Chapter 13
Autoinflammatory Conditions in Adolescence and Young Adulthood

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Introduction

The rarity of AIC can lead to delayed recognition throughout adolescence and into adulthood [1, 2]. Some resolve in childhood but more require long-term care into adult life.

The Eurofever project [2] has recruited patients from 28 countries with an age range of 0–67 allowing assessment of long-term outcomes and responses to modern treatment. However, the range of diseases and overlaps in presentation make it difficult to apply specific labels at times. Table 13.1 highlights the number of genetic variants for four well-characterized phenotypes of AIC (with more being identified all the time). The age range at diagnosis means that AYA with AIC are an important group to consider.

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Table 13.1 Demographic characteristics of patients from Eurofever project [2]

Disease	Familial Mediterranean fever (FMF)	Mevalonate kinase deficiency (MKD)	TNF receptor-associated periodic fever syndrome (TRAPS)	Cryopyrin-associated periodic fever syndrome (CAPS)
No of patients	346	114	158	133
No of countries	28	12	18	16
No of variants	28	48	46	27
No of combinations	33	50		
Heterozygous	26	46		
Homozygous	7	4		
Age at onset (years median and range)	3 (0–67)	0.5 (0–11)	4.3 (0–63)	0.8 (0–45)

Presenting Features of AIC

Key features suggesting possible AIC are recurrent febrile episodes, sometimes with predictable timing, associated with stereotypical and repeated symptoms of multi-organ inflammation. These include skin rashes that can be urticarial or neutrophilic, periorbital or perioral swelling, inflammation of mucosal and serous membranes, or serositis. Myalgia and arthralgia with intermittent muscle, joint, and fascial inflammation may mimic other rheumatological conditions like dermatomyositis. Gastrointestinal symptoms including vomiting and mouth ulcers are common with hepatosplenomegaly with or without lymphadenopathy. The central nervous system, hearing, and eye features all vary in severity. Acute phase reactants are raised, and neutrophilia is common with episodes, such that infections are rightly considered and ruled out with significant flares.

Pathogenesis

Many AIC are caused by defined mutations affecting function of the innate immune system. Some are clear monogenic autoinflammatory disorders (see Table 13.2). Other disorders, now considered to be related to autoinflammatory conditions (e.g., systemic onset juvenile idiopathic arthritis, chronic multifocal osteomyelitis, Behcet's disease, and the crystal arthritides), appear to be more polygenic. In these cases the autoinflammatory label is based more on interleukin 1 (IL1) overproduction or responses to anti-IL1 receptor blockade rather than genetics.

There is disordered control of the inflammasome and of apoptotic processes because of the genetic abnormalities [1] and cells have an abnormal way of sensing danger. The inflammasome is the part of the cell where caspase-1 and production of pro-inflammatory cytokines like IL1beta are activated and prepared for defending against infection. In AIC this response is apparently triggered spontaneously and

Table 13.2 Summary of autoinflammatory conditions

Name	Inheritance and associated gene	Mutated protein	Clinical features and treatment	AYA specifics
FMF	AR *MEFV* (16p13.3)	Pyrin	Attacks last 1–3 days with recurrent fever, serositis (abdominal and chest pain), arthralgias or arthritides, and severe headaches; boys get testicular pain and swelling and erysipelas-like skin eruption on legs. Amyloidosis complicates untreated, resistant, and non-compliant patients Increased CRP and WCC during attacks Treatment with colchicine	Fever is often the only presenting symptom in children. The symptoms tend to accumulate and progress toward adult life in this most common autoinflammatory disorder

TRAPS	AD *TNFRSF1A* (12p13)	Tumor necrosis factor 1	Recurrent fever, migrating muscle and joint involvement, abdominal pain, serosal inflammation, headache, chest pain, red swollen eyes, lymphadenopathy, steroid responsiveness of febrile attacks, conjunctivitis, periorbital edema, and amyloidosis Increased CRP and WCC during attacks Febrile episodes last for weeks; symptoms can be continuous Treatment with steroids and anakinra (IL1 blockade)	Differences between pediatric and adult-onset attacks in TRAPS associated with the R92Q mutation [3]. Attacks last longer in adult patients (mean/median from 7 to 21 days) than in children (from 4 to 9 days). Clinically features are similar, but adults had more chest pain and headaches than children, while children had more abdominal pain and pharyngitis [2]

(continued)

Table 13.2 (continued)

