

# New insights on multigenic autoinflammatory diseases

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**Abstract:** Autoinflammatory diseases are disorders of the innate immune system, which can be either monogenic due to a specific genetic mutation or complex multigenic due to the involvement of multiple genes. The aim of this review is to explore and summarize the recent advances in pathogenesis, diagnosis, and management of genetically complex autoinflammatory diseases, such as Schnitzler's syndrome; adult-onset Still's disease; synovitis, acne, pustulosis, hyperostosis, osteitis syndrome/chronic recurrent multifocal osteomyelitis/chronic non-bacterial osteomyelitis; Adamantiades-Behçet's disease; Yao syndrome; and periodic fever with aphthous stomatitis, pharyngitis, and adenitis syndrome. The PubMed database was screened for relevant articles using free text words and specific search strings. The search was limited to English-language articles, reporting the results of studies in humans, published through March 2021. Evidence from literature suggest that these rare multigenic autoinflammatory diseases can present with different clinical features and the diagnosis of these diseases can be challenging due to a combination of nonspecific manifestations that can be seen in a variety of other conditions. Diagnostic delays and disease complications may occur due to low disease awareness and the lack of pathognomonic markers. The pathogeneses of these diseases are complex and in some cases precise pathogenesis is not clearly understood. Conventional treatments are commonly used for the management of these conditions, but biologics have shown promising results. Biologics targeting proinflammatory cytokines including IL-1, IL-6, TNF- $\alpha$ , IL-17A and IL-18 have been shown to ameliorate signs and symptoms of different multigenic autoinflammatory diseases.

**Keywords:** Adamantiades-Behçet's disease, adult-onset Still's disease, autoinflammatory diseases, cytokines, interleukins

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## Introduction

Autoinflammatory diseases are disorders of the innate immune system characterized by severe stimulation of inflammatory pathways without involvement of antigen-directed autoimmunity. Over the last 20 years, there have been notable developments in the field of autoinflammation and research in this area has led to increased understanding of disease mechanisms and management of these conditions.<sup>1</sup> Autoinflammatory diseases can be either monogenic or multigenic (polygenic). In monogenic autoinflammatory syndromes, a specific genetic mutation can be identified, primarily due to errors in the innate immune mechanism.<sup>2</sup> Multigenic autoinflammatory syndromes are not

associated with a single, identified genetic mutation and their genetic characterization is complex due to the involvement of multiple genes. Certain multigenic autoinflammatory syndromes may present more frequently in adults such as Schnitzler's syndrome and Yao syndrome while other syndromes such as periodic fever with aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome and chronic recurrent multifocal osteomyelitis (CRMO) may occur frequently in children or early adolescence. Although PFAPA syndrome frequently occurs in pediatric patients, some published literatures have reported suspected cases in adults.<sup>3–8</sup> However, it is important to note that monogenic autoinflammatory condition may

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either present in adulthood due to either *de novo* mutations or presence of mosaicism. Classic examples are cryopyrin-associated autoinflammatory syndromes and tumor necrosis factor receptor associated periodic syndrome.<sup>9,10</sup> In addition, the phenotype of certain monogenic ones such as hyperimmunoglobulin D syndrome may be skewed in a growing child to become milder albeit requiring treatment based on persistent clinical symptoms and warranting a high index of suspicion from adult rheumatologists.<sup>11</sup> There are a growing number of multigenic autoinflammatory conditions that include Schnitzler's syndrome; adult-onset Still's disease (AOSD); synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome/ CRMO/chronic non-bacterial osteomyelitis (CNO); Adamantiades-Behçet's disease; Yao syndrome (YAOS); and PFAPA syndrome.<sup>1,2,12,13</sup> Among these conditions, patients with AOSD and Schnitzler's syndrome share some common features like spiking fever and skin rash.<sup>12,14-16</sup> Diagnosis and treatment of multigenic autoinflammatory diseases remain challenging due to their rarity and diverse presentations.

This review focuses on recent advances in genetically complex autoinflammatory diseases, including new insights regarding their pathogenesis, clinical overview, diagnosis, and management.

## Methods

The articles included in this narrative review were identified through literature searches of English publications in the PubMed database using the MeSH terms or keywords: 'Schnitzler's syndrome', 'Still's disease', 'AOSD', 'SAPHO syndrome', 'CRMO', 'Adamantiades-Behçet's disease', 'YAO syndrome', 'PFAPA syndrome', and search strings: 'Schnitzler's syndrome and pathogenesis', 'Schnitzler's syndrome and biomarker', 'Schnitzler's syndrome and diagnosis', 'Schnitzler's syndrome and treatment', 'Schnitzler's syndrome and IL-1 inhibitors', 'Schnitzler's syndrome and canakinumab'. 'AOSD and pathogenesis', 'AOSD and biomarker', 'AOSD and diagnosis', 'AOSD and treatment', 'AOSD and IL-1 inhibitors', 'AOSD and canakinumab'. 'SAPHO syndrome and pathogenesis', 'SAPHO syndrome and biomarker', 'SAPHO syndrome and diagnosis', 'SAPHO syndrome and treatment', 'SAPHO syndrome and IL-1 inhibitors', 'SAPHO syndrome and canakinumab'. 'CRMO and pathogenesis', 'CRMO and biomarker', 'CRMO and diagnosis', 'CRMO and treatment', 'CRMO and IL-1

inhibitors', 'CRMO and canakinumab'. 'Adamantiades-Behçet's disease and pathogenesis', 'Adamantiades-Behçet's disease and biomarker', 'Adamantiades-Behçet's disease and diagnosis', 'Adamantiades-Behçet's disease and treatment', 'Adamantiades-Behçet's disease and IL-1 inhibitors', 'Adamantiades-Behçet's disease and canakinumab'. 'YAO syndrome and pathogenesis', 'YAO syndrome and biomarker', 'YAO syndrome and diagnosis', 'YAO syndrome and treatment', 'YAO syndrome and IL-1 inhibitors', 'YAO syndrome and canakinumab'. 'PFAPA syndrome and pathogenesis', 'PFAPA syndrome and biomarker', 'PFAPA syndrome and diagnosis', 'PFAPA syndrome and treatment', 'PFAPA syndrome and IL-1 inhibitors', 'PFAPA syndrome and canakinumab'. In all, 275 relevant articles were identified, reporting the results of studies in humans, published from inception to March 2021. The articles were scrutinized, and the references listed are relevant to the objective of this review.

## Schnitzler's syndrome

### Overview

Schnitzler's syndrome is a rare, acquired autoinflammatory disease, with chronic urticarial rash, lymphadenopathy, bone pain, fatigue, systemic inflammatory response along with monoclonal gammopathy as main features.<sup>17</sup> The exact prevalence of the disease is unknown but since 1972, fewer than 300 cases have been reported in the scientific literature.<sup>18-20</sup>

### Pathogenesis

The etiology of Schnitzler's syndrome is yet to be elucidated. Multiple features indicate that it is an acquired autoinflammatory disorder,<sup>21,22</sup> with elevated levels of proinflammatory cytokine IL-1, including IL-1 $\beta$ , playing a central role in the pathophysiology of the disease.<sup>23,24</sup> However, a possible link between autoinflammation and the monoclonal component (monoclonal IgM or IgG gammopathy) remains to be determined, because the level of monoclonal component is highly variable in Schnitzler's syndrome, which can be very low or very high at once.<sup>25,26</sup> Lipsker *et al.* performed immunoblotting on epidermal and dermal skin extracts, and immunoelectron microscopic studies on Lowicryl K4M-embedded skin sections in 3 patients with Schnitzler syndrome. Data showed that two patients had IgM deposits in the epidermis around the keratinocytes and below the

lamina densa region of the anchoring fibrils, which suggest that monoclonal gammopathy plays a part in the pathophysiology of the skin rash and urticarial lesions.<sup>27</sup> Previous reports have shown that the aberrant nod-like receptor protein-3 (*NLRP3*) inflammasome signaling and cytokine pathway dysregulation play a key role in the pathogenesis of the disease.<sup>25,28</sup> A study conducted in adult patients with Schnitzler's syndrome has shown elevated levels of a chemoattractant, C-C motif chemokine ligand 2 [CCL2], in patients with Schnitzler's syndrome, and there was a correlation between systemic CCL2 levels and the disease activity, suggesting the potential of CCL2 as a biomarker of disease activity and treatment response.<sup>29</sup> In a prospective study, *ex vivo* cytokine profiles of Peripheral Blood Mononuclear Cells (PBMCs) was evaluated in 36 adult patients with Schnitzler syndrome prior to treatment and after initiation of anti-IL-1 therapy. The spontaneous production of TNF $\alpha$ , IL-6, IL-1 $\beta$ , IL-1 $\alpha$ , and IL-1RA by PBMCs was higher in patients with Schnitzler syndrome when compared with controls. In addition, the elevated levels of IL-1 $\beta$ , IL-1 $\alpha$ , IL-6, and TNF $\alpha$  may represent an initial aspect of the cytokine signature in Schnitzler syndrome.<sup>30</sup> An additional finding on the T cell cytokine profile was decreased levels of Th1, Th2, and Th17, including reduced IL-10 levels.<sup>30</sup>

