of 30 years in our center[12, 13].

Table IV: Unusual Associations in 174 Cases with Amyloidosis

| Disorder | Number of Cases |
|---|---|
| Hodgkin's lymphoma | 3 |
| Bronchial asthma | 3 |
| Henoch-Schönlein syndrome (HSS) | 3 |
| Cirrhosis | 2 |
| MPGN* | 1 |
| Rheumatic Heart Disease | 1 |
| Alveolar Microlithiasis | 1 |
| Myelofibrosis | 1 |
| Prader-Willi syndrome | 1 |
| Hyper-IgM syndrome | 1 |
| Mucocutaneous candidiasis | 1 |

* Membranoproliferative glomerulonephritis.

Four characteristic stages are described in amyloid nephropathy associated with FMF[9]. The first stage is the preclinical stage in which there are no clinical signs of amyloidosis, but amyloid deposits could be present in the body for an unknown period and be detected histologically in causal appendectomies, as well as in renal and rectal biopsies of patients with negative urinary findings. The second stage (proteinuric stage) is the longest stage and lasts for two to 10 years (usually 3-5 years). There is first intermittent and later continuous and increasing proteinuria without significant changes in urinary sediment. There is no disturbance in renal functions except for nonselective proteinuria. During the third stage (nephrotic stage), increasing proteinuria eventually results in full-blown nephrotic syndrome in six months to five years (usually 1-2 years). The degree of proteinuria may reach 20-30 g per day, and serum albumin levels may decrease to 1 g/dl. Severe edema develops and the disease course might be complicated by infections or renal vein thrombosis manifested as a sudden increase in proteinuria and acute deterioration of renal functions. The last stage is the uremic stage which lasts for six months to six years (usually 1-1.5 years). During this stage, the serum creatinine level increases and the features of renal failure appear.

Hypertension has been found to occur in 20-50 percent of adult patients, while its highest incidence has been 14 percent in pediatric cases[2, 5, 9, 10]. This wide range depends on the clinical stage and age of the patient with renal amyloidosis. The incidence of hypertension considering all stages was found to be as low as 2.8 percent in Hacettepe's pediatric series, leading to the conclusion that hypertension was a rare complication of childhood renal amyloidosis[10]. Proteinuria and edema may decrease or persist in some cases. The overall period from the first appearance of proteinuria to end-stage renal failure ranges from two to 13

years (mean four years). The amyloidogenic process is accelerated in young children. In our patients with FMF, amyloidosis occurred within approximately 4.7 years after the first attack of FMF.

Rheumatoid arthritis, which has been reported to be the most common cause of AA-type amyloidosis in Western countries, was third in rank of the causes in the Hacettepe series following FMF and chronic infections. Symptoms depend on the tissues involved. When the kidney or heart is affected, functional impairment may cause death. In our study, edema was the most common sign (87.8%), whereas hypertension was present in 2.8 percent of cases. The presenting features are shown in Table V. Proteinuria is the most common presenting feature of secondary amyloidosis and has been observed in 82-100 percent of cases, while nephrotic syndrome has been described in 37-87 percent of cases with amyloidosis[1,2,9]. In our pediatric series, proteinuria of varying degrees was present in all cases (100%) sixty-four percent of patients were nephrotic. Hematuria was noted in 7.2 percent of cases, hypoalbuminemia in 122 (7.3%) and azotemia in 56 (34.3%). Laboratory data are summarized in Table VI.

Table V: Presenting Features of 174 Cases with Renal Amyloidosis

| Sign | Number of Cases | % |
|---|---|---|
| Edema | 154 | 88.5 |
| Hepatomegaly | 30 | 17.0 |
| Splenomegaly | 18 | 14.3 |
| Hypotension | 9 | 5.1 |
| Hypertension | 5 | 2.8 |

Table VI Laboratory Data of Cases with Renal Amyloidosis at the Time of Diagnosis

| Findings | Number of Cases | % |
|---|---|---|
| Anemia | 47 (160)* | 29.4 |
| Leukocytosis | 91 (158) | 57.6 |
| Proteinuria | 174 (174) | 100.0 |
| Hematuria | 13 (166) | 7.2 |
| Hyposthenuria | 25 (145) | 17.4 |
| Azotemia | 56 (163) | 34.1 |
| Hypoalbuminemia | 122 (167) | 73.0 |
| Hyperlipidemia | 105 (155) | 67.7 |
| Hypercholesterolemia | 116 (148) | 78.3 |
| Decreased Clcr** | 44 (108) | 40.7 |

* Number of cases so tested in parentheses.
** Creatinine clearance.

