The combined prevalence of classified rare rheumatic diseases is almost double that of ankylosing spondylitis

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Abstract

Background: Rare diseases (RDs) affect less than 5/10,000 people in Europe and fewer than 200,000 individuals in the United States. In rheumatology, RDs are heterogeneous and lack systemic classification. Clinical courses involve a variety of diverse symptoms, and patients may be misdiagnosed and not receive appropriate treatment. The objective of this study was to identify and classify some of the most important RDs in rheumatology. We also attempted to determine their combined prevalence to more precisely define this area of rheumatology and increase awareness of RDs in healthcare systems. We conducted a comprehensive literature search and analyzed each disease for the specified criteria, such as clinical symptoms, treatment regimens, prognoses, and point prevalences. If no epidemiological data were available, we estimated the prevalence as 1/1,000,000. The total point prevalence for all RDs in rheumatology was estimated as the sum of the individually determined prevalences.

Results: A total of 76 syndromes and diseases were identified, including vasculitis/vasculopathy (n = 15), arthritis/arthropathy (n = 11), autoinflammatory syndromes (n = 11), myositis (n = 9), bone disorders (n = 11), connective tissue diseases (n = 8), overgrowth syndromes (n = 3), and others (n = 8). Out of the 76 diseases, 61 (80%) are classified as chronic, with a remitting-relapsing course in 27 cases (35%) upon adequate treatment. Another 34 (45%) diseases were predominantly progressive and difficult to control. Corticosteroids are a therapeutic option in 49 (64%) syndromes. Mortality is variable and could not be determined precisely. Epidemiological studies and prevalence data were available for 33 syndromes and diseases. For an additional eight diseases, only incidence data were accessible. The summed prevalence of all RDs was 28.8/10,000.

Conclusions: RDs in rheumatology are frequently chronic, progressive, and present variable symptoms. Treatment options are often restricted to corticosteroids, presumably because of the scarcity of randomized controlled trials. The estimated combined prevalence is significant and almost double that of ankylosing spondylitis (18/10,000). Thus, healthcare systems should assign RDs similar importance as any other common disease in rheumatology.

Keywords: Rheumatology, Rare diseases, Epidemiology, Vasculitis, Arthritis, Myositis, Fever

Background

Rare diseases (RDs) are a complex problem in medicine, and the definition of a RD varies around the world. The European Union (EU) defines a disease as rare when it affects less than 5 people in 10,000 living in the EU, which translates to approximately 370,500 individuals being affected. In the United States, the Rare Diseases Act of...
2002 defined a disease as rare when it affects less than 200,000 people. Patients frequently remain undiagnosed for many years, and treatment is often ineffectual. Data on prevalence, disease burden, treatment regimens, access to healthcare systems, and mortality are, to a great extent, unknown. Thus, RDs remain an unresolved challenge in modern medicine.

The classification, overall prevalence, and treatment options of rare rheumatic diseases are poorly defined. Disorders may affect the musculoskeletal apparatus with arthritis and myalgia but also involve other tissues in the form of myositis, vasculitis, autoimmune organ involvement, or bone diseases. Patients are often diagnosed as having a psychosomatic disorder due to missing or unrecognized somatic and/or objective findings. Patients not only have to cope with their disease burden, but are also at risk of developing additional psychiatric comorbidities. For example, patients with undiagnosed diseases in Germany have a prevalence of depressive symptoms three times higher than the average population (22% vs. 8.1%) [1, 2]. On the other hand, a verified diagnosis may aid the patient in accepting their diagnosis and coping with the ensuing symptoms and challenges. However, due to the scarcity of randomized controlled trials, treatment options for RDs are often limited and remain empirical. In addition, the definitions of key symptoms often vary in clinical studies, hampering uniform analyses.