#### *Clinical manifestations and diagnosis*

The main clinical features of Schnitzler's syndrome include fever, musculoskeletal pain, lymphadenopathy, with chronic urticarial exanthema and immunoglobulin (Ig) monoclonal gammopathy (IgM or IgG) being the hallmarks of the disease.<sup>21,23</sup> Patients with Schnitzler's syndrome may develop lymphoproliferative disease<sup>21</sup> and, in rare cases, if the disease is not properly treated, amyloid A (AA) amyloidosis may occur.<sup>23</sup>

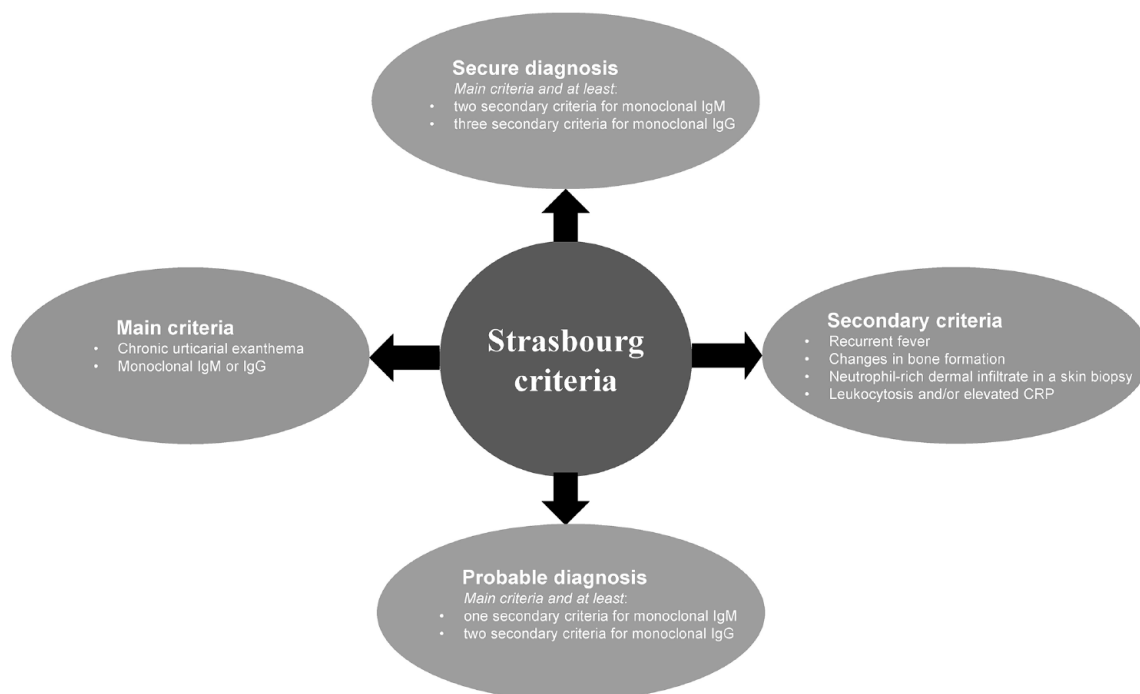
Schnitzler's syndrome is a diagnosis of exclusion due to its rarity, and it should be distinguished from other diseases which are more prevalent and have similar manifestations,<sup>31</sup> being chronic spontaneous urticaria the most crucial differential diagnosis.<sup>23</sup> The diagnosis of Schnitzler's syndrome is based on the Lipsker's criteria<sup>32</sup> or revised Lipsker's criteria known as the Strasbourg's criteria.<sup>18,23</sup> The Strasbourg criteria for diagnosis (81% sensitivity for a clear diagnosis) of Schnitzler's syndrome were defined at an international consensus meeting in 2012 and comprise two main and four secondary criteria (Figure 1).<sup>23</sup> These criteria

differentiate patients with definite and probable Schnitzler's syndrome. The skin biopsies of patients with Schnitzler's syndrome have shown increase in expression of cytokines including IL-1 $\beta$ , IL-6, IL-18, myeloperoxidase (a marker of neutrophil activation), and inflammasome components, such as apoptosis-associated speck-like protein containing CARD (ASC) and caspase-1.<sup>23,33</sup>

#### *Treatment*

Treatment with nonsteroidal antiinflammatory drugs (NSAIDs) and immunosuppressive drugs were less effective with inconsistent results.<sup>32</sup> IL-1 blockers have shown to be effective in the management Schnitzler's syndrome.<sup>34,35</sup> Data from a case report showed clinical improvement with the disappearance of fever, arthritis, and skin lesions in a patient with Schnitzler's syndrome after treatment with the IL-1 receptor antagonist anakinra.<sup>36</sup> Rilonacept is an IL-1 trap molecule which can block IL-1 $\alpha$  and IL-1 $\beta$  signaling. Data from a prospective study have shown that rilonacept was effective in patients with Schnitzler's syndrome with significant reductions in health assessment scores and physician's global assessment scores versus baseline levels.<sup>37</sup> In a retrospective study, out of 42 patients enrolled, 29 received anakinra and responded to the treatment. After a median follow-up of 36 months, the effectiveness of treatment remained unchanged.<sup>35</sup>

Canakinumab, a fully human monoclonal antibody against IL-1 $\beta$ , was shown to induce a rapid and sustained clinical response and was effective in treating patients with Schnitzler's syndrome. In a study, an adult patient with Schnitzler's syndrome received canakinumab treatment every 8 weeks for 6 consecutive months and the clinical response to treatment was fast with sustained remission<sup>38</sup> (Table 1). Krause and colleagues<sup>39</sup> reported the results of a Phase II, randomized controlled study, which evaluated the effects of canakinumab in 20 adult patients with Schnitzler's syndrome. Data showed that on Day 7, complete clinical response was significantly higher in patients who received canakinumab ( $n=7$ ) compared to patients who received placebo ( $n=13$ ) (71% vs 0%;  $p=.001$ ). The long-term extension study of 15 patients with Schnitzler's syndrome has shown that canakinumab could effectively reduce the clinical signs and symptoms of the disease, decrease the levels of inflammatory markers (CRP and SAA), and sustained the quality of life of the patients over 4 years.<sup>28</sup>



**Figure 1.** Strasbourg criteria for the diagnosis of Schnitzler's syndrome. CRP, C-reactive protein; Ig, immunoglobulin. Adapted from Gellrich and Günther.<sup>23</sup>

**Table 1.** Treatment options for the multigenic autoinflammatory diseases.

| Disease               | Conventional treatment/targeted therapy        | Design  | References  |
|-----------------------|--|---|---|
| Schnitzler's syndrome | Anakinra                                       | Case report   | Faggioli <i>et al.</i> <sup>36</sup> (n = 1)  |
|                       | Canakinumab                                    | RCT, case report                                      | Krause <i>et al.</i> <sup>39</sup> (n = 20); Vanderschueren and Knockaert <sup>38</sup> (n = 1)   |
|                       | Riloncept                                      | Prospective study                                     | Krause <i>et al.</i> <sup>37</sup> (n = 8)  |
| AOSD                  | NSAIDs   | Observational study                                   | Iliou <i>et al.</i> <sup>40</sup> (n = 30); Gerfaud-Valentin <i>et al.</i> <sup>41</sup> (n = 28)   |
|                       | DMARDs (methotrexate, cyclosporine)            | Observational study, retrospective study              | Iliou <i>et al.</i> <sup>40</sup> (n = 19); Gerfaud-Valentin <i>et al.</i> <sup>41</sup> (n = 33); Kalyoncu <i>et al.</i> <sup>42</sup> (n = 202); Franchini <i>et al.</i> <sup>43</sup> (n = 35); Fujii <i>et al.</i> <sup>44</sup> (n = 13)   |
|                       | Corticosteroids/ glucocorticoids/ (Prednisone) | Observational study, retrospective study, case report | Iliou <i>et al.</i> <sup>40</sup> (n = 39); Gerfaud-Valentin <i>et al.</i> <sup>41</sup> (n = 51); Kalyoncu <i>et al.</i> <sup>42</sup> (n = 199); Franchini <i>et al.</i> <sup>43</sup> (n = 45); Antoniou <i>et al.</i> <sup>45</sup> (n = 1) |
|                       | Anakinra <sup>#</sup>                          | Observational study, retrospective study              | Iliou <i>et al.</i> <sup>40</sup> (n = 10); Gerfaud-Valentin <i>et al.</i> <sup>41</sup> (n = 6); Franchini <i>et al.</i> <sup>43</sup> (n = 5)   |
|                       | Canakinumab <sup>**</sup>                      | RCT, case report                                      | Feist <i>et al.</i> <sup>46</sup> (n = 301); Kedor, Listing <i>et al.</i> <sup>47</sup> (n = 18); Cavalli <i>et al.</i> <sup>48</sup> (n = 4); Kontzias and Efthimiou <sup>49</sup> (n = 2)   |

(Continued)