The age at onset of renal amyloidosis associated with untreated FMF appears to differ in various ethnic groups[9]. The majority of cases may occur in childhood as early as the first decade of life in our country, other Middle Eastern and some African countries, while renal amyloidosis occurs after the second decade in the majority of cases in some European countries[2, 10]. We found that the majority of our cases presented between the second half of the first decade and the first half of the second decade of life. The variation in onset of development of renal amyloidosis associated with FMF could be explained by possible genetic factors. Our proposal is that different phenotypes can arise due to population-specific mutations, the presence and effect of modulator alleles, and the effect of enviromental factors.

*Pathologic Findings*

Classically, the kidneys are described as large pale kidneys. However, they may demonstrate prominent contraction with granular cortical surfaces, especially when associated with prolonged hypertension.

*A) Light Microscopic Findings*: The earliest deposits in glomerular amyloidosis are in the mesangium. Initially, their distribution occurs irregularly (segmental form) (Fig. 4), but as deposition increases the involvement becomes more uniform. It

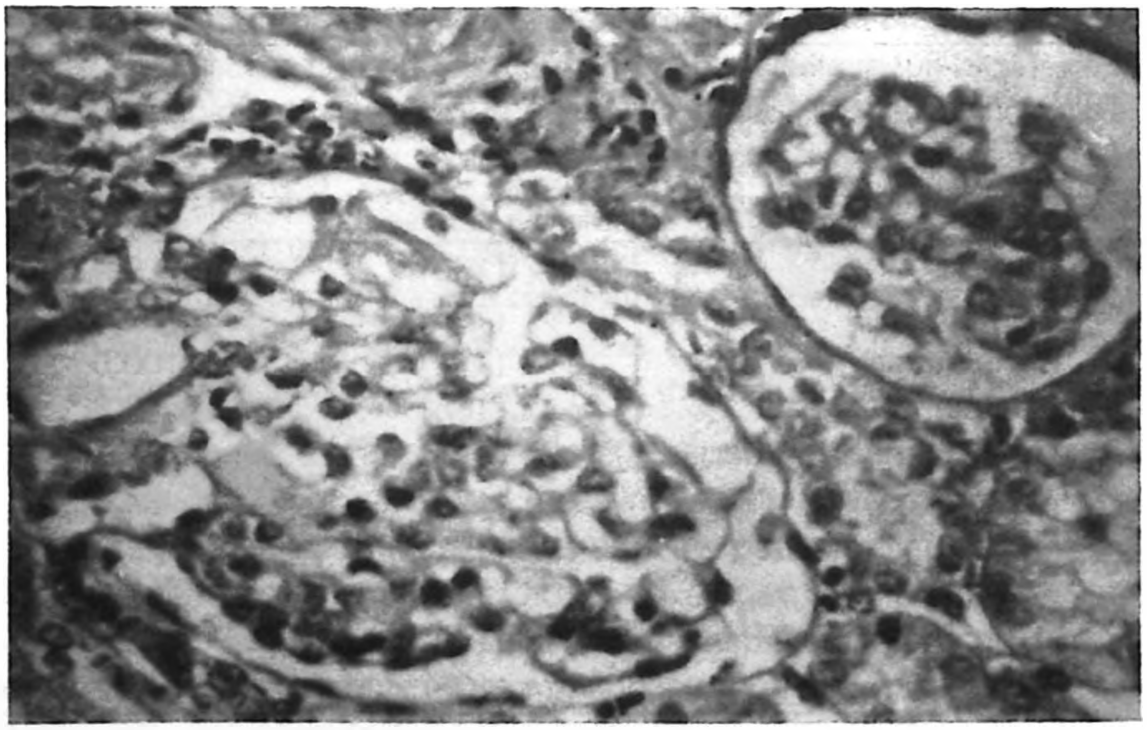


Fig. 4: Segmental amyloid deposition in a glomerulus (Grade I). HE x 450.