RDs in rheumatology may be analyzed systematically by prevalence, genetic background and pathogenesis, clinical involvement, treatment options, and prognosis. Prevalence data vary according to age, as well as global and ethnic background. For example, seronegative symmetrical synovitis with pitting edema (RS3PE) has a high prevalence among the elderly, with 0.09% of all individuals over the age of 50 years being affected in Japan [3], but seems to be a quite rare disorder among younger individuals. Similarly, the prevalence of adult onset Still’s disease (AOSD) varies globally: 3.4–6.9/100,000 in Norway [4], 6.77/100,000 in Turkey [5], and 3.9/100,000 in Japan [6]. With respect to ethnic background, the estimated worldwide prevalence of Gaucher’s disease is 1–2/100,000, but in Ashkenazi-Jews the prevalence may be as high as 1/850 [7].

The pathogenesis and genetic backgrounds of some RDs in rheumatology have been studied increasingly in recent years, and in some cases well elucidated. Blau syndrome was described in 2001 and is characterized by mutations in the CARD15/NOD2 gene [8] and overexpression of autoinflammatory cytokines [9]. Interestingly, mutations in CARD15/NOD2 are also associated with other diseases with inflammatory involvement, such as Crohn’s disease and arthritis [10]. Familial cold urticaria (FCU), Muckle-Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease (NOMID) or chronic infantile neurologic cutaneous articular syndrome (CINCA) were originally thought to be three similar but distinct diseases. Further evidence has shown that all three syndromes are the result of mutations in the same gene, CIAS1. They are now referred to as different phenotypes of the same disorder, namely cryopyrin-associated periodic syndrome (CAPS) [11, 12]. The MEFV gene, best known for causing familial Mediterranean fever (FMF) equally demonstrates the importance of genetics in RDs [13, 14]. Heterozygous mutations in MEFV are also found in many children with periodic fever, stomatitis, pharyngitis, adenitis (PFAPA) [15, 16]. Findings suggest that exon variants in MEFV may also be associated with AOSD [17].

With respect to pathogenesis, infectious agents may also play a role in RDs. As some diseases follow a distinct seasonal pattern, infectious pathogenesis has been suggested for Kawasaki disease [18, 19], and IgA-vasculitis (formerly Henoch-Schönlein purpura) [20, 21]. Furthermore, some diseases are probably modulated by hormonal alterations, such as pachydermoperiostosis [22]. Although a disease-causing genetic mutation has been detected [23], males are seemingly more commonly and severely affected [24]. RDs in rheumatology involve a variety of tissues and organ systems. For example, joints are affected by pigmented villonodular synovitis [25], the skeletal system by Camurati-Engelmann disease [26], and internal organs by AOSD [27]. The skin is involved in pyogenic arthritis, pyoderma gangrenosum, acne (PAPA) syndrome [28], blood vessels in granulomatosis with polyangiitis (GPA) [29], connective tissue in systemic sclerosis [30], and muscles in inclusion body myositis (IBM) [31].

Treatment options often, but not exclusively, include corticosteroids, such as in RS3PE [32] and eosinophilic-myalgia syndrome [33]. Although research on RDs is often limited to retrospective, single center trials or case reports only, randomized controlled trials (RCTs) have been increasingly available in recent years for some conditions, such as granulomatosis with polyangiitis [34], PFAPA syndrome [35], and FMF [36].

The disease course may be classified as self-limited (e.g., Kawasaki disease), chronic with a variable remitting-relapsing course during treatment (e.g., Takayasu arteritis), and chronic with a predominantly progressive and difficult to control course (e.g., systemic sclerosis).

The prognosis for RD varies and may be affected by the primary disease, complications, and treatment, especially long-term immunosuppression.
The objective of this study was to analyze the complexity of RDs in rheumatology. Based on data from the literature, we identified some of the most important sets of rheumatic diseases and calculated their combined prevalence. Our data may give better insight into this area of rheumatology, aid specialized centers for RDs, and raise overall awareness in the healthcare field.