**Table 1.** (Continued)

| Disease                           | Conventional treatment/<br>targeted therapy              | Design  | References   |
|-----------------------------------|--|---|--|
|                                   | Infliximab, etanercept,<br>adalimumab                    | Observational study;<br>retrospective study       | Gerfaud-Valentin <i>et al.</i> <sup>41</sup> (n = 17); Franchini<br><i>et al.</i> <sup>43</sup> (n = 2)  |
|                                   | Tocilizumab  | RCT, case series, case report                     | Kaneko <i>et al.</i> <sup>50</sup> (n = 27); Reihl Crnogaj <i>et al.</i> <sup>51</sup><br>(n = 8); Bannai <i>et al.</i> <sup>52</sup> (n = 7)  |
|                                   | Sarilumab  | Case report                                       | Simeni Njonjou <i>et al.</i> <sup>53</sup> (n = 1)   |
| SAPHO/CRMO/<br>CNO                | Infliximab, etanercept,<br>adalimumab                    | Case report                                       | Ben Abdelghani <i>et al.</i> <sup>54</sup> (n = 6); Deutschmann<br><i>et al.</i> <sup>55</sup> (n = 1)   |
|                                   | Tocilizumab  | Case report                                       | Sato <i>et al.</i> <sup>56</sup> (n = 2)   |
|                                   | Anakinra   | Case report                                       | Wendling <i>et al.</i> <sup>57</sup> (n = 6); Colina <i>et al.</i> <sup>58</sup> (n = 1);<br>Eleftheriou <i>et al.</i> <sup>59</sup> (n = 1)   |
|                                   | Canakinumab  | Case report                                       | Moussa <i>et al.</i> <sup>60</sup> (n = 3)   |
|                                   | Secukinumab  | Case report                                       | Sun <i>et al.</i> <sup>61</sup> (n = 1)  |
| Adamantiades-<br>Behçet's disease | NSAIDs, DMARDs,<br>glucocorticoids or<br>corticosteroids | RCT, retrospective study, case<br>report          | Yazici <i>et al.</i> <sup>62</sup> (n = 37); Simsek <i>et al.</i> <sup>63</sup> (n = 30);<br>Mat <i>et al.</i> <sup>64</sup> (n = 42); Emmi, Vitale <i>et al.</i> <sup>65</sup><br>(n = 35); Kashiwado <i>et al.</i> <sup>66</sup> (n = 1) |
|                                   | Infliximab, etanercept,<br>adalimumab                    | Prospective study, case report                    | Hibi <i>et al.</i> <sup>67</sup> (n = 18); Saulsbury <i>et al.</i> <sup>68</sup> (n = 1);<br>Watanabe <i>et al.</i> <sup>69</sup> (n = 1); Inoue <i>et al.</i> <sup>70</sup> (n = 20)  |
|                                   | Anakinra   | Case report                                       | Botsios <i>et al.</i> <sup>71</sup> (n = 1); Caso <i>et al.</i> <sup>72</sup> (n = 1);<br>Cantarini <i>et al.</i> <sup>73</sup> (n = 9)  |
|                                   | Canakinumab  | Case report                                       | Vitale <i>et al.</i> <sup>74</sup> (n = 3); Cantarini <i>et al.</i> <sup>75</sup> (n = 1)  |
|                                   | Rituximab  | Case report                                       | Sadreddini <i>et al.</i> <sup>76</sup> (n = 1)   |
|                                   | Ustekinumab  | Case report                                       | Baerveldt <i>et al.</i> <sup>77</sup> (n = 1)  |
|                                   | Alemtuzumab  | Retrospective study                               | Mohammad <i>et al.</i> <sup>78</sup> (n = 32)  |
| Yao syndrome                      | Glucocorticoid<br>(prednisone)                           | Retrospective study                               | Yao and Shen <sup>79</sup> (n = 19)  |
|                                   | Sulfasalazine  | Retrospective study                               | Yao and Shen <sup>79</sup> (n = 22)  |
|                                   | Tocilizumab  | Retrospective study                               | Yao and Shen <sup>79</sup> (n = 1)   |
|                                   | Canakinumab  | Retrospective study                               | Yao <sup>80</sup> (n = 7); Yao and Shen <sup>79</sup> (n = 2)  |
|                                   | Anakinra   | Retrospective study                               | Yao and Shen <sup>79</sup> (n = 2)   |
| PFAPA syndrome                    | Corticosteroids  | Case report, registry study,<br>prospective study | Więsik-Szewczyk <i>et al.</i> <sup>81</sup> (n = 1); Ter Haar<br><i>et al.</i> <sup>82</sup> (n = 81); Król <i>et al.</i> <sup>83</sup> (n = 77)   |
|                                   | Colchicine   | Case report, registry study,<br>RCT               | Więsik-Szewczyk <i>et al.</i> <sup>81</sup> (n = 1); Ter Haar<br><i>et al.</i> <sup>82</sup> (n = 3); Butbul Aviel <i>et al.</i> <sup>84</sup> (n = 8)   |
|                                   | Anakinra   | Prospective study, case report                    | Stojanov <i>et al.</i> <sup>85</sup> (n = 5); Cantarini <i>et al.</i> <sup>86</sup> (n = 1)  |
|                                   | Canakinumab  | Case report, case review                          | Lopalco <i>et al.</i> <sup>87</sup> (n = 1); Soylu <i>et al.</i> <sup>88</sup> (n = 1)   |

\*Approved by US FDA; #Approved by European Medicines Agency.

n, number of patients received the respective therapy.

Anakinra, canakinumab and riloncept are IL-1 inhibitors; infliximab, etanercept and adalimumab are anti-TNF- $\alpha$  agents; tocilizumab and sarilumab are IL-6 inhibitors; secukinumab is an IL-17A inhibitor; NSAIDs, DMARDs, corticosteroids and glucocorticoids are conventional treatment.

## Adult onset Still's disease

### Overview

AOSD is a rare, systemic autoinflammatory disorder characterized by a classic triad of high spiking fever, arthralgia/arthritis, skin rash, being commonly accompanied by hyperferritinemia, lymphadenopathy, and leukocytosis. The estimated incidence of AOSD is approximately 0.16 cases in 100,000 people in Western France,<sup>89,90</sup> the annual incidence of AOSD is approximately 0.4 per 100,000 people in Northern Norway<sup>91</sup> and the estimated prevalence of AOSD is 3.9 per 100,000 people in Japan.<sup>92</sup> A study in patients with AOSD in Turkey reported an annual incidence of 0.62 and overall prevalence of 6.77 per 100,000 population.<sup>93</sup> Globally, the estimated annual incidence of AOSD is between 0.16 and 0.62 (per 100,000 persons) and its approximate prevalence 1–24 per million.<sup>90,91,94,95</sup> Data from US nationwide inpatient sample (NIS) database have shown that 5,820 AOSD patients were hospitalized between 2009 and 2013.<sup>96</sup> AOSD is associated with significant morbidity-mortality and life-threatening manifestations, with a negative impact on the health-related quality of life of patients.<sup>96</sup> Macrophage activation syndrome is a severe, life-threatening complication of both sJIA and AOSD.<sup>97–100</sup>

### Pathogenesis

The pathogenesis of AOSD is complex and not clearly understood. Studies have shown that activation of the innate immune system and dysregulation of proinflammatory cytokines together mediate the pathogenesis of AOSD.<sup>101</sup> Increased levels of *NLRP3* inflammasome and its correlation with disease activity suggests the involvement of *NLRP3* in the pathogenesis of AOSD.<sup>102</sup> The activation of inflammasome *NLRP3* can lead to overproduction of cytokines IL-1 $\beta$  and IL-18.<sup>102–105</sup> These cytokines can trigger the dysregulation of downstream inflammatory cytokines, such as IL-6, IL-8, IL-17, and TNF- $\alpha$ , which are involved in the pathogenesis of AOSD.<sup>15,105–110</sup> Levels of the serological marker serum ferritin are often elevated in patients with AOSD, with ferritin elevations correlating with disease activity. Serum ferritin levels > 5 times the normal upper limit in fever of unknown origin suggest AOSD with a sensitivity of up to 80%, which can increase to 93% if combined with glycosylated ferritin of less than 20%.<sup>89</sup> In addition, there is increasing evidence of uncontrolled T-cell and macrophage

activation – inducing proinflammatory cytokines, such as IL-1, IL-6, IL-18, TNF- $\alpha$ , and interferon (IFN)- $\gamma$  overproduction – playing a crucial role in the pathogenesis of AOSD.<sup>15,51,106,111</sup>

A study has shown higher levels of serum IL-33 and its soluble ST2 receptor in patients with active AOSD.<sup>112</sup> With reduction of disease activity, there is a decrease in serum IL-33 levels. Therefore, the IL-33/ST2 signaling pathway might play a key role in the pathogenesis that causes inflammation and skin manifestations in AOSD.<sup>112</sup> Another study which evaluated SDF-1/CXCL12 and soluble CXCR4 (sCXCR4) levels and their clinical relevance observed higher levels of serum CXCL12 and serum sCXCR4 in patients with AOSD versus healthy volunteers. The results from this study showed that sCXCR4 is a potential clinical biomarker for AOSD and higher levels of CXCR4/CXCL12 may trigger the inflammatory conditions and skin manifestations associated with AOSD.<sup>113</sup> Higher levels of IL-18 have been identified in AOSD patients.<sup>97,111,114,115</sup>