may form nodules (nodular form) (Fig. 5) or spread instead along the capillary

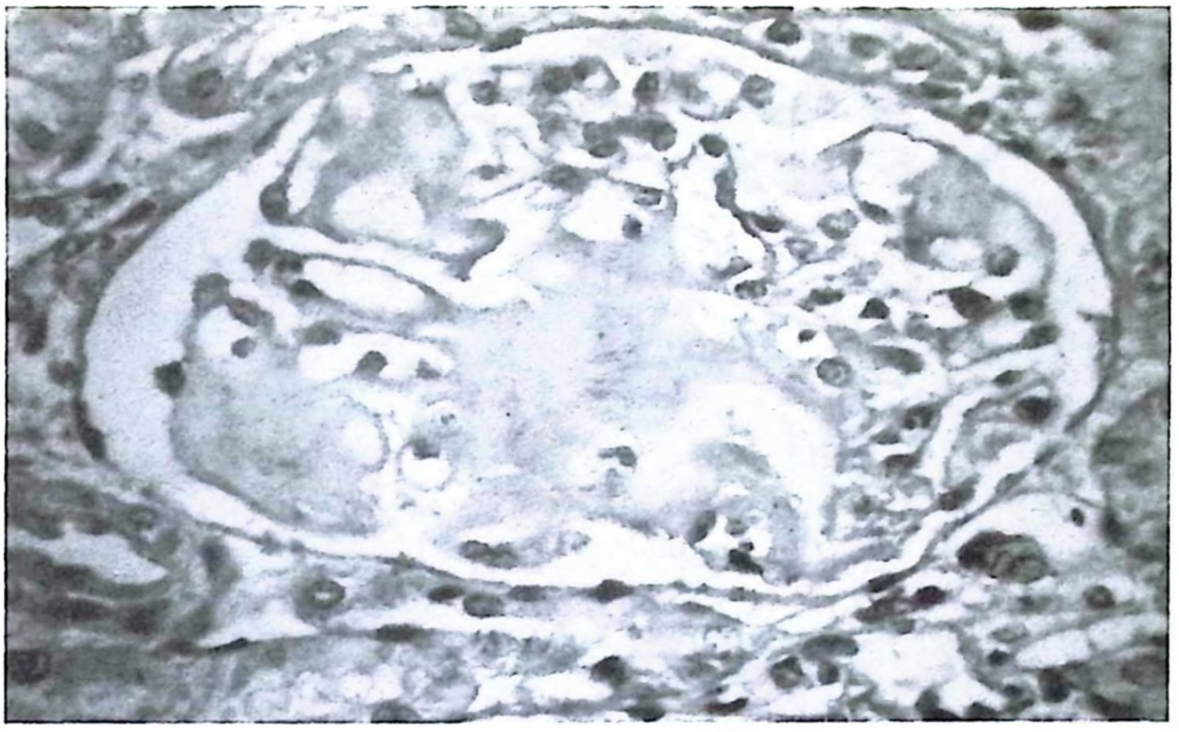


Fig. 5: Nodular type of amyloid deposition (Grade II). HE x 450.

walls (diffuse form) (Fig. 6). In some cases, there may be a combination of nodular