**Results**

The diseases extracted from the databases are summarized in Table 2 of Appendix. The 76 syndromes and diseases were classified as follows: vasculitis/vasculopathy (n = 15), arthritis/arthropathy (n = 11), autoinflammatory syndromes (n = 11), myositis (n = 9), bone disorders (n = 11), connective tissue diseases (n = 8), which include inflammatory as well as non-inflammatory conditions, overgrowth syndromes (n = 3), and others (n = 3). A definitive genetic cause was identified in 26 diseases (34%). Out of the 76 conditions, 34 diseases (44%) were classified as chronic, primarily progressive, and difficult to control. Twenty-seven diseases (35%) were classified as chronic with a variable remitting-relapsing course. Six diseases (7%) were classified as self-limited. Acute phase reactants may be elevated in 49 diseases (64%). Corticosteroids are used as a therapeutic option in 49 diseases (64%). The mortality was variable and could not be determined precisely, but nine diseases (11%) were considered severe and potentially lethal if left untreated.

Prevalence data were available for 28 syndromes and diseases. For an additional five diseases, estimated prevalence data were already available. For another eight diseases, only incidence data were available. The prevalence of 38 diseases was estimated at 1/1,000,000, for 4 diseases at 1/100,000, and for 1 disease at 1/10,000. The combined prevalence per 10,000 is given in Table 1 (see also Figs. 1 and 2). The summed prevalence of all available and estimated RDs was 28.8/10,000.

**Discussion**

RDs are challenging for patients, healthcare professionals, and societies. Signs and symptoms often remain unrecognized and patients are excluded from specific treatment. Patients are frequently diagnosed with a psychosomatic disorder. Conversely, some patients with true extrasomatic diagnoses insist on the presence of a RD and cause significant expenses to healthcare systems. To overcome this bias, the importance of RDs should be recognized in public healthcare.

The knowledge of RDs is mostly available from case reports or case studies. On one hand, these studies are important in order to document essential information, such as commonly reported symptoms, different treatment regimens, and outcomes. However, such studies may involve reporting bias and, thus, are difficult to compare. For example, multicentric histiocytosis is a disease primarily reported in Caucasian women. However, this may be due to increased awareness in Western countries. Furthermore, women may consult a doctor more often and simulate a female Caucasian predominance [37].

Most studies scrutinizing RDs are designed as single center, retrospective studies due to a lack of patient numbers or networks. Larger registries would provide an opportunity to conduct retrospective or prospective and multicenter studies with a greater number of participating patients. Therefore, further development of international expert centers and registries is in great demand. In recent years, advances have been made due to the establishment of international expert/reference centers. For example, the Eurofever project for autoinflammatory diseases provided classification criteria and evaluated treatment options for multiple disorders [38, 39].

In addition, genetic testing has become increasingly available and, thus, more important in recent years. For example, whole exome sequencing in patients with similar symptoms without previous knowledge of candidate genes led to the identification of WISP 3 and SLCO2A1 as the pathogenic mutations in progressive pseudorheumatoid dysplasia [40] and primary hypertrophic osteoarthropathy [23].

In this study, we aimed to identify and classify RDs in rheumatology. We were able to show that the most common symptoms in rare rheumatic diseases are arthritis (31.0%, 89.3/100,000), followed by vasculitis (26.6%, 76.8/100,000), and connective tissue involvement (16.0%, 46.1/100,000), which in this study includes inflammatory as well as non-inflammatory conditions. Importantly, the total prevalence of a symptom was commonly dominated by only a few comparatively prevalent diseases. For example, systemic sclerosis (prevalence: 22.5/100,000) makes up 48.8% of all rare rheumatic diseases with connective tissue involvement.