### Clinical manifestations and diagnosis

Patients with AOSD usually present with high spiking quotidian fever, arthralgia and/or arthritis, a characteristic salmon-colored skin rash (usually concomitant with episodes of fever), lymphadenopathy, leukocytosis, and hyperferritinemia.<sup>12,14–16</sup> A study investigated 66 patients with AOSD over an 18-year period and most prominent symptoms observed in patients were high fever (91%), arthralgia (89%) and cutaneous rash (56%).<sup>116</sup> Joint involvement is common in patients with AOSD; arthritis, usually mild and localized at the beginning, can aggravate through the course of the disease, becoming more severe and polyarticular. The most commonly involved joints are the knees, wrists, ankles, elbows, and proximal interphalangeal joints. AOSD often spares the distal interphalangeal joints of the hand and shoulders. Narrowing of the intercarpal or carpometacarpal joint spaces has been observed in up to 75% of patients with chronic articular AOSD.<sup>43,116–121</sup> The characteristic rash in Still's disease is transient, nonpruritic, salmon-colored, with macular or maculopapular lesions, which are often observed during febrile episodes, predominantly in the late afternoon or evening. The typical rash appears mainly on the trunk and proximal extremities, in some occasions being misdiagnosed as an adverse reaction to medicines.<sup>116,122</sup> In rare cases, neurological and vascular manifestations are present,

and the diagnosis may become more challenging due to a less frequent clinical presentation.<sup>123</sup> A rapid and efficient, non-invasive diagnosis method is needed for a better<sup>43</sup> management of AOSD.<sup>124</sup>

The diagnosis of AOSD depends on the disease presentation upon exclusion of differential diagnoses including infection, malignancy, and other rheumatic inflammatory diseases.<sup>125</sup> Although AOSD has been regarded as being part of the same disease spectrum of systemic juvenile idiopathic arthritis (sJIA), the patterns of disease course, their clinical and laboratory features may differ between adults and children, possibly because children – with a more naïve immune system – may react differently on first exposure to antigens. The current ILAR classification criteria for sJIA are based on clinical and analytical manifestations in the first 6 months of illness and the presence of arthritis at presentation is mandatory. On the other hand, the Yamaguchi criteria for AOSD diagnosis, only require the presence of arthralgia for more than 2 weeks.<sup>126</sup> Comparison of clinical characteristics of AOSD and sJIA have shown significant female predominance among patients with AOSD ( $p < 0.05$ ). Significantly increased serum ferritin levels, hepatomegaly, and splenomegaly were observed more frequently with AOSD ( $p < 0.05$ ). Arthritis was more common among sJIA patients than among AOSD patients ( $p < 0.05$ ).<sup>97,127</sup> More AOSD patients versus sJIA patients presented with a sore throat (81% vs 46%;  $p = 0.03$ ).<sup>128</sup> AOSD patients had a significantly higher serum ferritin concentration than sJIA patients during the active disease phase ( $p < 0.01$ ).<sup>127,128</sup>

To identify AOSD patients, the Yamaguchi's criteria are widely used being a sensitive tool (sensitivity 96.2% and specificity 92.1%) for diagnosis and classification of AOSD<sup>129</sup> (Table 2), followed by Cush's criteria (sensitivity 80.6%)<sup>130–132</sup> and Fautrel's criteria (sensitivity 80.6% and specificity 98.5%) (Table 2).<sup>133–135</sup> Recently, Crispín's clinical scale (sensitivity 76.9% and specificity 98%) (Table 2) has also been adopted.<sup>89,135</sup>

### Treatment

NSAIDs, disease-modifying anti-rheumatic drugs (DMARDs), glucocorticoids or corticosteroids have been used as conventional treatments for AOSD.<sup>40–44,51,136</sup> Tocilizumab, an IL-6 inhibitor, has shown efficacy in the treatment of patients with refractory AOSD.<sup>50–52,137,138</sup> Data from a

multicenter retrospective study involving 27 patients  $\geq 16$  years of age with AOSD showed that the remission was achieved in all patients, except one, with either anakinra or tocilizumab treatment. Response to treatment mainly depended on disease phenotype, such as arthritis and a chronic articular phenotype was associated with response to tocilizumab therapy, whereas the systemic form and the absence of arthritis were associated with response to anakinra therapy. This study has shown the therapeutic implications of the phenotypic dichotomy of AOSD.<sup>94</sup> This suggests that AOSD treatment can be tailored, at least in some patients, based on the clinical presentation. There are limited data on the effectiveness of rilonacept in AOSD, but available reports have shown that rilonacept is effective in reducing the symptoms related to arthritis and other systemic symptoms, in patients with AOSD.<sup>15,139,140</sup>

Canakinumab has shown rapid and sustained improvement of both articular and systemic features in AOSD.<sup>49</sup> Canakinumab was approved by the US Food and Drug Administration and the European Medicines Agency for Still's disease, which is supported by the concept of a disease continuum that includes both SJIA and AOSD.<sup>141</sup> Feist *et al.*<sup>46</sup> have shown that treatment with canakinumab in a subgroup of patients with sJIA  $\geq 16$  years of age, who are representative of AOSD patients, led to an improvement in the systemic and arthritic components of the disease in older adolescents and young adults. The available data indicate that canakinumab is effective and well tolerated for treating AOSD.<sup>45,47–49,110,142,143</sup> A study has shown that treatment of adult patients with AOSD and active joint involvement with canakinumab led to a clinically significant improvement of outcome measures including DAS28-ESR, DAS28-CRP, ACR30, ACR50 and ACR70 and remission, compared with placebo. It was difficult to complete the recruitment of this trial due to the rarity and severity of the disease as well as the conditional approval of canakinumab for AOSD by the EMA; therefore, the study was terminated prematurely.<sup>47</sup> A retrospective real-life study in a cohort of 50 adult patients with refractory Still's disease have shown high rates of sustained remission in patients treated with canakinumab. A complete response was observed in 78% of patients. Of 50 patients, 37 had a follow-up longer than 1 year and 27 more than 2 years and canakinumab had a long-term efficacy in the majority of patients with a significant steroid sparing effect.<sup>144</sup>

**Table 2.** Criteria for diagnosis of AOSD.

| <b>(A) Yamaguchi criteria*</b>   |  |                           |
|--|--|---------------------------|
| <b>Major criteria</b>  | <b>Minor criteria</b>  | <b>Exclusion criteria</b> |
| Arthralgia or arthritis ( $\geq 2$ weeks)  | Lymphadenopathy  | Infection                 |
| Fever $> 39^{\circ}\text{C}$ ( $\geq 1$ week)  | Sore throat  | Rheumatic diseases        |
| Typical rash (“salmon-pink”)   | Hepatomegaly or splenomegaly   | Malignant diseases        |
| Leucocytosis $> 10,000/\text{mm}^3$ ( $> 80\%$ PMN cells)  | Elevated AST, ALT, and LDH<br>Negative RF (IgM) and ANA                                |                           |
| <b>(B) Fautrel’s criteria**</b>  |  |                           |
| <b>Major criteria</b>  | <b>Minor criteria</b>  | -                         |
| Arthralgia   | Maculopapular rash   |                           |
| Spiking fever $\geq 39^{\circ}\text{C}$  | Leucocytosis $\geq 10,000/\text{mm}^3$   |                           |
| Transient erythema   |  |                           |
| Pharyngitis  |  |                           |
| PMN cells $\geq 80\%$  |  |                           |
| Glycosylated ferritin $\leq 20\%$  |  |                           |
| <b>(C) Crispin’s clinical scale for diagnosis#</b>   |  |                           |
| <b>Findings</b>  | <b>Description</b>   | <b>Score</b>              |
| Arthritis  | Presence of synovitis  | 10                        |
| Pharyngitis  | Present during the onset of the disease  | 7                         |
| Still rash   | Macular or maculopapular, pink-salmon, non-pruriginous rash that accompanies the fever | 5                         |
| Splenomegaly   | Detected clinically or by imaging technique ( $> 11$ cm)                               | 5                         |
| Neutrophilia   | PMN cells $\geq 9.500/\text{mm}^3$   | 18                        |
| Total  |  | 45                        |
| *Five or more criteria are required, with two or more being major criteria for diagnosis of AOSD.  |  |                           |
| **Four or more major criteria are required, or three major and two minor criteria.   |  |                           |
| #At least 30 points in patients with fever of unknown origin allows for the diagnosis of AOSD without further studies (specificity ~98%).                            |  |                           |
| ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; PMN, polymorphonuclear; RF, rheumatoid factor |  |                           |
| [Source: Seco <i>et al.</i> <sup>89</sup> ].   |  |                           |

