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# An Overview of the Amyloidosis in Children with Rheumatic Disease

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## 1. Introduction

Amyloidosis is a disease resulting from extra cellular accumulation of insoluble proteins in different organs and blood vessels. The term systemic amyloidosis is used to define applied to a variety of disease entities with a wide morphological and clinical spectrum (1). All amyloid proteins have biophysically comparable features (congo red binding, green color in polarized light, fibrillar appearance on electron microscopy) (2). Depending on the organ involvement type and amount, amyloid may cause progressive and life threatening organ dysfunction (3). There are numerous distractive types of amyloid fibrils are now known (4-7). The main protein types leading to amyloidosis are shown in Table 1.

In children, the most common form of amyloidosis is reactive AA amyloidosis due to hereditary periodic fever (HPF) syndromes. The genetics causes of these syndromes derive from defects of the innate immunity and have been well defined at the clinical and genetically level are. Familial Mediterranean Fever (FMF), Hyperimmunoglobulinaemia D and periodic fever syndrome (HIDS), tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) and the cryopyrin-associated periodic syndrome (CAPS), which encompasses Muckle- Wells syndrome (MWS), familial cold autoinflammatory syndrome (FCAS), and chronic infantile neurological cutaneous and articular syndrome (CINCA).

Juvenile idiopathic arthritis (JIA) is one of the more common chronic diseases of childhood, with a prevalence of approximately 1 per 1,000 (8). The most dramatic systemic inflammation is seen in patients with systemic JIA. This disorder is somewhat different from the other forms of JIA. A role for T cell and antigen –specific responses and many of the manifestations seem to be caused by the overproduction of IL-6 (figure 1). The prevalence of secondary amyloidosis in JIA varies between 1% and 10% (9-11). Risk for amyloidosis in systemic JIA patients is associated with a long-lasting inflammation (12). Although its frequency is dramatically decreasing, probably in relation with a more active DMARD treatment policy (13) Cantarini et al (14) suggest that MEFV may represent a triggering factor for the development of inflammatory state in systemic JIA, that may be an autoinflammatory disorder in itself rather than a subtype of JIA. Amyloid A precursor, serum amyloid A (SAA), is a major acute phase reactant, therefore being raised in chronic inflammatory diseases (15,16).

| Amyloid protein | Precursor protein |
|---|---|
| AA | Serum amyloid A protein |
| AL | Monoclonal Ig light chains |
| AH | Monoclonal Ig light chains |
| Aβ2M | β2-microglobulin |
| AFib | Fibrinogen α-chain |
| Acys | Cystatin C |
| ALys | Lysozyme |
| AApoAI Apolipoprotein AI | AApoAI Apolipoprotein AI |
| AApoAII Apolipoprotein AII | AApoAII Apolipoprotein AII |
| ATTR Transthyretin | ATTR Transthyretin |
| AGel Gelsolin | AGel Gelsolin |