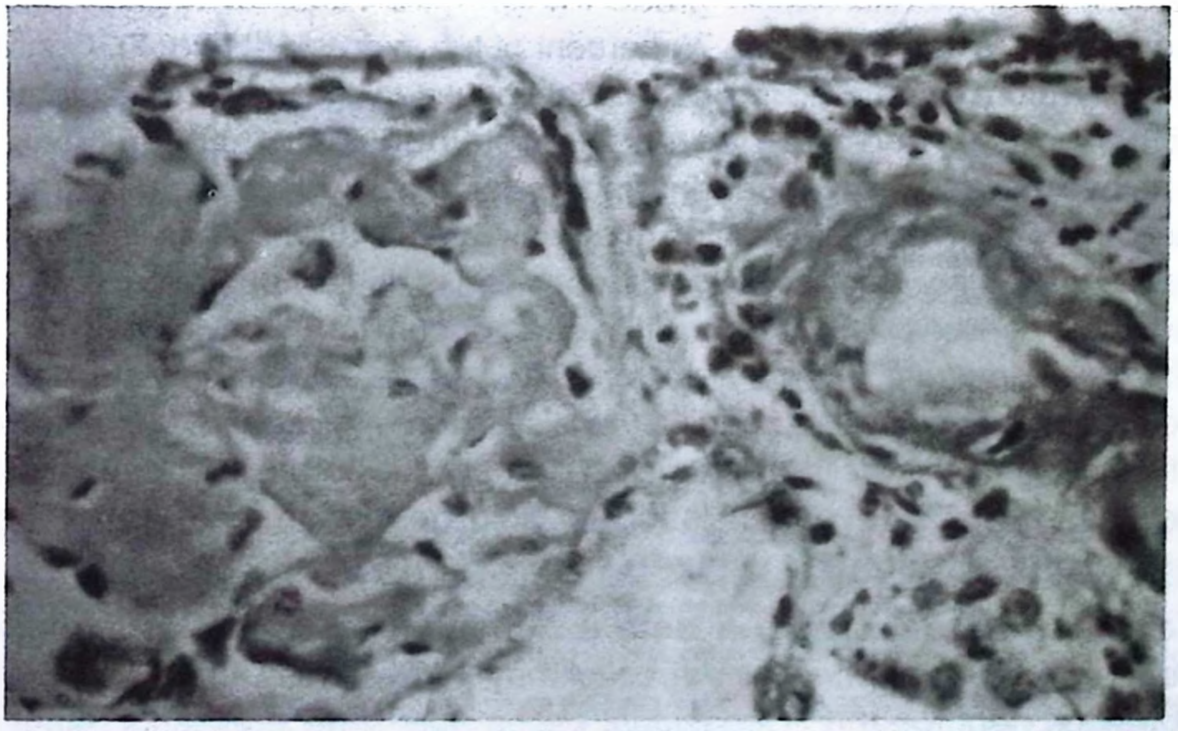


Fig. 6: Diffuse form. Diffuse staining of capillary walls and an adjacent muscular artey is seen (Grade III). Congo red x 450.

and diffuse forms (mixed form) (Fig. 7)[10]. The amount of glomerular amyloid has