## SAPHO/CRMsO/CNO

### Overview

SAPHO syndrome is a rare disease with chronic osteoarticular and dermatological disorders.<sup>145,146</sup> SAPHO generally occurs in adults.<sup>146</sup> SAPHO

affects the skeletal system including the anterior chest wall, long bones and spine, and may involve polyostotic lesions, as seen in bone scintigraphy the characteristic “bull’s head”, which is a sign of increase tracer uptake in the regions of sternocostoclavicular and manubriosternal joints.<sup>146,147</sup> The



annual prevalence of SAPHO syndrome varies from 0.00144 in 100,000 people in Japan to less than 1 in 10,000 in the White population.<sup>148–150</sup> In another report, the annual prevalence of SAPHO is estimated to be less than 1/10,000.<sup>151,152</sup> In a cross-sectional study on a cohort of SAPHO patients, prevalence of fibromyalgia in SAPHO syndrome was approximately 18%.<sup>151</sup>

CNO/CRMO are rare diseases with disorders of chronic osteoarticular inflammation and skin manifestations.<sup>146</sup> CRMO/CNO predominantly affects children.<sup>146,153</sup> CRMO/CNO affect the skeletal system including the anterior chest wall, long bones and spine, and may involve polyostotic lesions.<sup>146</sup> The estimated prevalence of CRMO/CNO is 1–2 per million population, mostly affecting children.<sup>154</sup> Incidence rate of CNO was estimated at 0.4 per 100,000 children/year in Germany.<sup>155,156</sup> A chart review from a retrospective single-center analysis reported incidences of CNO increased from approximately 2.5 cases per year (1998–2007) to 4.7 CNO cases per year, which suggest that the suspected lower incidence rate of CNO may be an underestimation.<sup>155</sup>

### Pathogenesis

The precise pathogenesis of SAPHO syndrome remains unclear. However, it is believed to be related to genetic factors, infections, and immune dysregulation.<sup>157</sup> As in Schnitzler's syndrome and AOSD, overproduction of IL-1 $\beta$  was also reported in SAPHO syndrome.<sup>158</sup> Studies have shown dysregulation of cytokines, including IL-1 $\beta$ , IL-8, IL-17, IL-18, and TNF- $\alpha$ , to be potentially involved in the pathogenesis of SAPHO.<sup>159,160</sup> A study that measured the expression of receptor activator nuclear factor  $\kappa$ -B ligand (RANKL)/osteoprotegerin (OPG) in patients with SAPHO syndrome reported higher levels of RANKL in patients with active disease.<sup>150,161</sup> Another study, comparing patients with SAPHO with healthy controls, found that the proportion of natural killer (NK) cells was significantly lower in SAPHO patients and the ratio of T-helper cell 17 (Th17) and regulatory T-cells (Treg) was higher. A depletion of NK cells and an imbalance of Th17 and Treg cells in SAPHO patients could be related to immune inflammation-mediated pathogenesis.<sup>162</sup>

JAK/STAT signaling pathway may play a role in the pathogenesis of SAPHO syndrome. A retrospective review of data from a cohort of SAPHO patients has shown benefits with the use of

tofacitinib, a Janus kinase (JAK) 1/3 inhibitor. A decrease in systemic inflammation, reduction in pain and rash, improvement in quality of life and remission on MRI was observed with tofacitinib treatment.<sup>163</sup> Although tofacitinib is not approved for use for SAPHO, these findings provide evidence that tofacitinib could be a potential therapeutic option for the treatment of SAPHO syndrome.<sup>163,164</sup>

Studies have shown that activation and expression of inflammasome components, such as apoptosis-associated speck-like protein (ASC), *NLRP3*, and caspase-1, are elevated in CRMO/CNO patients, which may contribute to pathogenesis of the disease.<sup>154,165,166</sup>

### Clinical manifestations and diagnosis

Patients with SAPHO syndrome present with sterile joint inflammation (*synovitis*), skin manifestations, such as severe *acne* and palmoplantar *pustulosis*, *hyperostosis* and non-infectious *osteitis*.<sup>146,167,168</sup> In CRMO/CNO, symptoms are heterogeneous, such as swelling of the affected area, severe bone pain, fever, malaise, and weight loss. The symptoms related to bone inflammation and pain can often get worse at night. In patients with CRMO/CNO, sporadic inflammatory bone pain occurs as recurrent flares due to osteomyelitis, which presents as multiple aseptic foci.<sup>154</sup>

Diagnosis of SAPHO/CRMO/CNO is based on clinical and radiological findings.<sup>146</sup> The diagnosis of CRMO/CNO is mainly achieved by exclusion of differential diagnoses, such as bacterial osteomyelitis and malignancy.<sup>154,169,170</sup>

For diagnosis of patients with CNO, clinical score from Jansson *et al.*,<sup>171</sup> blood test, bone biopsy, microbiological investigations, radiological findings on MRI are generally used.<sup>155</sup> The Jansson score includes white blood cell counts, symmetric bone lesions, marginal sclerosis, normal body temperature, vertebral, clavicular, or sternal lesions, greater than two lesions in radiological imaging, and CRP  $\geq 10$  mg/l. Scores of 39 or higher indicate CNO.<sup>155</sup> The clinical presentation of CNO range from self-limited unifocal to chronic recurrent multifocal bone inflammation.<sup>155,165,172,173</sup>

In most SAPHO/CRMO/CNO patients, polyostotic involvement is observed. Bone scintigraphy has shown a characteristic 'bull's head' sign in the sternocostoclavicular and manubriosternal joints,

**Table 3.** Diagnostic criteria for SAPHO syndrome.

| Benhamou and colleagues   | Kahn and Khan   | Kahn  |
|---|---|---|
| At least 1 of the following 4 conditions:<br>(1) Osteoarticular manifestation of PPP              | At least 1 of the following 3 conditions:<br>(1) Acute, subacute, or chronic arthritis associated with PPP, pustular psoriasis, or SA | At least 1 of the following 5 conditions:<br>(1) Bone–joint involvement associated with SA  |
| (2) Osteoarticular manifestations of acne conglobate, acne fulminans, or hidradenitis suppurativa | (2) Chronic recurrent multifocal sterile and axial osteomyelitis, with or without dermatosis  | (2) Bone–joint involvement associated with PPP and psoriasis vulgaris   |
| (3) Hyperostosis (of the ACW, limbs or spine) with or without dermatosis                          | (3) Any sterile osteitis associated with PPP, pustular psoriasis, or SA   | (3) Isolated sterile hyperostosis/osteitis  |
| (4) CRMO involving the axial or peripheral skeleton with or without dermatosis                    |   | (4) CRMO (children)   |
|   |   | (5) Bone–joint involvement associated with chronic bowel diseases<br>Exclusion: Infectious osteitis, tumoral conditions of bone, non-inflammatory condensing lesions of bone. |

ACW, anterior chest wall; CRMO, chronic recurrent multifocal osteomyelitis; PPP, palmoplantar pustulosis; SA, severe acne; SAPHO, synovitis, acne, pustulosis, hyperostosis, and osteitis.  
[Source: Liu *et al.*<sup>150</sup>].

which is considered as a characteristic of SAPHO syndrome.<sup>146,174,175</sup> The most widely applied diagnostic criteria for SAPHO syndrome were developed by Benhamou and colleagues<sup>176–178</sup> (Table 3).

### Treatment

Conventional treatments for SAPHO include NSAIDs, DMARDs, glucocorticoids or corticosteroids, bisphosphonates and antibiotics.<sup>157,167,179</sup> NSAIDs, DMARDs, glucocorticoids or corticosteroid, bisphosphonates and antibiotics have also been used as conventional treatments for CRMO/CNO.<sup>180–182</sup> Pamidronate, a bisphosphonate, has shown efficacy on osteoarticular manifestations of SAPHO, but did not improve cutaneous lesions.<sup>157,183</sup> Gil *et al.*<sup>184</sup> described a case in which an adult patient with SAPHO syndrome who developed palmoplantar pustulosis and sternoclavicular osteitis received treatment with bisphosphonate, systemic corticosteroid, and cyclosporine which resulted in complete resolution of the articular and dermatologic manifestations without any side effects. Bisphosphonate has shown a favorable treatment response in pediatric SAPHO syndrome.<sup>185</sup> In an observational study, clinical data of 24 adult patients with SAPHO syndrome were analyzed. Out of 17 patients who received the combination treatments of NSAIDs and

DMARDs, 15 experienced an improvement in their symptoms. In total, 18 patients with SAPHO syndrome received bisphosphonates, and 4 patients received TNF blockers. Among the patients who received TNF blockers, adalimumab was ineffective in one patient; however, the disease activity was controlled in that patient by add-on treatment with DMARDs. Patients with SAPHO syndrome responded to NSAIDs, DMARDs, and bisphosphonates combination therapy. TNF blockers were shown to be effective in patient with SAPHO syndrome refractory to NSAIDs and DMARDs.<sup>186</sup> The CNO/CRMO subgroup of the Childhood Arthritis and Rheumatology Research Alliance (CARRA) held meetings to develop standardized treatment regimens for CNO/CRMO and enable comparative effectiveness treatment strategies, which resulted in 3 consensus treatment plans for pediatric patients with CNO/CRMO refractory to NSAIDs. The 3 consensus treatment plans are sulfasalazine or methotrexate, TNF inhibitors with optional methotrexate, and bisphosphonates.<sup>187</sup>