Name	Inheritance and associated gene	Mutated protein	Clinical features and treatment	AYA specifics
MKD Hyper-IgD syndrome (HIDS)	AR *MVK* (12q24)	Mevalonate kinase	Recurrent fever, polymorphous rash, arthralgias, abdominal pain, vomiting and diarrhea, lymph node enlargement, headache, splenomegaly, oral and genital aphthosis, large joint arthritis, and high rate of self-resolution during adulthood. Increased CRP and WCC during attacks Attacks last 3–7 days Treatment with anakinra (IL1 blockade) or anti-TNF	Attacks may decrease in frequency and severity in young adult life in some patients, but remission is unlikely. Menstruation can precipitate attacks
DADA2	AR CECR1 (Cat Eye Syndrome Chromosome Region 1) gene	Adenosine deaminase 2	Early-onset vasculopathy livedoid skin rash, systemic manifestations with fever, CNS involvement and mild immunodeficiency, hemorrhagic and ischemic strokes Treatment possible anti-TNFs or stem cell transplant 3,4	

FCAS	AD *NLRP3/CIAS1*	Cryopyrin	Recurrent fever, cold-induced urticaria-like rash, conjunctivitis, and arthralgias Treatment with anakinra (IL1 blocker)
MWS	AD *NLRP3/CIAS (1q44)*		Recurrent fever, urticaria-like rash, conjunctivitis, arthralgias, sensorineural deafness, and amyloidosis Treatment with anakinra (IL1 blocker)
NOMID/ CINCA	AD/sporadic *NLRP3/CIAS1*		Sub-continuous fever, chronic urticaria-like rash, uveitis, papilledema, deforming arthritides involving large joints (patellar), aseptic chronic meningopathy, sensorineural deafness, and amyloidosis Treatment with anakinra (IL1 blocker)

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Table 13.2 (continued)

Name	Inheritance and associated gene	Mutated protein	Clinical features and treatment	AYA specifics
NLRP12	AD *NLRP12 (19q13.42)*	NLRP12 (monarch-1)	Recurrent fever after cold exposure, arthralgias, and cold-induced urticaria-like rash	
Schnitzler's syndrome	Unknown		Fever, urticarial rash, joint pain and swelling, swollen glands, increased plasma cells, and monoclonal gammopathy Treatment IL1 blockade (anakinra or canakinumab)	Rare onset in late adolescence, usually presents in middle age
Blau syndrome	AD *NOD2/ CARD15* (16q12)	NOD2	Intermittent fever, granulomatous dermatitis with ichthyosis-like changes, granulomatous polyarthritis, recurrent panuveitis, and onset before 5 years	Usually a diagnosis of young children, NOD2-associated autoinflammatory disease associated with *CARD15/ NOD2* polymorphisms and with phenotypic resemblance to BS has been reported in adults also

Early-onset sarcoidosis	Sporadic		
PAPA	*AD* *PSTPIP1* (15q24–q25.1)	CD2 antigen-binding protein 1	Pyoderma gangrenosum, cystic acne, and sterile pyogenic oligoarthritis after minor knocks or damage
MS	AR *LPIN2* (18p11.31)	Lipin	Recurrent multifocal osteomyelitis, dyserythropoietic anemia, and chronic dermatosis
DIRA	AR *IL1RN* (2q14)	Interleukin-1 Receptor antagonist	Neonatal onset-multifocal osteomyelitis, periostitis of ribs and long bones, joint swellings neonatal onset-pustular rash, and dramatic response to anakinra

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Table 13.2 (continued)

Name	Inheritance and associated gene	Mutated protein	Clinical features and treatment	AYA specifics
PFAPA	Unclear, likely polygenic	No defined abnormal protein	Periodicity with a fever element Symptoms usually start age 2–5 with attacks of fever lasting 3–6 days. Corticosteroids can abort attacks, colchicine can be helpful, and adenotonsillectomy can cure the syndrome in many patients	Attacks are often outgrown within a decade, but some may require transition of care
CNO	Unclear, likely polygenic	No defined abnormal protein	Wide range of severity – see Chap. 17	See Chap. 17

FMF familial Mediterranean fever, *TRAPS* tumor necrosis factor receptor-associated periodic syndrome, *FCAS* familial cold autoinflammatory syndrome, *MWS* Muckle-Wells syndrome, *NOMID* neonatal onset multisystem inflammatory disease, *MKD* mevalonate kinase deficiency syndrome, *NLRP12AD* NLRP12-associated autoinflammatory disorder, *DADA2* deficiency of adenosine deaminase 2, *BS* Blau syndrome, *EOS* early-onset sarcoidosis, *MS* Majeed syndrome, *PAPAs* pyogenic arthritis, pyoderma gangrenosum, acne, syndrome, *DIRA* deficiency of interleukin-1 receptor antagonist, *PFAPA* periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis, *CNO* Chronic non-bacterial osteomyelitis, *PFAPA* periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis, *AR* autosomal recessive, *AD* autosomal dominant

is exaggerated with vast overproduction of pro-inflammatory cytokines (especially IL1). In contrast to autoimmune diseases, there is no autoantibody production and no antigen-specific T lymphocyte response.