Table 1. Amyloid proteins and their precursors

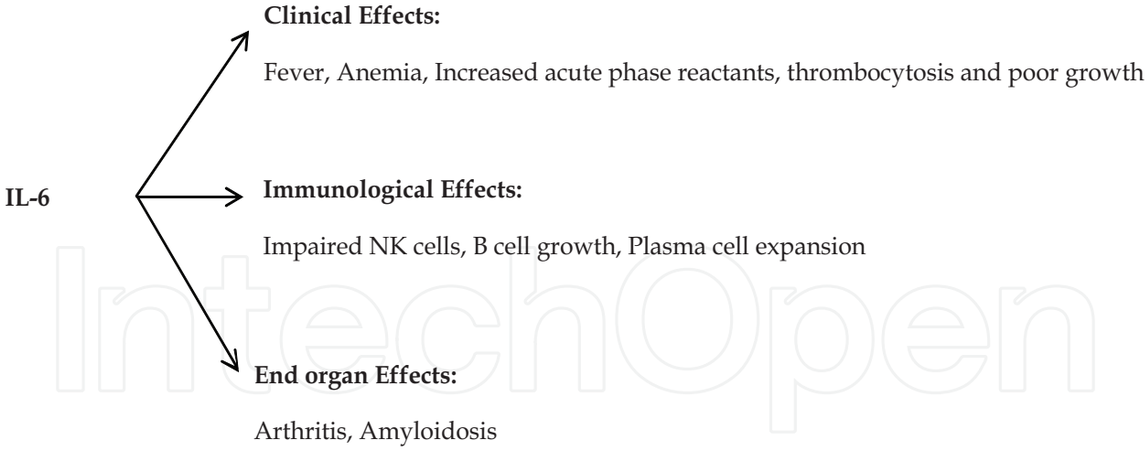


Fig. 1. IL-6 is an important mediator in systemic JIA and causes many different manifestation

AL amyloidosis is generally seen in the elderly. β2-microglobulin amyloidosis (Aβ2M amyloidosis) is seen in patients with renal failure. AFib and ACys amyloidoses are hereditary, autosomal dominant, and late-onset diseases having rarely been reported in children (6,7). Apart from the AL and AA amyloidosis, the kidney is also rarely affected by hereditary type amyloidoses, such as amyloid of fibrinogen (AFib), Apolipoprotein AI (AApoAI), and lysozymederived (ALys) amyloidosis (17).

This review discusses the pathogenesis, common causes clinical manifestations, diagnosis, and treatment of amyloidosis in children.

## 2. Pathogenesis

Amyloidosis is a general denominator for a group of diseases that are characterized by extracellular deposition of fibrils of aggregated proteins (18). These fibrils consist of polymers in a β sheet configuration of a precursor protein. SAA is a precursor protein in reactive amyloidosis and an acute phase protein that is mainly produced in the liver upon stimulation with various pro-inflammatory cytokines, interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and IL-6. It is found in plasma as an apolipoprotein of HDL cholesterol. During active inflammation serum concentrations beyond 1000 mg/l can be reached, which is 1000-fold higher than the constitutional concentration (19-21). Although the size of the SAA protein produced by the liver is 104 amino acids, amyloid fibrils found in patients with AA amyloidosis mainly consist of an accumulation of the 76 N-terminal amino acids of this protein, although proteins of different length have been reported (22,23). Polymerization of SAA into amyloid fibrils requires removal of the C-terminal of the AA protein (24). The C-terminal portion of SAA is cleaved off by macrophages. The persistent augmentation of an inflammatory pathway through the innate immune system might be crucial in the deposition of the amyloid protein leading to the clinical picture of renal amyloidosis (25).

## 3. Clinical manifestations

Amyloidosis is a multisystemic disease. Therefore, clinical manifestations vary widely, nonspecific and depending on the involved organ(s) and the amount of amyloid fibrils deposited. Several organs can be affected by AA amyloidosis, but the kidneys are most frequently involved.

Reactive amyloidosis usually presents as proteinuria with or without renal impairment. Renal involvement is found in >90% of patients (26). In addition, other organs including heart, peripheral nerves, thyroid, gastrointestinal system, and bone marrow can be involved by the type of amyloid fibrils. Clinically, it is difficult to distinguish AA and AL amyloidosis from each other because of overlapping clinical presentations. Gastrointestinal involvement is seen in about 20% of patients with reactive amyloidosis, and may present as diarrea, malabsorption or gastrointestinal pseudo-obstruction (23,26).Amyloidotic goitre, hepatomegaly, splenomegaly and polyneuropathy are less frequently encountered features of reactive amyloidosis (27,28). Amyloidosis can cause bleeding diathesis due to factor X deficiency, liver disease, or infiltration of blood vessels (29). In contrast to other types of amyloidosis, cardiac involvement is rare in reactive amyloidosis (30). Involvement of heart and kidneys are the most important predictors affecting survival (25). Infiltration of amyloid fibrils may cause enlargement of muscles and arthropathy. The clinical manifestations of Aβ2M amyloidosis include carpal tunnel syndrome, bone cysts, spondyloarthropathy, pathologic fractures, and swollen painful joints (31).