TNF- $\alpha$  antagonists have shown a favorable treatment response in pediatric SAPHO syndrome.<sup>185</sup> TNF inhibitors, such as etanercept, adalimumab, infliximab are generally used in SAPHO syndrome after methotrexate failure.<sup>54</sup> Anti-TNF- $\alpha$  agents

have shown promising results in SAPHO syndrome<sup>167,179,185,188</sup> and in CRMO/CNO.<sup>55,172,182,189</sup> In a case study, tocilizumab was shown to be effective in controlling symptoms and inflammatory markers in adult patients with CRMO/CNO.<sup>56</sup>

IL-inhibitors also seem to be effective in the treatment of patients with SAPHO and CRMO/CNO. As per available data related to IL-1 inhibition, most patients with SAPHO show a significant improvement in musculoskeletal manifestations.<sup>188</sup> IL-1 inhibition with anakinra has shown efficacy in the treatment of SAPHO syndrome. In a case study, anakinra treatment in a patient with SAPHO syndrome resulted in resolution of systemic and osteoarticular symptoms.<sup>58,159</sup> In a study, treatment with canakinumab was associated with variable outcomes in patients with CRMO/CNO.<sup>60</sup> Secukinumab, an IL-17A inhibitor, successfully treated refractory mandibular lesions in an adult patient with SAPHO syndrome.<sup>61</sup>

## Adamantiades-Behçet's disease

### Overview

Adamantiades-Behçet's disease is a multisystem, autoinflammatory disease of unknown etiology characterized by recurrent painful mucocutaneous ulcerations, and idiopathic systemic vasculitis that affects both large and small blood vessels. It can also present with arthralgia/arthritis, other skin lesions, uveitis and neurological manifestations.<sup>190-198</sup> The incidence of Adamantiades-Behçet's disease varies according to geographic location, with the highest prevalence of 20-420 (per 100,000 people) in Turkey, followed by 80 in Iran, 20 in Saudi Arabia, and 17 in Iraq.<sup>199</sup> In the United Kingdom, the prevalence of Adamantiades-Behçet's disease is 0.64 cases per 100,000 population.<sup>199,200</sup> A study in United States reported an overall incidence of 0.38 per 100,000 population and prevalence rate of 5.2 per 100,000 population.<sup>201</sup>

### Pathogenesis

The pathogenesis of Adamantiades-Behçet's disease is still unclear. IL-1 seems to play a crucial role in the pathogenesis of Adamantiades-Behçet's disease, as IL-1 levels were shown to be significantly higher in patients with Adamantiades-Behçet's disease versus healthy controls.<sup>202-204</sup> Elevated levels of serum IL-6 were also seen in patients with active Adamantiades-Behçet's disease, which may correlate with disease activity.<sup>205-207</sup>

Functional abnormalities of Toll-like receptors in monocytes have been noted in patients with Adamantiades-Behçet's disease, and may be correlated with disease activity. One of the most consistent findings in the pathogenesis of Adamantiades-Behçet's disease is hyperactive state of neutrophils. The antigen presenting cells (macrophages) stimulate immune cells by Toll-like receptors activation and the innate and adaptive immune pathways together with neutrophil activation play a crucial role in the pathogenesis of Adamantiades-Behçet's disease.<sup>195,208</sup>

Histocompatibility leucocyte antigen (HLA)-B51, a class I MHC antigen, represents the strongest genetic risk factor associated with Adamantiades-Behçet's disease. Other HLA-independent loci, such as IL23R/IL12RB2 and IL10 (allele rs1518111 A) have also been associated with Adamantiades-Behçet's disease.<sup>195,209</sup> Data from a gene expression study, which identified genes that might be related to pathogenesis of Adamantiades-Behçet's disease, have shown that 1103 genes and 652 genes were differentially expressed in the CD8<sup>+</sup> CD27<sup>-</sup> CD28<sup>-</sup> and CD8<sup>+</sup> CD27<sup>+</sup> CD28<sup>+</sup> T-cell subsets, respectively, of patients with Adamantiades-Behçet's disease.<sup>210</sup> A case-control study found that the gene expression of TNF- $\alpha$  increased in patients with Adamantiades-Behçet's disease, suggesting that TNF- $\alpha$  has a role in the pathogenesis of the Adamantiades-Behçet's disease.<sup>211</sup>

### Clinical manifestations and diagnosis

The notable clinical manifestations in patients with Adamantiades-Behçet's disease are recurrent oral and genital ulcerations, and ocular inflammation. Articular, neurological, and gastrointestinal involvement are also reported.<sup>190-193</sup> Cardiopulmonary signs and symptoms may be the first manifestation.<sup>197</sup> The diagnosis of Adamantiades-Behçet's disease is challenging, because it is mainly based on clinical manifestations, which are frequent manifestations (oral aphthosis, genital aphthosis, pseudofolliculitis, erythema nodosum) also seen in other diseases.<sup>199</sup> The International Criteria for Behçet Disease (ICBD) was developed in collaboration with the experts from 27 countries to address the diagnostic dilemma of Adamantiades-Behçet's disease. ICBD is a point score system, a scoring  $\geq 4$  is classified as Adamantiades-Behçet's disease. As per ICBD, ocular lesions, genital aphthosis and oral aphthosis are assigned 2 points each, while skin lesions, vascular manifestations and neurological

**Table 4.** International criteria for Adamantiades-Behçet's disease.<sup>212</sup>

| Sign and symptom            | Points |
|-----------------------------|--------|
| Oral aphthosis              | 2      |
| Genital aphthosis           | 2      |
| Ocular lesions              | 2      |
| Skin lesions                | 1      |
| Vascular manifestations     | 1      |
| Positive pathergy test**    | 1      |
| Neurological manifestations | 1      |

\*International criteria for Adamantiades-Behçet's disease is based on point score system. Scoring  $\geq 4$  indicates Adamantiades-Behçet's diagnosis.  
 \*\*Pathergy test is an optional criterion. The primary scoring system does not include pathergy testing. Where pathergy testing is conducted 1 extra point can be added for a positive result.  
 Adapted from Davatchi et al. JADV 2014;28:338–347.

manifestations are assigned 1 point each. If pathergy test is done, an additional 1 point is assigned.<sup>212</sup> The diagnostic criteria for Adamantiades-Behçet's disease are presented in Table 4.<sup>212</sup>

#### Treatment

NSAIDs, DMARDs, glucocorticoids or corticosteroids have been used as conventional treatments for Adamantiades-Behçet's disease.<sup>62–66,213</sup> Higher doses of corticosteroids are effective for treatment of acute exacerbations of Adamantiades-Behçet's disease with vascular involvement, NBD and refractory or severe gastrointestinal involvement.<sup>198,214</sup> The treatment goal is to prevent irreversible organ damage by suppressing inflammatory exacerbations.<sup>198</sup> A combination of immunosuppressants, such as azathioprine, cyclosporine-A or cyclophosphamide is recommended for the management of acute deep vein thrombosis in Adamantiades-Behçet's disease.<sup>198,214</sup> Oral and genital ulcers should be treated with topical steroids. Apremilast, an oral phosphodiesterase 4 inhibitor, is effective for oral ulcer, which is the most common symptom of Adamantiades-Behçet's disease.<sup>215</sup> Apremilast has been approved for treatment of recurrent oral ulcers in patients with Adamantiades-Behçet's disease in Japan after successful clinical trials.<sup>216,217</sup> Studies have shown

that colchicine was effective in preventing acute arthritis, recurrent mucocutaneous lesions and arthritis episodes of Adamantiades-Behçet's disease. In a 2-year randomized, controlled study, 116 adult patients with Adamantiades-Behçet's disease with active mucocutaneous disease without eye or major organ involvement, received either colchicine or placebo. Data showed that compared to placebo group, complete response (sustained absence of any lesions) to treatment was significantly higher in colchicine group, which showed reduced occurrence of genital ulcers ( $p=0.004$ ), erythema nodosum ( $p=0.004$ ), and arthritis ( $p=0.033$ ) in women, and reduced occurrence of arthritis ( $p=0.012$ ) in men. Colchicine was effective for treating the arthritis and some of the mucocutaneous manifestations of Adamantiades-Behçet's disease.<sup>198,214,218,219</sup>

Emerging evidence supports the use of biologics in patients with refractory, severe Adamantiades-Behçet's disease, and especially for those with ocular,<sup>220,221</sup> central nervous system,<sup>221</sup> and gastrointestinal<sup>70,221,222</sup> involvements, anti-TNF- $\alpha$  therapy has been shown to have benefits.<sup>68,69,198</sup> Infliximab and adalimumab can be useful in managing patients with intestinal Adamantiades-Behçet's disease, especially in severe or refractory cases.<sup>223</sup> In a case study, tocilizumab has been

shown to be effective in the treatment of intestinal Adamantiades-Behçet's disease.<sup>224</sup>

