2

An Overview of the Amyloidosis in Children with Rheumatic Disease

Betül Sözeri, Nida Dincel and Sevgi Mir
Ege University Faculty of Medicine, Department of Pediatrics
Bornova, Izmir
Turkey

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

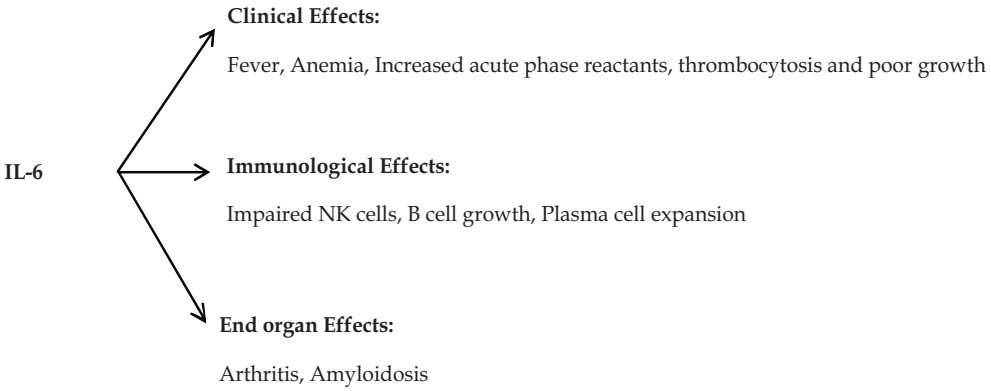


Fig. 1. IL-6 is an important mediator in systemic JIA and causes many different manifestation

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.

8. References

[1] Bugov B, Lubomirova M, Kiperova B (2008). Biopsy of subcutaneous fatty tissue for diagnosis of systmemic amyloidosis. Hippokratia 12,4: 236-239.

[2] Strege RJ, Saeger W, Linke RP (1998). Diagnosis and immunohistochemical classification of systemic amyloidoses. Report of 43 cases in an unselected autopsy series. Virchows Arch. Jul;433(1):19-27.

[3] Merlini G, Bellotti V (2003). Molecular mechanisms of amyloidosis. N Engl J Med. 349:583–596.

[4] Glenner GG (1980). Amyloid deposits and amyloidosis. The b- fibrilloses. Engl J Med 302: 1283–1292; 1333–1343.

[5] Kazatchkine M, Husby G, Araki S (1993). Terminology. Nomenclature of amyloid and amyloidosis. WHO-IUIS nomenclature sub-committe. Bull WHO 71: 105–108.

[6] Perfetto F, Moggi-Pignone A, Livi R, Tempestini A, Bergesio F, Matucci-Cerinic M (2010). Systemic amyloidosis: a challenge for the rheumatologist. Nat Rev Rheumatol 6:417–429.

[7] Picken MM (2007). New insights into systemic amyloidosis: the importance of diagnosis of specific type. Curr Opin Nephrol Hypertens 16:196–203.

[8] Andersson Gare B (1999). Juvenile arthritis: who gets it, where and when? A review of current data on incidence and prevalence. Clin Exp Rheumatol;17:367–74.