In kidney involvement; asymptomatic proteinuria is the most common initial presentation, gradually progressing to nephrotic syndrome and/or renal dysfunction. In the series reported by the Turkish FMF study group, the presenting clinical features of the patients with amyloidosis secondary to FMF were as follows: 32% proteinuria, 40% nephrotic

syndrome, and 28% chronic renal failure (24). The patients having glomerular amyloid deposition are more common and have a poorer prognosis than patients having vascular and tubular amyloid deposition in rheumatoid arthritis-related AA amyloidosis (32). Nishi et al. (33) showed that 10–30% of patients with renal amyloidosis might have only mild proteinuria and normal renal function.

## 4. Diagnosis

Suspicion is essential in subjects having an underlying disease with a potential to cause amyloidosis. Amyloidosis should be suspected typically in a patient who presents with proteinuria. In fact, in patients who are candidates for this complication, secondary amyloidosis should also be considered in the differential diagnosis of cardiomyopathy, peripheral neuropathy, hepatomegaly, or in the presence of symptoms related to the gastrointestinal tract. The diagnosis of amyloidosis is based on the demonstration of amyloid fibrils in the biopsy of the involved tissue. Renal, rectal or abdominal fat biopsies may also reveal amyloid deposition. The deposited amyloid fibrils are extracellular, eosinophilic, and metachromatic on light microscopy. Congo red staining is necessary for diagnosis. Amyloid fibrils appear faintly red on Congo red staining and show the characteristic apple-green birefringence under polarized light. Actually, infiltrative renal diseases including amyloidosis must be considered in the differential diagnosis of all patients having chronic kidney disease and normal or large sized kidneys. AA amyloidosis can also be diagnosed using serum amyloid P component scintigraphy (34).

## 5. Underlying causes of secondary amyloidosis

### 5.1 Familial mediterranean fever

FMF is characterized by recurrent periodic fever episodes and serositis along with an increased acute inflammatory response (35,36). FMF is the overall most common autoinflammatory disease and has prevalences as high as 1/ 1,000–1/250 among Jews, Turks, Armenians, and Arabs (37). The most seri o u s complication of the disease is the development of AA type amyloidosis, first diagnosed by Mamou and Cattan in 1952 (38). This is due to caused by accumulation of amyloid fibrils in the extracellular spaces of various organs and tissues, most notably the kidneys, liver and spleen, leading to organ failure (39). Several genetic and environmental factors modify the risk for reactive amyloidosis (23).

The typical manifestation of amyloidosis in a FMF patient is defined with nephrotic ranged proteinuria, and uremia, arising from deposition of amyloid fibrils in the kidneys. The phenotypic features of the disease and the frequency of amyloidosis differs among various ethnic groups and it was emphasized by several authors that Turks have more severe disease with a higher incidence of amyloidosis (40).

FMF is caused by a mutation in the *MEFV* (pyrin) gene. Although some mutations have been described, the four most prevalent ones (M694V, M680I, M694I and V726A) account for over 80% of cases (41-43).

Pyrin expressed primarly in the innate immune system (granulocyte, dendritic cell, etc.).

Both pyrin and a related gene, cryopyrin, contain an N- terminal domain that encodes a death domain –related structure, now known as the pyrin domain, or PyD. Both pyrin and cyropyrin interact through their PyDs with a common adaptor protein, apoptotic speck