Anakinra and canakinumab have shown some benefit in Adamantiades-Behçet's disease including in patients with mucocutaneous manifestations and in intestinal Adamantiades-Behçet's disease.<sup>71,74,214,223,225–228</sup> Data from studies have shown that IL-1 inhibitors could effectively control mucocutaneous and ocular manifestations in patients with Adamantiades-Behçet's disease.<sup>229–231</sup> In a retrospective study, 36 patients with Adamantiades-Behçet's disease treated with anakinra or canakinumab were enrolled and divided into two groups. Patients showing a treatment duration of at least 52 weeks and no secondary inefficacy during the first follow-up year were included in group 1 and patients showing primary or secondary inefficacy within the first 52 weeks of treatment were included in group 2. Anakinra was administered in 13/18 patients and canakinumab in 5/18 patients, in both the groups. Data from this study showed that within the 3-month follow-up, clinical response (complete resolution of all active Adamantiades-Behçet's disease-related clinical manifestations) was obtained in 100% (18/18) of patients in group 1 and 38.9% (7/18) of patients in group 2 ( $p < 0.0001$ ), which demonstrated that anakinra and canakinumab were effective in Adamantiades-Behçet's disease.<sup>232</sup> In another retrospective study, 19 patients with Adamantiades-Behçet's disease-uveitis received treatment with IL-1 inhibitors (anakinra [ $n = 13$ ] and canakinumab [ $n = 6$ ] and followed-up for 12 months. The number of patients presenting with ocular flares (ocular inflammatory manifestations that occurred after a period of remission) and the number of reported ocular flares decreased during the 12-month follow-up period. Anakinra and canakinumab were shown to be effective in managing Adamantiades-Behçet's disease-related uveitis with a significant reduction of ocular inflammatory flares.<sup>233</sup>

Rituximab, alemtuzumab, and ustekinumab have been evaluated in a number of studies and were shown to be effective in Adamantiades-Behçet's disease. Sadreddini *et al.* reported one case in which a patient with Adamantiades-Behçet's disease with visual loss due to retinal vasculitis was resistant to prednisolone and azathioprine treatment, was successfully treated with rituximab and disease remission was sustained for 24 months. In another study, 32 patients with Adamantiades-Behçet's disease received alemtuzumab and 84% patients achieved partial or complete remission

after receiving the first course of alemtuzumab. Relapse-free survival rates was observed in 83.6% patients at 6 months. Another case study reported an improvement in PASI 50 and PASI 75 scores in patients with Adamantiades-Behçet's disease treated with ustekinumab.<sup>76–78,234–237</sup> In an open-label prospective study, 30 patients with Adamantiades-Behçet's disease, who were diagnosed with active oral ulcers resistant to colchicine, received ustekinumab. Compared with baseline, the median number of oral ulcers per patient was significantly lower ( $p < 0.0001$ ) at Week 12 with ustekinumab treatment. Complete response was achieved in 60.0% of patients at Week 12 and 88.9% of patients at Week 24. Ustekinumab was effective in treating Adamantiades-Behçet's disease related oral ulcers that are resistant to colchicine treatment.<sup>238</sup>

## Yao syndrome

### Overview

YAOS, formerly called nucleotide-binding oligomerization domain 2 (NOD2)-associated auto-inflammatory disease, is characterized by fever, polyarthritis, dermatitis, distal extremity swelling, gastrointestinal and sicca-like symptoms associated with specific variants of NOD2 sequence. YAOS is predominantly observed in white adults at an estimated disease prevalence of 1–10 per 100,000 population.<sup>239</sup> It might be the most common form of sporadic autoinflammatory disease occurring in adults.<sup>22,239,240</sup>

### Pathogenesis

The molecular mechanisms and underlying pathogenesis of YAOS are unclear, but there is a genetic association with certain NOD2 variants.<sup>239,241</sup> A study that examined NOD2 expression and activation of signaling pathway reported that NOD2 transcript level and basal p38 mitogen-activated protein kinase activity was elevated in peripheral blood mononuclear cells from IVS8 + 158 YAOS patients. Also, the cells of the patients had high basal IL-6 levels which were increased by muramyl dipeptide stimulation, indicating that NOD2 expression and pathway activation are aberrant in YAOS.<sup>242</sup> In a case series,<sup>241</sup> genetic testing in three YAOS patients detected presence of the following heterozygous NOD2 variants:

- Q902 K/rs201035873 (c.2704 C > A) in exon 7

- R541 P/rs753857915 (c.1622G > C) in exon 4
- Y514 H/rs540122692 (c.1540 T > C) in exon 4

A recent study<sup>243</sup> reported that the following NOD2 variants are linked to YAOS:

- c.2555A > G (p. Asn852Ser) in exon 6
- c.2264 C > T (p. Ala755Val) in exon 4
- c.2774A > G (p. asp925gly) in exon 8
- c.160G > A (p. Glu54Lys) in exon 2
- c.140 C > T (p.S47L) in exon 2

IL-1 antagonist can improve the overall symptoms and physical function in patients, which suggest a potential role of IL-1 in the pathogenesis of YAOS.<sup>79</sup>

#### *Clinical manifestations and diagnosis*

As in AOSD, recurrent fever may occur in patients with YAOS, with febrile episodes lasting from days to several weeks. Erythematous patches or plaques can be seen in patients with YAOS, and recurrent mild to moderate abdominal pain, bloating, cramping, and diarrhea may also be present.<sup>80,240,241</sup> YAOS is a systemic inflammatory disease which can lead to chronic pain syndrome and disability, but it rarely affects the solid internal organs.<sup>79</sup>

The diagnosis of YAOS is mainly dependent on the phenotype and genotype characteristic of the disease.<sup>22,79,244</sup> The criteria for diagnosis of YAOS are summarized in Table 5.<sup>79,240</sup> Endoscopic, radiological, or histologic examinations have shown no evidence of inflammatory bowel disease. There may be an occasional non-specific focal colitis away from the ileum. Arthritis can occur periodically in approximately 90% of patients. Asthma and urinary stones are common comorbidities associated with YAOS.<sup>240</sup> Early recognition of the disease can minimize extensive testing, and with a correct diagnosis, physicians will be able to better manage the disease.<sup>22,79</sup>

#### *Treatment*

The therapeutic regimen for YAOS consists of glucocorticoids and/or sulfasalazine as the first-line treatment option. Glucocorticoids have been shown to reduce disease severity and duration of flares, and treatment with sulfasalazine resulted in a significant symptomatic improvement in patients with YAOS.<sup>22,79,240</sup>

In a retrospective study, tocilizumab was shown to improve the symptoms and physical function of adult patient with YAOS.<sup>79</sup> Treatment with canakinumab was also shown to be effective, which improved the overall symptoms and physical function of the patients with YAOS.<sup>22,79,240</sup> Data from a retrospective study have shown that canakinumab was effective and well tolerated in adult patients with YAOS and may be considered as a therapeutic option.<sup>80</sup>

## **PFAPA syndrome**

### *Overview*

PFAPA syndrome is the most common autoinflammatory disease in children, but its hereditary basis remains uncharacterized and specific genetic causes are yet to be identified.<sup>245,246</sup> Although, PFAPA is the most common periodic fever disease in children, some studies have reported it in adults.<sup>3,4</sup> PFAPA syndrome has a delayed onset during adulthood. Clinical features of PFAPA in adults which are mainly overlapping with those of children are fever, oral aphthous, pharyngitis, cervical lymphadenopathy, abdominal pain, headache, and nausea.<sup>247</sup> Among the key signs and symptoms of PFAPA syndrome, the occurrence of recurrent fever with erythematous pharyngitis represent the most strongly associated diagnosis of PFAPA syndrome in adulthood.<sup>248</sup> The estimated incidence of PFAPA is 2.3 per 10 000 children up to 5 years of age in Norway.<sup>1,249</sup>

### *Pathogenesis*

PFAPA is a genetically complex autoinflammatory disease with disorders of innate and adaptive immunity.<sup>250</sup> PFAPA syndrome indicates a heterogenous, polygenic, or complex inheritance. In several PFAPA cohorts, two types of mutations with a functional effect on the inflammasomes (MEFV E148Q and NLRP3 Q703 K) were seen. Therefore, inflammasome-related genes may play a role in PFAPA pathogenesis.<sup>251</sup> The exact pathogenetic processes underlying the symptoms of PFAPA syndrome are still unknown. An analysis of the upstream regulator of immune pathways indicated that activation of toll-like receptors (TLRs), production of IFN- $\gamma$ , and decrease in 1,25-dihydroxyvitamin D may be associated with the immune pathways involved in the pathogenesis of PFAPA.<sup>252</sup> The elevated serum IL-1 $\beta$  concentrations and elevated proinflammatory cytokine production by monocytes of PFAPA