This leads to recurrent episodes of infection-like, inflammatory symptoms with raised inflammatory cytokines but without a specific infective or disease-driven trigger. Flares can occur with stress including psychological stress, menstruation, physical exercise, immunizations, minor trauma, surgery, or viral infections but more usually without any specific trigger.

AICs have variable genetic penetrance and may only be diagnosed in adult life [4, 5]. As relatively recently described conditions, still considered to be incredibly rare, they may not appear in adolescent or adult differential diagnoses lists. Any late diagnosis really does matter, however, as treatment is needed as early as possible to avoid complications such as life-threatening systemic secondary amyloidosis, reported in up to 25% of patients.

Labelling the genetically negative cases is difficult in practice. It is important for teams to have access to a diagnostic chart of classical features to aid the acquisition of clinical skill from the experience of diagnosing these conditions. The NOMID Alliance (www.autoinflammatory.org) have helpful information for young people and professionals alike for this aspect of care.

Types of Autoinflammatory Conditions

A summary summarizing current knowledge AIC is given in Table 13.2.

AYA-Specific Features of AIC

These rare conditions are usually diagnosed in childhood in specialist services, but late diagnoses still occur in AYAs due to lack of awareness. The implications of a late diagnosis in

young adult life are significant especially as, for example, NOMID/CINCA can cause developmental delay if untreated early in childhood [6, 7]. It is also potentially devastating to face the fact of a lifelong genetic disorder being diagnosed for the first time as an AYA. A crucial long-term outcome of AIC if untreated is amyloidosis, and therefore keeping AYA engaged with treatment for AIC is key (see Chap. 19). Specific AYA considerations for AIC are summarized in Table 13.2.

Principles of Treatment in AICs

Three treatment objectives are (i) controlling symptoms, (ii) improving quality of life, and (iii) preventing long-term complications. Colchicine is still the mainstay of treatment in FMF. But for most of the other conditions, IL1 blockade has proved to be effective where other treatments including treatment with steroids have failed to bring lasting control [4].

Transition and Practical Care Considerations

There are no specific publications prepared for transition in AIC, and principles for support of psychological well-being and coping strategies are therefore extrapolated from work on other genetic conditions that cause chronic health problems (see Chap. 21).

Treatment with very expensive biologic therapies such as canakinumab has led to national schemes, e.g., through the National Amyloidosis Centre in the UK. In this care pathway, there is the benefit of major expertise in rare conditions focused in one place but with the drawback of the need to travel for medical care.

There is always the need to balance short-term well-being with known long-term risks of untreated conditions in terms of potential neurological impairment in CAPS or the development of amyloidosis in later life. In young people the concept

of long-term preventive treatment versus screening for amyloidosis with treatment at a later date also needs to be discussed. There is the possibility of episodic flare aborting treatment for acute flares versus long-term regular treatment to maintain symptom control. The counselling for each of these aspects of care is now to be assisted by data from disease registries and their potential to answer the questions of long-term or lifelong treatment.

Psychological Well-Being and Coping Strategies

Having a rare disease that no one knows much about during adolescence can prove a real challenge for the AYA especially during transition [8]. However, this is also an opportunity for them to become real experts in their own condition and to take self-advocacy to a new level as in reality they can easily know more about the condition than many of the HCPs that they will encounter. It is empowering to have clear links to good sources of up-to-date information that the AYA could refer the HCP to and again the NOMID Alliance (www.autoinflammatory.org) can prove invaluable.

Key Management Points

1. Bouts of illness in TRAPS may last longer in older young people and adults.
2. Amyloidosis risk may be higher in childhood-onset patients, longer disease duration, and higher penetrance, e.g., in R92Q-related disease [3].
3. Canakinumab supply issues require centralized referral.
4. Neurological involvement in CAPS is frequent, and most patients have difficulties with school performance and consequences for adult life chances [6].

5. Care should be by combined inter-specialty teams that have a focused special interest in the conditions combining rheumatology and immunology.
6. Long-term outcome studies are vital including scoring for the autoinflammatory disease activity and damage indices (ADDI).

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