Our study has several limitations. First, the nomenclature for diseases and syndromes is often used interchangeably, and the same disease or a variation in the same group of diseases is sometimes named differently. For example, CAPS is formerly known as Muckle-Wells, CINCA/NOMID, or familial cold autoinflammatory syndrome [12]. This may lead to incomplete search results and impede the comparability of available studies. Second, most prevalence data are almost exclusively based on retrospective analyses of hospital information or questionnaires. Prevalence data also vary according to ethnic background, geography, and age, which makes the use of overall prevalence data quite uncertain. For
example, FMF or Behçet’s are more common in Mediterranean and Middle Eastern populations [41, 42] and rare in other regions, demonstrating the difficulty in using a local geographic prevalence. Similarly, although currently considered a RD by the European definition, an Italian study found an unexpectedly high overall prevalence of 8.5/10,000 for cryoglobulinemic vasculitis, which would no longer be defined as a RD. Although this study had some limitations, including the implementation of a questionnaire leading to a higher participation rate in the elderly population than the younger age groups, we decided to exclude cryoglobulinemic vasculitis from our list of rare rheumatological diseases. Our reasoning for this was the methodically more accurate estimation of prevalence by this study [43]. A well-known, verified RD, systemic sclerosis is quite common in Choctaw Native Americans (prevalence 66/100,000 in Oklahoma Choctaws and 469/100,000 in full-blooded Choctaws [44]), but rare among all other studied populations [45]. This may be due to a unique HLA haplotype, but other environmental factors may also play a role. Furthermore, our estimates of prevalence data may be somewhat inaccurate. We probably underestimated the prevalence by choosing 1 in 1,000,000 rather than 1 in 100,000, and the total prevalence of rare rheumatic diseases is likely to be even higher than our estimate of 29.6/10,000.

Prevalence data may also differ depending on age. For example, giant cell arteritis is probably extremely rare in younger patients but quite frequent in patients older than 55 years of age (UK 250/100,000 [46]), with age-independent prevalence data being difficult to obtain. Because the overall estimated prevalence may be even higher than 1/10,000, we also excluded giant cell arteritis from our list of RDs in rheumatology.

Similarly, we also excluded systemic lupus erythematoses, one of the better known “rare” diseases in
rheumatology from our study, as recent epidemiological studies suggest that it is probably not a rare disease by the above mentioned European definition [47]. Furthermore, we also excluded rhusus syndrome, because it is suspected to be an overlap of systemic lupus erythematodes and rheumatoid arthritis and thus its prevalence may be difficult to obtain and distinguish [48].

The classification system we used also has its limitations. Conditions can be classified by their etiology or by their clinical appearance. As the etiology of many rare diseases remains unknown, we decided to classify diseases according to their main organ system involved in the clinical appearance of the disease. Exceptions include the category of autoinflammatory and overgrowth syndromes, where multiple organ systems may be involved, and the conditions in one group have a basic (suspected) etiology in common. However, overlaps between included conditions may have occurred because of the complex nature of some RDs.

Another pitfall is that diagnostic and/or classification criteria may differ in varying definitions of the diseases (e.g., familial Mediterranean fever), are not well established, and have been suggested based on radiographic or histological findings. In most cases, no validation studies are available to confirm specificity and sensitivity.

We observed that RCTs are available only for some RDs, such as Behcet’s disease [49] or ANCA-associated vasculitis [34]. Furthermore, most follow-ups of patients with RDs are rarely published. Larger patient cohorts would be necessary to obtain reliable data on outcome, disease progression, morbidity, and mortality. Treatment complications in most, if not all, RDs may be due to the
disease itself or adverse events to immunosuppressive treatment. These data merit in-depth analyses, as they may shed more light on the disease and its pathophysiology or potential treatment options.

Incidence and prevalence data have become available for increasingly more RDs and, in some cases, the prevalence has even increased in recent years (e.g., Kawasaki disease) [50]. This trend may be due to a true increase in incidence, increased diagnosis of previously undiagnosed patients due to an upsurge in physician or patient awareness (internet, patient support groups, RD associations, etc.), or simply due to better national reporting systems and databases. In addition, an increased overall life expectancy in the general population has led to an

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**Fig. 3** Overview of the combined prevalence per 100,000 per classification

**Excluded:** N = 5
- Reactive arthritis
- Polymyositis/scleroderma overlap
- Systemic lupus erythematoses
- Cryoglobulinemic vasculitis
- Giant cell arteritis

**Merged:** N = 7 —> 3
- CAPS (CINCA, Muckle-Wells, familial cold urticaria)
- CREST/systemic sclerosis
- Dermatomyositis/polymyositis

**Total syndromes included in analysis:** 76
increased incidence and prevalence of conditions that predominantly affect the elderly (e.g., GCA). Continuously better treatment options may also lead to prolonged overall survival with an increase in prevalence rates.