protein (ASC). ASC itself participates in apoptosis, recruitment, and activation of pro-caspase-1 (also named as IL-1β converting enzyme) and nuclear factor –kB, a transcription factor involved in initiation and resolution of the inflammatory response (44).
Wild –type pyrin has been found either to inhibit or accentuate caspase-1 activity and it is key molecule in the inflammasome. The net effect of pyrin, and the molecular mechanisms of FMF-associated mutations, remains controversial. This results in clinical attacks of inflammation in the form of fever and serositis along with increased acute-phase reactants (APRs) (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and SAA). The continuous elevation of these APRs during and even between attacks predisposes to the development of AA systemic amyloidosis. This inflammatory state is what probably results in the variety of problems related to clinical inflammation observed in patients with FMF (25). If the child has not been treated properly and if secondary amyloidosis develops, urinalysis will reveal proteinuria (45). If proteinuria is not diagnosed, it will progress to full-blown nephrotic syndrome.
Not all FMF patients having amyloidosis, suggests the presence of other contributing factors. The role of genetic background was established by comparing the incidence of amyloidosis in Jewish patients from different ethnic origins. Apart from ethnicity, several other genetic risk factors have been defined. The M694V mutation has been shown to be a strong risk factor of developing amyloidosis in different ethnic groups (46-49). We studied in 308 patients with FMF and detected amyloidosis 8 (2.6% ) patients with amyloidosis homozygous for the M694V mutation had earlier onset and, a more severe course (50).
Another factor that modulates the risk of developing amyloidosis is the SAA1 gene haplotype. Single nucleotide polymorphisms in the gene coding for SAA define 3 haplotypes: 1.1, 1.3 and 1.5. Patients with a 1.1/1.1 genotype have an increased risk for amyloidosis of 3–7-fold, independent of MEFV genotype (40,51). In addition, there is 4.5–6-fold increased risk of developing amyloidosis in affected family members of FMF patients who have already developed amyloidosis (36,52).
Colchicine treatment has changed the course of FMF by both reducing attack frequency and severity and preventing amyloidosis. Goldinger first described its effectiveness in 1972 and since then colchicine became the drug of choice for FMF (53). Colchicine, an alkaloid, binds to β-tubulin hindering its polarization with consequent defective transfer and mitosis, inhibition of neutrophil chemotaxis, and reduced expression of adhesion molecules (24).
Before the advent of colchicine, amyloidosis was relatively frequent. It occurred in up to 60%–75% of patients over the age of 40, and the incidence varied among different ethnic groups (54). Akse Onal et al. (37) observed a dramatic decrease of secondary amyloidosis in Turkey. They think that the decrease of the rate of amyloidosis in childhood is due to better education of Turkish physicians on the subject and the improvement in the infectious milieu of young children.

### 5.2 TNF receptor-associated periodic syndrome

This dominantly inherited disorder was first described in a large family of Irish/Scottish ancestry and hence named familial Hibernian fever (55). It is the second most common periodic fever disorder. Dominantly inherited heterozygous mutations in TNFRSF1A, encoding the TNF receptor 1 cause TRAPS (56). Because all known mutations are in the

extracellular domain of the receptor, it has been hypothesized that TRAPS mutations interfere with the shedding of the TNF receptor (57). Impaired receptor shedding might then lead to repeated signaling and prolongation of the immune response. TNFRSF1A mutations cause to reduced cell surface expression of mutant receptors. This would lead to deficiency of anti inflammatory soluble TNF receptors. Patients experience recurrent, often prolonged fevers that can be accompanied by severe abdominal pain, pleurisy, arthritis a migratory skin rash with underling fasciitis and/or periorbital edema (58,59). The age of onset varies widely, but most patients become symptomatic within the first decade of life. Attacks persist for a minimum of 3 days, but usually last longer, up to several weeks (60,61). Some TRAPS patients eventually develop systemic AA amyloidosis. An estimated 14%–25% of TRAPS patients develop reactive amyloidosis (57,62). The risk of amyloidosis appears to be greater among patients with cysteine mutations (63). Affected family members of TRAPS patients with amyloidosis are at increased risk and it is advisable to screen urine samples at regular intervals for proteinuria. Treatment depends on the severity of the disease. For patients with infrequent attacks and normal SAA, prednisone during attacks may be effective (61). For patients with more severe disease, etanercept or adalimumab as anti-TNF agents were found to be effective. IL-1 receptor antagonist has also shown to be effective in non-responsive patients (64).