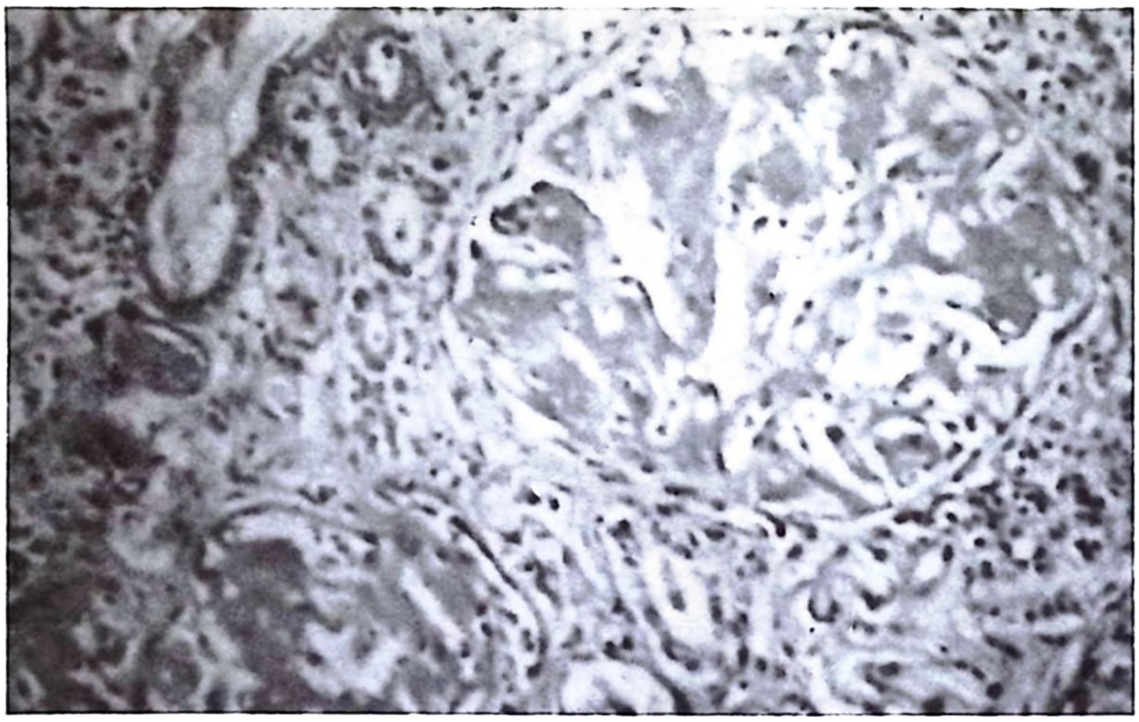


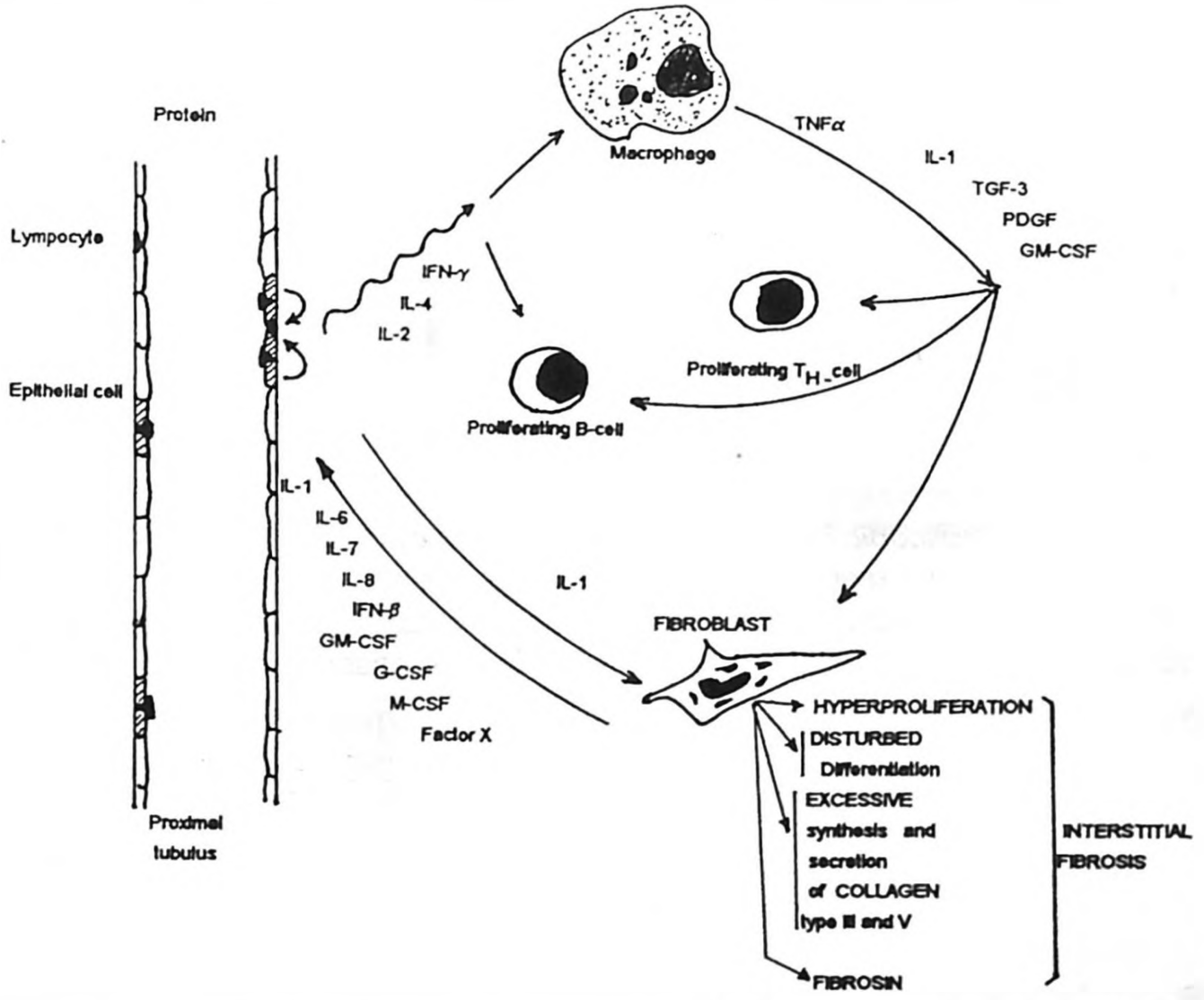
Fig. 7: Mixed form (Grade III). Note both diffuse staining of capillary walls and nodule formation in the mesangium.