In this study, we found that the cumulative prevalence of RDs in rheumatology is at least 28.8/10,000, which is almost double that of ankylosing spondylitis (18/10,000) [51], a rather common disease seen in practice. This observation suggests that symptoms should be carefully acknowledged in all patients, especially when an overt psychopathology is present, as many patients with a yet undiagnosed disorder show signs of depression or other psychosomatic disorders [1], which can obscure the differentiation between primary disease and secondary complication even more for the treating physician. Our study may aid physicians as a simple tool for diagnosing patients with an undiagnosed rheumatic disease by comparing the symptoms, prevalence, and likeliness of one disorder to another.

**Conclusion**

Our study shows that RDs in rheumatology are not as rare as previously thought, affecting at least 28.8/10,000 people. Therefore, for every patient diagnosed with ankylosing spondylitis, 1.6 patients may suffer from a rare rheumatic disease. Although research and case reports of RDs are important, international expert centers are necessary to initiate and perpetuate patient cohorts and registries, establish classification/diagnostic criteria, and conduct clinical trials. Standard questionnaires and laboratory analyses may aid in obtaining better insight into the pathophysiology of RDs.

**Methods and materials**

The abstract archives of the European League Against Rheumatism, the American College of Rheumatology, Orpha.net, and the PubMed database were searched for the following terms: “rare” in combination with arthritis, arteritis, connective tissue disease, rheumatic, and vasculitis. Furthermore, terms were used in various combinations including arthralgia, autoimmune, fever, inflammation, joint pain, muscle pain, myalgia, and swollen joint. Identified syndromes were then classified according to their main appearance under the following terms: arthritis/arthropathy, bone disorders, autoinflammatory syndromes, connective tissue diseases, myositis/myopathy, overgrowth syndromes, vasculitis/vasculopathy, and others. Furthermore, we conducted a search of the literature and analyzed each disease according to the following criteria: prevalence, genetics/pathogenesis, diagnostic criteria, symptoms, laboratory findings, therapy, and prognosis. Diseases and syndromes were assessed for their overall prevalence and excluded if they did not meet the European definition of a RD (< 5/10,000) (see Fig. 3).

If more than one prevalence was available, the prevalence data were averaged accordingly.

For statistical reasons, we estimated the prevalence for diseases for which no epidemiological data were available as one of three possible values: < 1/1,000,000, 1/100,000 or 1/10,000. The overall total prevalence for all RDs in rheumatology was estimated by summing up the available or estimated individual prevalence of each disease.

**Appendix**

See Table 1, 2.