### 5.3 Cryopyrin-associated periodic syndrome

Cryopyrin-associated periodic syndromes (CAPS) are a group of rare autoinflammatory diseases including familial cold urticaria (FCAS), Muckle-Wells syndrome (MWS), and chronic infantile neurologic cutaneous articular syndrome (CINCA), also known as neonatal onset multisystem inflammatory disease (NOMID). CAPS are all caused by mutations in CIAS1 encoding cryopyrin, which is a component of the IL-1β inflammasome (56). These are all transmitted in an autosomal-dominant fashion. FCAS is characterized by recurrent, short attacks of fever, urticarial skin rash, arthralgia and conjunctivitis after exposure to cold. The peak of the attack occurs at 6–8 h and lasts up to 24 h. Amyloidosis is a rare complication of FCAS (2–4%) (65). In MWS, the typical attack includes fever, rash, arthralgia, arthritis, myalgia, headaches, conjunctivitis, episcleritis, and uveitis lasting up to 3 days. Progressive sensorineural hearing loss develops in the second and fourth decades. Amyloidosis develops in 25% of the cases (66). The onset of CINCA-NOMID is at or within several weeks of birth. It is characterized by urticaria-like rash, fever, chronic aseptic meningitis, eye findings including conjunctivitis, uveitis, and papillitis of the optic nerve. Half of patients develop a severe arthropathy.Patients have typical morphological changes of short stature, frontal bossing, macrocephaly, saddle nose, short, thick extremities with clubbing of fingers, and wrinkled skin. If untreated, 20% die by age 20 years, and others develop amyloidosis (67). [In CINCA and MWS, corticosteroid therapy can be useful in selected patients. Anti-IL-1 agents are very effective in all CAPS patients.

### 5.4 Hyper IgD syndrome

HIDS was identified as a separate disease entity in 1984 (68). It is inherited as an autosomal recessive trait. HIDS is caused by mutations in the MVK gene, on chromosome 12, which encodes mevalonate kinase. Mutations associated with HIDS lead to markedly reduced mevalonate kinase enzymatic activity. Excessive production of pro inflammatory cytokines by HIDS mononuclear cells may result from excessive accumulation of mevalonic acid

substrate, recent data support an alternative hypothesis related to deficiencies in nonsterol isoprenoids synthesized through the mevalonate pathway. This is characterized by fever, arthralgia, abdominal pain, diarrhea, maculopapular rash, and lymphadenopathy lasting 3–7 days. An attack can be provoked by minor trauma, vaccination or stress. The attacks usually recur every 4–6 weeks, but there is considerable inter- and intraindividual variation. Secondary amyloidosis has been reported in 3% of the patients, which is rarer than that reported for the other monogenic autoinflammatory syndromes (69). Corticosteroids are ineffective in preventing or treating attacks. A number of treatments have been tried including biologics. Simvastatin used because of its inhibition of HMG-CoA reductase, the enzyme proximal to mevalonate kinase in the isoprenoid pathway (70).

### 5.5 Deficiency of the Interleukin-1 receptor antagonist

DIRA is a rare autosomal recessive autoinflammatory disease caused by mutations affecting the gene *IL1RN* encoding the endogenous IL-1 receptor antagonist (9, 10). Children with DIRA present with strikingly similar clinical features including systemic inflammation in the perinatal period, bone pain, characteristic radiographical findings of multifocal sterile osteolytic bone lesions, widening of multiple anterior ribs, periostitis, and pustular skin lesions. Amyloidosis associated with this syndrome have been reported yet.