been classified as grade I, II or III. Amyloid deposits were found to occupy 25 percent of glomerular tuft in grade I (Fig. 4) 25-75 percent glomerular tuft in grade 2 (Fig. 5) and more than 75 percent of tuft in grade III (Fig. 7). Consistent with the literature, we found no correlation between the amount of glomerular amyloid deposits and the degree of proteinuria. On hematoxylin-eosin (HE)-stained sections, an important finding for amyloidosis is an increment of mesangial matrix with pink-staining material without an increase in mesangial cellularity. In AA amyloidosis, amyloid deposition is usually perireticular, whereas an additional pericollagenous deposition often occurs in AL amyloidosis[1]. In early stages, the glomerular capillary walls are free of detectable amyloid deposits. As the deposits increase, the capillary walls become thickened. It is noteworthy that thickening of the walls of arterioles/arteries due to amyloid deposits does not necessarily cause hypertension[10]. Amyloid deposition tends to involve the whole vessel wall, and may occur in vessels of all sizes.

Amyloid may be deposited in both a subepithelial and a subendothelial distribution. The subepithelial deposits may form diffuse spikes and mimic membranous nephropathy. Occasional cases may show crescents, giant cells and sclerosis in glomeruli. Tubuli show no changes in the early stages. Later on, deposition occurs along the tubular basement membrane. The increased

accumulation of amyloid in glomeruli, tubuli, loops of Henle and interstitium may lead to tubular atrophy. In our series of 174 cases, we found that the creatinine clearance was very low in grade III cases, particularly in those with tubular atrophy.

Interstitial fibrosis may be seen occasionally, and there is a significant negative correlation between the degree of interstitial fibrosis (particularly, in the renal cortex) and the creatinine clearance. Therefore, it is not suprising that even cases with mild amyloidosis accompanied by interstitial fibrosis may have renal failure[10]. The leakage of proteins through the disturbed glomerular basement membranes may cause a series of immunological events leading to renal cortical interstitital fibrosis, the pathogenesis of which is described in detail in Figure 8.




Endogenous proteins pass into urine through the areas of podocyte denudation caused by subepithelial amyloid deposits. These proteins, then reabsorbed by proximal tubulus epithelial cells (PTECs) and processed as antigen. PTECs probably express these antigens in association with MHC-Class II molecules on their surface and present them to intraepithelial lymphocytes which subsequently release several cytokines. These mediators cause activation and proliferation of local macrophages and T-cells. Further release of various cytokines can also activate renal fibroblast cell system and activated renal fibroblasts may respond with hyper proliferation, disturbed differantiation and synthesis of fibrosin and excessive amounts of collagen. These events end up with renal cortical interstitial fibrosis leading chronic renal failure. IL-1: Interleukin 1, IL-2: Interleukin 2, IL-4: Interleukin 4, IL-1: Interleukin 1, INF β: Interferon-β, INFT: Interferon-T, INF, Tumor necrosis factor, TGF-3: T cell growth factor, PDGF: Platelet derived growth factor, GCSF: Granulocyte macrophage colony stimulating factor, MCSF: Macrophage colony stimulating factor, TH: T-Helper cell ICAM 1, intercellular adhesion molecule 1, HLA: Human Leukocyte antigen, ICAM-1: Intercellular adhesion molecule-1.