[9] David J, Vouyiouka O, Ansell BM, Hall A, Woo P (1993). Amyloidosis in chronic juvenile arthritis: a morbidity and mortality study. Clin Exp Rheum 11:85–90.
[10] Filipowicz-Sosnowska AM, Rozropwicz-Denisiewicz K, Rosenthal CJ, Baum J. (1978). The amyloidosis of juvenile rheumatoid arthritis: comparative studies in Polish and American children. Arthitis Rheum 37:699–703.
[11] Ozdogan H, Kasapcopur O, Dede H, Arisoy N, Beceren T, Yurdakul S Yazici H (1991). Juvenile chronic arthritis in a Turkish population. Clin Exp Rheumatol 9:431–5.
[12] Savolainen HA, Isomaki HA (1993). Decrease in the number of deaths from secondary amyloidosis in patients with juvenile rheumatoid arthritis. J Rheumatol 20:1201-3.
[13] Immonen K, Savolainen HA, Hakala M (2007). Why can we no longer find juvenile idiopathic arthritis-associated amyloidosis in childhood or in adolescence in Finland? Scand J Rheumatol 36:402–403.
[14] Cantarini L, Lucherini OM, Simonini G, Galeazzi M, Baldari CT, Cimaz R (2010). Systemic-onset juvenile idiopathic arthritis complicated by early onset amyloidosis in a patient carrying a mutation in the MEFV gene. Rheumatol Int. 2010 Jan 1.
[15] Woo P (1992). Amyloidosis in pediatric rheumatic diseases. J Rheumatol Suppl 35:10−16.
[16] Grateau G (2003). Musculoskeletal disorders in secondary amyloidosis and hereditary fevers. Best Pract Res Clin Rheumatol 17:929−944.
[17] Rysavá R (2007). AL amyloidosis with renal involvement. Kidney Blood Press Res 30:359–36.
[18] Merlini G, Bellotti V (2003). Molecular mechanisms of amyloidosis. N Engl J Med 349:583–596.
[19] Hoffman JS, Benditt EP (1982). Changes in high density lipoprotein content following endotoxin administration in the mouse. Formation of serum amyloid protein-rich subfractions. J Biol Chem 257:10510–10517.
[20] Marhaug G (1983). Three assays for the characterization and quantitation of human serum amyloid A. Scand J Immunol 18:329–338.
[21] Benson MD, Scheinberg MA, Shirahama T, Cathcart ES, Skinner M (1977). Kinetics of serum amyloid protein A in casein-induced murine amyloidosis. J Clin Invest 59:412–417.
[22] Husebekk A, Skogen B, Husby G, Marhaug G (1985). Transformation of amyloid precursor SAA to protein AA and incorporation in amyloid fibrils in vivo. Scand J Immunol 21:283–287.
[23] van der Hilst JC, Simon A, Drenth JP (2005). Hereditary periodic fever and reactive amyloidosis. Clin Exp Med. 2005 Oct;5(3):87-98.
[24] Ben Chetritt R (2003). FMF and renal amyloidosis. Phenotypegenotype correlation, treatment and prognosis. J Nephrol 16:431–434.
[25] Ozen S (2004). Renal amyloidosis in familial Mediterranean fever. Kidney Int 65:1118–1127.
[26] Gertz MA, Kyle RA (1991). Secondary systemic amyloidosis: response and survival in 64 patients. Medicine (Baltimore)70:246–256.
[27] Mainenti PP, Cantalupo T, Nicotra S, Camera L, Imbriaco M, Di Vizio D et al (2004). Systemic amyloidosis: the CT sign of splenic hypoperfusion. Amyloid 11:281–282.

[28] Tuglular S, Yalcinkaya F, Paydas S, Oner A, Utas C, Bozfakioglu S et al (2002). A retrospective analysis for aetiology and clinical findings of 287 secondary amyloidosis cases in Turkey. Nephrol Dial Transplant 17:2003–2005.

[29] Sucker C, Hetzel GR, Grabensee B, Stockschlaeder M, Scharf RE (2006). Amyloidosis and bleeding: pathophysiology, diagnosis, and therapy. Am J Kidney Dis 47:947–955.

[30] Dubrey SW, Cha K, Simms RW, Skinner M, Falk RH (1996). Electrocardiography and Doppler echocardiography in secondary (AA) amyloidosis. Am J Cardiol 77:313–315.

[31] Drüeke TB, Massy ZA (2009). Beta2-microglobulin. Semin Dial 22:378–380.

[32] Uda H, Yokota A, Kobayashi K, Miyake T, Fushimi H, Maeda A, Saiki O (2006). Two distinct clinical courses of renal involvement in rheumatoid patients with AA amyloidosis. J Rheumatol 33:1482–1487.

[33] Nishi S, Alchi B, Imai N, Gejyo F (2008). New advances in renal amyloidosis. Clin Exp Nephrol 12:93–101.

[34] Hawkins PN (2002). Serum amyloid P component scintigraphy for diagnosing and monitoring amyloidosis. Curr Opin Nephrol Hypertens 11:649–655.

[35] Ozen S, Berdeli A, Türel B et al (2006). Arg753Gln TLR-2 polymorphism in familial Mediterranean fever: linking the environment to the phenotype in a monogenic inflammatory disease. J Rheumatol 33:2498–2500.

[36] Saatci U, Bakkaloglu A, Ozen S et al (1993). Familial Mediterranean fever and amyloidosis in children. Acta Paediatr 82 (8):705–706.

[37] Akse-Onal V, Sağ E, Ozen S, Bakkaloglu A, Cakar N, Besbas N, Gucer S. (2010). Decrease in the rate of secondary amyloidosis in Turkish children with FMF: are we doing better? Eur J Pediatr. 169(8):971-4. .

[38] Mamou H, Cattan R. (1952). La maladie periodique sur 14 cas personnels dont 8 compliqués de nephropathies. *Semaine hop. Paris*; 28: 1062.

[39] Falk RH, Comenzo RL, Skinner M (1997). The systemic amyloidoses. N Engl J Med 337:898–909.