### 5.6 Juvenile idiopathic arthritis

Juvenile idiopathic arthritis is the most common rheumatic disease of childhood. The diagnostic criteria requires a child younger than 16 years of age with arthritis for at least 6 weeks' duration with exclusion of other identifiable causes of arthritis. Juvenile idiopathic arthritis has been classified into seven subtypes. Secondary amyloidosis used to be one of the most serious and fatal complications of JIA. The form of JIA is important; amyloidosis has been observed mainly in systemic and polyarticular forms. Amyloidosis is typically accompanied by elevated levels of SAA and CRP. The prevalence of secondary amyloidosis (SA) in juvenile idiopathic arthritis (JIA) varies between 1% and 10% (9-11) Secondary amyloidosis due to JIA has been decreasing dramatically in recent years, which is due to earlier recognition and better management of the disease and the introduction of new biologic agents. In this decade, amyloidosis is a rare entity in JIA.

### 5.7 Other diseases

Crohn's and Behçet's disease are known to be associated with secondary amyloidosis in severe cases. The mechanism may be speculated to be due to uncontrolled inflammation similar to that in monogenic autoinflammatory diseases. Also, sickle cell anemia, chronic granulomatous disease associated aspergillosis, and Hodgkin's disease are other diseases that have been very rarely associated with AA type of amyloidosis in children in the medical literature (71).

## 6. Treatment

The diagnosis of amyloidosis and typing are crucial for the patient. In practice, specific treatment of the underlying disorder, aiming to suppress the inflammatory activity is the major strategy.

Treatment options of amyloidosis will be discussed in three main headings:

1. *Reducing the production of amyloidogenic precursor protein (AA and AL amyloidosis) and enhancing the clearance of amyloidogenic precursor protein (Aβ2M amyloidosis) and trying to break down the amyloid deposits*:
   Colchicine is the prototype drug that decreases production of amyloidogenic precursor protein. Biologic treatment, such as anti-TNF, anti-IL-1 therapy, may have a beneficial effect on the suppression of inflammation on amyloidosis. There are reports suggesting the effectiveness of anti-TNF and anti IL-1 antagonists on regression of secondary amyloidosis in FMF (72).
2. *Specific treatment strategies for secondary amyloidosis*:
   New treatment options directed to affect the amyloid structure (e.g., diflunisal for hereditary amyloidosis) or to prevent fibrillogenesis (e.g., eprodisate for AA amyloidosis) or to weaken their structural stability (e.g., iododoxorubicin) are being investigated (73). Eprodisate inhibits polymerization of amyloid fibrils and deposition of the fibrils in tissues by interfere with interactions between amyloidogenic proteins and glycosaminoglycans. Eprodisate therapy slowed the progression of renal disease compared to placebo. However, the drug had no significant effect on progression to end-stage renal disease or risk of death (73).
3. *Renal replacement therapy.*

## 7. Conclusions

The chronic inflammatuar and autoinflammatory diseases occur with persistant inflammation therefore they are the most common cause of reactive amyloidosis in children. Understanding the pathophysiology of this group of diseases will improve our data on the mechanisms of amyloid formation and therapy options.

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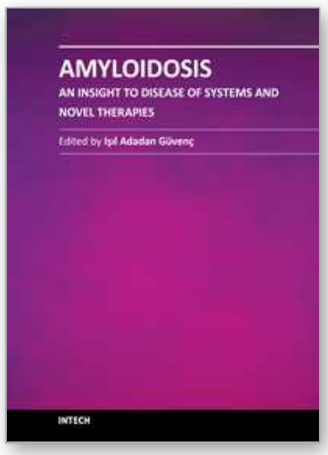


**Amyloidosis - An Insight to Disease of Systems and Novel Therapies**

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Amyloidosis is a benign, slowly progressive condition characterized by the presence of extracellular fibrillar proteins in various organs and tissues. It has systemic or localized forms. Both systemic and localized amyloidosis have been a point of interest for many researchers and there have been a growing number of case reports in the literature for the last decade. The aim of this book is to help the reader become familiar with the presentation, diagnosis and treatment modalities of systemic and localized amyloidosis of specific organs or systems and also cover the latest advancements in therapy.



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