Fig. 8: Pathogenesis of renal cortical interstitial fibrosis in amyloidosis (modified from Ref. 16).

A well-known complication of amyloidosis is renal vein thrombosis starting in the small vessels of the kidney and spreading to major veins[14]. The interstitial deposition of amyloid and foam cells can be seen in some cases[1, 10, 14].

*B) Immunofluorescence Findings*: Little systematic data are available in the literature regarding immunofluorescence findings in human renal amyloidosis[1]. If positive, the immunofluorescence staining patterns are homogeneous, non-granular and non-linear, forming round and confluent masses. We demonstrated positive fluorescence in 68.5 percent of 57 cases with tissue-diagnosed renal amyloidosis and observed various combinations of depositions of immunoreactants with the exception of IgE and albumin antisera, which yielded continuously negative reactions (Table VII)[15].

Table VII: Distribution of the Deposits of the Immunoreactants in 57 Patients with Renal Amyloidosis

| Immune Reactants | No. of Specimens stained | Positive Staining | |
|---|---|---|---|
| | | No. | % |
| C3 | 57 | 31 | 54.3 |
| IgM | 57 | 25 | 43.8 |
| IgG | 57 | 11 | 19.2 |
| IgA | 57 | 10 | 17.9 |
| Fibrinogen | 47 | 25 | 53.2 |

*C) Electron Microscopic Findings*: Electron microscopic (EM) studies may show amyloid fibrils in the mesangium and basement membranes of capillary walls. In the subepithelial location, spikes can be demonstrated. One may occasionally recognize the fragmentation and double-contour of basement membranes[1, 10].

*Diagnosis*

Amyloidosis can be suspected clinically in a certain group of patients with particular clinical manifestations (proteinuria, hepatosplenomegaly, etc.) associated with chronic inflammatory conditions, heredofamilial syndromes and neoplastic disorders. However, the diagnosis of amyloidosis should depend on identification of amyloid on biopsy taken from the involved tissue. The amyloid is identified by demonstrating the characteristic apple-green birefringence with polarized light in tissues stained with Congo red (Fig. 9).

In recent years, antibodies against all known amyloid fibril proteins have become available and can be used in both immunofluorescence and immunoperoxidase techniques for the detection and classification of amyloid. Tissue biopsies can be taken from the rectum, subcutanous fat, gastric mucosa, gingiva, liver, sural nerve, bone marrow and kidney. EM studies can show amyloid fibrils which are

rigid, non-branching and 10-15 nm in diameter. However, EM alone is not sufficient for the diagnosis of amyloidosis. In vivo scintigraphy with $^{123}$I-labelled human serum amyloid P component allows the amyloid deposits to be visualized and quantified[3]. In heredofamilial conditions, genetic and chromosomal studies must be performed.