[40] Yalçinkaya F, Cakar N, Misirlioğlu M, Tümer N, Akar N, Tekin M, Taştan H, Koçak H, Ozkaya N, Elhan AH (2000). Genotype-phenotype correlation in a large group of Turkish patients with familial mediterranean fever: evidence for mutation-independent amyloidosis. Rheumatology (Oxford). Jan;39(1):67-72.

[41] The French FMF Consortium (1997). A candidate gene for familial Mediterranean fever. Nat Genet 17:25–31.

[42] The International FMF Consortium (1997). Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever. Cell 90:797–807.

[43] Touitou I, Lesage S, McDermott M, Cuisset L, Hoffman H, Dode C (2004). Infevers: an evolving mutation database for auto-inflammatory syndromes. Hum Mutat 24:194–1.

[44] Padeh S, Berkun Y. Auto-inflammatory fever syndromes (2007). Rheum Dis Clin North Am. 33(3):585-623.

[45] Lidar M, Livneh A (2007). Familial Mediterranean fever: clinical, molecular and management advances. Neth J Med 65:318–324.

[46] Mimouni A, Magal N, Stoffman N, Shohat T, Minasian A, Krasnov M et al (2000). Familial Mediterranean fever: effects of genotype and ethnicity on inflammatory attacks and amyloidosis. Pediatrics 105:E70.

[47] Mansour I, Delague V, Cazeneuve C, Dode C, Chouery E, Pecheux C et al (2001). Familial Mediterranean fever in Lebanon: mutation spectrum, evidence for cases in Maronites, Greek orthodoxes, Greek catholics, Syriacs and Chiites and for an association between amyloidosis and M694V and M694I mutations. Eur J Hum Genet 9:51–55.

[48] Brik R, Shinawi M, Kepten I, Berant M, Gershoni-Baruch R (1999). Familial Mediterranean fever: clinical and genetic characterization in a mixed pediatric population of Jewish and Arab patients. Pediatrics 103:e70.

[49] Cazeneuve C, Sarkisian T, Pecheux C, Dervichian M, Nedelec B, Reinert P et al (1999). MEFV-gene analysis in Armenian patients with Familial Mediterranean fever: diagnostic value and unfavorable renal prognosis of the M694V homozygous genotype – genetic and therapeutic implications. Am J Hum Genet 65:88–97.

[50] Ozalkaya E, Mir S, Sozeri B, Berdeli A, Mutlubas F, Cura A (2010). Familial Mediterranean fever gene mutation frequencies and genotype-phenotype correlations in the Aegean region of Turkey.Rheumatol Int. Mar 9.

[51] Gershoni-Baruch R, Brik R, Zacks N, Shinawi M, Lidar M, Livneh A (2003). The contribution of genotypes at the MEFV and SAA1 loci to amyloidosis and disease severity in patients with familial Mediterranean fever. Arthritis Rheum 48:1149–1155.

[52] Tunca M, Akar S, Onen F, Ozdogan H, Kasapcopur O, Yalcinkaya F et al (2005). Familial Mediterranean fever (FMF) in Turkey: results of a nationwide multicenter study. Medicine (Baltimore) 84:1–11.

[53] Goldinger SE (1972). Colchicine for familial Mediterranean fever. N Engl J Med 287:1302.

[54] Gafni J, Ravid M, Sohar E (1968). The role of amyloidosis in familial Mediterranean fever. A population study. Isr J Med Sci 4:995–999.

[55] Williamson LM, Hull D, Mehta R, Reeves WG, Robinson BH, Toghill PJ (1982). Familial Hibernian fever. Q J Med 51:469–480.

[56] Masters SL, Simon A, Aksentijevich I, Kastner DL. (2009). Horror autoinflammaticus: the molecular pathophysiology of autoinflammatory disease (*).Annu Rev Immunol. 27:621-68.

[57] McDermott MF, Aksentijevich I, Galon J, McDermott EM, Ogunkolade BW, Centola M et al (1999). Germline mutations in the extracellular domains of the 55 kDa TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory syndromes. Cell 97:133–144.

[58] Hull KM, Drewe E, Aksentijevich I, Singh HK, Wong K et al., (2002). The TNF receptor-associated periodic syndrome (TRAPS): emerging concepts of an autoinflammatory disorder. Medicine 81:349–68.

[59] Hull KM, Wong K, Wood GM, Chu WS, Kastner DL (2002). Monocytic fasciitis: a newly recognized clinical feature of tumor necrosis factor receptor dysfunction. Arthritis Rheum 46:2189–94.

[60] McDermott EM, Smillie DM, Powell RJ (1997). Clinical spectrum of familial Hibernian fever: a 14-year follow-up study of the index case and extended family. Mayo Clin Proc 72:806–817.