**Table 5.** Diagnostic criteria for Yao syndrome.

| Clinical criteria   | Comments  |
|---|---|
| Major   | 1. Periodic occurrence $\geq$ twice<br>2. Recurrent fever or dermatitis or both   |
| Minor   | 1. Oligo- or polyarthralgia/inflammatory arthritis, or distal extremity swelling<br>2. Abdominal pain or diarrhea or both<br>3. Sicca-like symptoms<br>4. Pericarditis or pleuritis or both |
| Molecular criterion*  | NOD2 IVS8 + <sup>158</sup> or R702 W or both, or other rare variants  |
| Exclusion criteria  | High titer antinuclear antibodies, inflammatory bowel disease, Blau syndrome, adult sarcoidosis, primary Sjögren syndrome and monogenic autoinflammatory diseases                           |
| Yao syndrome is diagnosed if two major criteria, at least one minor criterion, the molecular criterion, and exclusion criteria are fulfilled.<br>*The genetic testing was performed at the Center for Genetic Testing at Saint Francis, Tulsa, Oklahoma.<br>[Source: Yao and Shen <sup>79</sup> ] |   |

patients upon stimulation of lipopolysaccharide indicate that dysregulation of the immune responses could be associated with PFAPA flares.<sup>252–254</sup> Previous reports have shown that a variant upstream of IL-12A (rs17753641) is associated with PFAPA syndrome. The monocytes from patients heterozygous or homozygous for the rs17753641 risk allele secreted higher levels of IL-12p70 upon stimulation with IFN- $\gamma$  and lipopolysaccharide. Data also suggest that abnormal antigen-presenting cell function, and T-cell activity and polarization, are associated with the pathogenesis of PFAPA.<sup>255</sup> An analysis in patients with PFAPA showed that B-cell adapter protein (*PIK3AP1*) and spondin-2 (*SPON2*) gene regions are differentially methylated, which suggests that *PIK3AP1* and *SPON2* could play a role in PFAPA syndrome.<sup>246</sup> There are few studies which have surveyed familial clustering in PFAPA syndrome, and some reports from those studies are in favor of positive family history, which have shown that siblings and parents of PFAPA patients are similarly affected.<sup>245,256–258</sup> In a study, comprehensive genetic analysis of families with PFAPA syndrome has shown the absence of a common gene harboring exonic mutations in the affected patients, which indicates that PFAPA syndrome is either inherited as a Mendelian disease with high genetic heterogeneity, or transmitted as an oligogenic or complex trait.<sup>259</sup> One study reported 27% of variants in *MEFV* and *NLRP3* genes in a cohort of 62 patients with PFAPA.<sup>260</sup> In another study two mutations were observed, one in *NLRP3* and one in *MEFV*, both known to be associated with

PFAPA and found in one family.<sup>259</sup> In a study by Padeh *et al.*, 28 patients of Arab and Jewish origin with PFAPA syndrome were analyzed of which six patients (21%) were found heterozygotes for M694 V and were carriers of FMF gene. The authors indicated that the reported frequency of FMF genes might be similar to that of a normal population.<sup>261</sup>

#### *Clinical manifestations and diagnosis*

PFAPA syndrome is characterized by recurrent fever, as in AOSD and YAOS, which last for approximately 3–6 days and occurring once every 3–8 weeks. Other characteristics – which include pharyngitis, stomatitis, cervical adenitis, and leukocytosis – are variable in their appearance.<sup>246,262,263</sup> As per recent reports, there are genetic similarities between PFAPA and Behçet's syndrome. PFAPA shares risk loci at *IL12A*, *STAT4*, *IL10*, and *CCR1-CCR3* with Behçet's syndrome and recurrent aphthous stomatitis.<sup>264,265</sup> Based on some common genetic and clinical similarities, it has been suggested that PFAPA together with recurrent aphthous stomatitis and Behçet's syndrome form a construct which Manthiram *et al.* proposed to name Behçet Spectrum of Disorders.<sup>264,265</sup>

PFAPA syndrome is diagnosed based on clinical criteria and by exclusion of other etiologies. Elevated white blood cell counts and C-reactive protein levels may be seen during episodes.<sup>266</sup> Differential diagnoses include infectious

pharyngitis and cyclic neutropenia. The absence of symptoms related to seasonal flares, upper respiratory tract infection, and negative pharyngeal swabs can facilitate diagnosis. The main differential diagnosis depends on the age of patients. Compared with children, the clinical picture is more heterogeneous in nature in adults; hence, PFAPA can be a diagnostic challenge for treating physicians.<sup>81,248</sup> For PFAPA, as per Eurofever/PRINTO clinical classification, at least 7 criteria need to be met out of 8 proposed criteria, which are presence of pharyngotonsillitis, cervical lymphadenitis, periodicity and duration of episodes 3–6 days, and absence of diarrhea, chest pain, skin rash, and arthritis.<sup>267</sup> PFAPA diagnostic criteria according to Marshal, Pedeh and Cantarini are presented in Table 6.<sup>81,248,261,268</sup>

### Treatment

The pharmacological management of PFAPA includes colchicine for prophylaxis of attacks. Data from two randomized controlled trials which

compared tonsillectomy against non-surgical interventions have shown the effectiveness of tonsillectomy in children with PFAPA syndrome.<sup>269</sup> Tonsillectomy with or without adenoidectomy can be useful in some pediatric patients,<sup>81,269</sup> whereas available data suggest that tonsillectomy is not so effective in adults.<sup>81,247</sup> At the onset of fever in patients, prednisone can be effective in the resolution of fever episodes in pediatric<sup>81</sup> and adult patients.<sup>86</sup> Corticosteroids are effective for the resolution of flares in pediatric<sup>270–272</sup> and adult<sup>81,270,272</sup> patients with PFAPA. Steroids can be used during each episode.<sup>1</sup> Prednisone use has shown improved response in adult patients.<sup>81,247</sup> The use of prednisolone at the time of fever onset has been shown to be useful in a randomized clinical trial because fever was decreased in pediatric patients with PFAPA syndrome.<sup>273</sup> Studies have shown that colchicine might be an effective preventive therapy in pediatric patients with PFAPA.<sup>84,261,274</sup> Pediatric<sup>85,88,275</sup> and adult<sup>86,87,275</sup> patients with PFAPA have shown a prompt clinical response to the IL-1 inhibitors, anakinra and canakinumab.

**Table 6.** Diagnostic criteria for PFAPA according to Marshal, Padeh and Cantarini.

(a) Diagnostic criteria of PFAPA based on Marshall et al.<sup>268</sup>

1. Regularly recurring fevers with early age of onset (patients < 5 years of age)
2. Constitutional symptoms in the absence of upper respiratory infection with at least 1 of the following clinical signs:
  - aphthous stomatitis
  - pharyngitis
  - cervical lymphadenitis
3. Exclusion of cyclic neutropenia
4. Completely asymptomatic interval between episodes (resolve spontaneously within 4–5 days)
5. Normal growth and development without long-term sequelae of the disease

(b) Diagnostic criteria of PFAPA according to Padeh et al.<sup>261</sup>

1. Monthly fevers – cyclic fever at any age group
2. Exudative tonsillitis + negative throat culture
3. Cervical lymphadenitis
4. Possibly aphthous stomatitis
5. Completely asymptomatic interval between episodes
6. Rapid response to a single dose of corticosteroids (60 mg prednisone)

(c) Proposed diagnostic criteria for adult-onset PFAPA according to Cantarini et al.<sup>248</sup>

1. Age = 16
  2. Recurrent fever accompanied by erythematous pharyngitis and/or cervical lymphadenitis
  3. Increased inflammatory markers during attacks
  4. Intervals between disease flare without any symptoms
- Exclusions:
- infections, autoimmune and neoplastic diseases as well as monogenic autoinflammatory diseases and febrile polygenic autoinflammatory diseases
  - throat swab performed during fever has to be negative and antibiotic therapy considered ineffective

[Source: Więsik-Szewczyk *et al.*<sup>81</sup>].



## Conclusion

Schnitzler's syndrome, AOSD, SAPHO syndrome/ CRMO/CNO, Adamantiades-Behçet's disease, YAOS, and PFAPA syndrome are a group of rare multigenic autoinflammatory diseases that can present varied clinical features. Diagnosis of these diseases can be challenging due to a combination of nonspecific manifestations that can also be seen in a variety of other conditions. Diagnostic delays and disease complications may occur as a consequence of low disease awareness and the lack of pathognomonic markers.

The pathogenesis of the multigenic autoinflammatory diseases are complex and, in some cases, precise pathogenesis is not clearly understood. Therefore, further research is warranted to understand the pathogenesis of these diseases.

Although conventional treatments are commonly used, biologics have shown promising results in the management of multigenic autoinflammatory diseases. Biologics targeting proinflammatory cytokines including IL-1, IL-6, TNF- $\alpha$ , IL-17A and IL-18 have been shown to ameliorate signs and symptoms of different multigenic autoinflammatory diseases.

## Declarations

### *Ethics approval and consent to participate*

As this work is a review, therefore did not require an ethical board approval.

### *Consent for publication*

Not applicable

### *Author contributions*

**Petros Efthimiou:** Conceptualization; Writing – review & editing.

**Olga Petryna:** Conceptualization; Writing – review & editing.

**Priscila Nakasato:** Conceptualization; Writing – review & editing.

**Apostolos Kontzias:** Conceptualization; Writing – review & editing.

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Not applicable

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