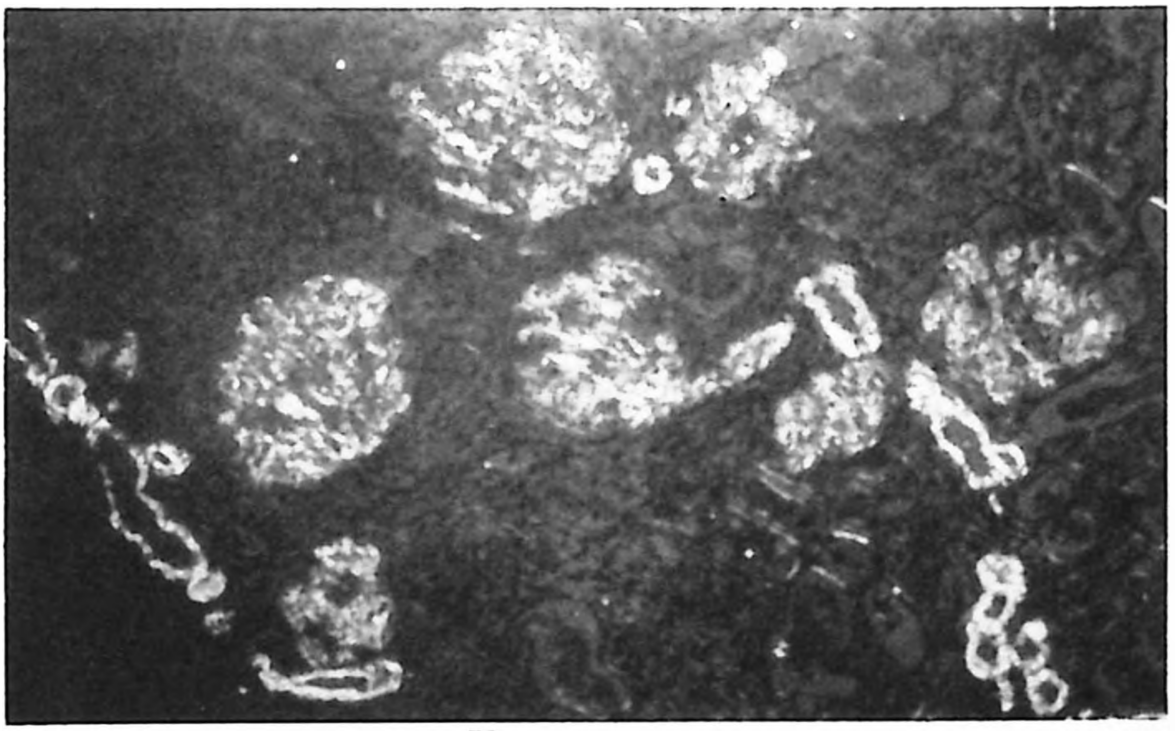


Fig. 9: Apple-green double refractility of glomerular, vascular and tubular (trace) amyloid depositions under polarized light. Congo red Polarized microscopy x 10.

*Treatment and Prognosis*

There is no specific treatment which can prevent the development of amyloidosis or halt the disease progression. The prognosis of patients with renal amyloidosis is poor when compared with that of other renal diseases[1,2,16]. The aim of therapy in AA amyloidosis is control of the underlying disease, e.g. by colchicine in FMF, cytotoxic agents and dimethyl sulphoxide (DMSO) in juvenile rheumatoid arthritis, and appropriate treatment of chronic infections[2,17]. In dialysis-related amyloid, a successful renal transplant rapidly reduces $\beta_2$-microglobulin levels to the normal range. Management of patients with amyloidosis involves supportive therapy. Failure of vital organs should be corrected promptly and aggressively, including allogeneic transplantation whenever possible. It is now clear that patients with renal insufficiency due to renal amyloidosis can be treated by regular hemodialysis or by continuous ambulatory peritoneal dialysis since these therapeutic modalities improve both the quality and duration of life. Renal transplantation has been done for more than 20 years in renal amyloidosis patients with end-stage renal failure.

Though recurrence of amyloid disease has been observed to occur in 13 percent of transplanted kidney cases, renal transplantation is a valuable treatment modality for patients with amyloidosis and end-stage renal failure[18].

In summary, renal amyloidosis is not a rare condition in biopsy-requiring nephrotic syndromes in childhood, and it is practically a secondary (reactive, AA) type of amyloidosis. The age at onset of renal amyloidosis varies in differenet ethnic populations. In our series including 174 children with renal amyloidosis, the onset of renal involvement occurred mainly between the ages of nine and 14. Thus, it is of great importance to consider FMF in the differential diagnosis of childhood nephrotic syndrome in the first two decades of life in our country. On the other hand, before the complication of renal amyloidosis occurs, colchicine therapy must be used in the course of FMF.

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