[61] Hull KM, Drewe E, Aksentijevich I, Singh HK, Wong K, McDermott EM et al (2002). The TNF receptor-associate periodic syndrome (TRAPS) – emerging concepts of an autoinflammatory disorder. Medicine 81:349–368.

[62] Galon J, Aksentijevich I, McDermott MF, O'Shea JJ, Kastner DL (2000). TNF receptor-associated periodic syndromes (TRAPS): mutations in TNFR1 and early experience with Etanercept therapy. FASEB J 14:A1150.

[63] Aksentijevich I, Galon J, Soares M, Mansfield E, Hull K, Oh HH, Goldbach-Mansky R, Dean J, Athreya B, Regianato AJ, Henrickson M, Pons-Estel B, O'Shea JJ, Kastner DL (2001). The tumor necrosis factor receptor associated periodic syndrome: new mutations in TNFRSF1A, ancestral origins, genotypephenotype studies, and evidence for further heterogeneity of periodic fevers. Am J Hum Genet 69:301–314.

[64] Gottorno M, Pelagatti MA, Meini A, Obici L, Barcellona R, Federici S, Buoncompagni A, Plebani A, Merlini G, Martini A (2008). Persistent efficacy of anakinra in patients with tumor necrosis factor receptor associated periodic syndrome. Arthritis Rheum 58:1516–1520.

[65] Hoffman HM, Wanderer AA, Broide DH (2001). Familial cold autoinflammatory syndrome: phenotype and genotype of an autosomal dominant periodic fever. J Allergy Clin Immunol 108:615–620.

[66] Hawkins PN, Lachmann HJ, Aganna E, McDermott MF (2004). Spectrum of clinical features in Muckle-Wells syndrome and response to anakinra. Arthritis Rheum 50:607–612.

[67] Feldmann J, Prieur AM, Quartier P, Berquin P, Certain S, Cortis E, Teilac-Hamel D, Fischer A, de Saint BG (2002). Chronic infantile neurological cutaneous and articular syndrome is caused by mutations in CIAS1, a gene highly expressed in polymorphonuclear cells and chondrocytes. Am J Hum Genet 71:198– 203.

[68] van der Meer JWM, Vossen JM, Radl J, van Nieuwkoop JA, Meyer CJ, Lobatto S et al (1984). Hyperimmunoglobulinaemia D and periodic fever: a new syndrome. Lancet 1:1087–1090.

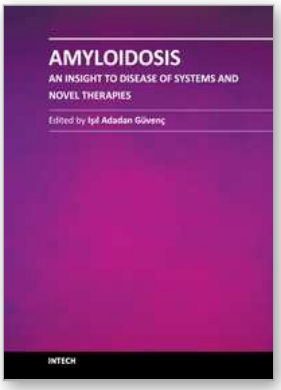
[69] Samuels J, Ozen S (2006). Familial Mediterranean fever and the other auto inflammatory syndromes: evaluation of the patient with recurrent fever. Curr Opin Rheumatol 18:108–117.

[70] Simon A, Bijzet J, Voorbij HA, Mantovani A, van der Meer JW, Drenth JP (2004). Effect of inflammatory attacks in the classical type hyper-IgD syndrome on immunoglobulin D, cholesterol and parameters of the acute phase response. J Intern Med 256:247–253.

[71] Bilginer Y, Akpolat T, Ozen S(2011).Renal amyloidosis in children.Pediatr Nephrol. Mar 1.

[72] Gottenberg JE, Merle-Vincent F, Bentaberry F, Allanore Y, Berenbaum F, Fautrel B, Combe B, Durbach A, Sibilia J, Dougados M, Mariette X (2003). Anti-tumor necrosis factor alpha therapy in fifteen patients with AA amyloidoses secondary to inflammatory arthritis. Arthritis Rheum 48:2019–20.

[73] Dember LM, Hawkins PN, Hazenberg BP, Gorevic PD, Merlini G, Butrimiene I, Livneh A, Lesnyak O, Puéchal X, Lachmann HJ, Obici L, Balshaw R, Garceau D, Hauck W, Skinner M (2007). Eprodisate for AA Amyloidosis Trial Group. Eprodisate for the treatment of renal disease in AA amyloidosis. N Engl J Med 356:2349–2360.



Amyloidosis - An Insight to Disease of Systems and Novel Therapies

Edited by Dr. Işıl Adadan Güvenç

ISBN 978-953-307-795-6
Hard cover, 194 pages
Publisher InTech
Published online 16, November, 2011
Published in print edition November, 2011

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.

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821