**Table 1** Results from the literature analyses

| Classification                      | N   | Combined prevalence/100,000 | %/All RD (prevalence) |
|-------------------------------------|-----|----------------------------|-----------------------|
| Vasculitis                          | 15  | 76.8                       | 26.55                 |
| Arthritis                           | 11  | 89.3                       | 30.9                  |
| Autoinflammatory                    | 11  | 21.105                     | 7.32                  |
| Bone disorders                      | 11  | 4.15                       | 1.44                  |
| Myositis                            | 9   | 19.5                       | 6.76                  |
| Connective tissue disease           | 8   | 46.1                       | 15.99                 |
| Others                              | 8   | 30.89                      | 10.72                 |
| Overgrowth syndromes                | 3   | 0.3                        | 0.1                   |
| Total                               | 76  | 288.15                     | 100                   |
| Disease                                                                 | Prevalence                                                                 | Genetics/ pathogenesis                                                                 | Diagnostic criteria                                                                 | Clinical features                                                                 | Laboratory findings                  | Therapy                                      | Prognosis/ Complications                  | Classification                                |
|------------------------------------------------------------------------|---------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|----------------------------------------|---------------------------------------------|---------------------------------------------|---------------------------------------------|
| Buerger’s disease (thromboangiitis obliterans) [52–56]                | Most common in Middle and Far East, estimated prevalence: 5/100,000 (Japan) 0.65/100,000 (Taiwan) → 2.8/1 000,000 | Probably immune-mediated vasculitis, possibly associated with infectious agent; strong association with smoking; segmental occlusive inflammatory vasculitis (mainly small vessels, arteries and veins) | Many different diagnostic criteria (e.g., by Shionoya and Olin)                       | Disease onset in middle-aged, predominantly males; ischemic pain in extremities, numbness, skin ulcers, thrombophlebitis, Raynaud’s phenomenon | Inflammatory markers usually normal          | Smoking cessation, prostaglandin analogs, maximize blood supply, reduce risk of vasoconstriction (avoid coldness, etc.) | Remitting-relapsing, life expectancy usually normal, but morbidity increased (e.g., amputations) | Vasculitis/ vasculopathy                      |
| Eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss syndrome) [57–63] | 178/1,000,000 (estimated, Japan) 10.7/1,000,000 (France) 14/1,000,000 (Sweden) → 1.4/100,000 | Association with multiple different HLA genotypes, possibly IgG4-related disorder; Th-2 and eosinophils seem to play a major role in pathogenesis; small vessel necrotizing vasculitis | ACR criteria, Chapel Hill nomenclature definition                                  | Disease onset in middle-aged males and females; asthma, weight loss, mononeuritis multiplex, non-erosive sinusitis/polypsis, skin lesions, lung infiltrates, pleural effusion, cardiomyopathy, glomerulonephritis | 30 – 40% ANCA-positive (mainly MPO, but proteinase 3 also possible), eosinophilia; depending on organ involvement, elevated renal enzymes possible; elevated IgG4 can be found | Corticosteroids, immunosuppressants, rituximab | Chronic or remitting-relapsing, main complication with increased mortality is cardiomyopathy but overall mortality low | Vasculitis/ vasculopathy                      |
| Degos disease (malignant atrophic papulosis) [64–67]                  | Unknown, less than 200 cases reported, estimated <1/1,000,000              | Unknown; autosomal dominant inheritance discussed; thrombo-obliterative vasculopathy | Clinical and histopathological diagnosis                                            | Onset usually at age 20–50 years, papular skin lesions with central atrophy and peripheral telangiectatic rim, sudden onset systemic involvement possible with high morbidity and mortality (bowel perforation, thrombosis, hemorrhage) | Coagulopathy in some patients             | Anticoagulants, treprostinil, eculizumab | Limited and systemic variant, systemic variant has over 50% mortality within 2–3 years (due to bowel perforation and peritonitis) | Vasculitis/ vasculopathy                      |
| Disease                                      | Prevalence                                      | Genetics/pathogenesis                                                                 | Diagnostic criteria                      | Clinical features                                                                 | Laboratory findings          | Therapy                                                                 | Prognosis/Complications                  | Classification                          |
|---------------------------------------------|------------------------------------------------|---------------------------------------------------------------------------------------|------------------------------------------|-----------------------------------------------------------------------------------|-------------------------------|------------------------------------------------------------------------|------------------------------------------|------------------------------------------|
| Hughes-Stovin syndrome (incomplete/vascular Behcet’s disease) [68, 69] | Unknown, ~ 40 cases described, estimate < 1/1,000,000 | Unknown; angiodysplasia and infections discussed, maybe variant of Behcet’s disease; absence of oral/gential ulcers important for distinction | Clinical and radiographic diagnosis       | Predominantly young males affected, multiple lung aneurysms cause cough, dyspnea, fever, chest pain, hemoptysis | Leukocytosis, anemia, elevated ESR and CRP | Corticosteroids, immunosuppressants, anticoagulant/thrombolytic agents, surgery | Poor prognosis, massive hemoptysis and aneurysmal rupture are main causes of death | Vasculitis/vasculopathy                  |
| Hypocomplementemic urticarial vasculitis (McDuffie syndrome) [70–74] | Unknown, estimate < 1/1,000,000 | Mutations in DNASE1L3 described, possible association with SLE, inflammation of dermal capillaries and postcapillary venules; possibly IgG4-related disease | Proposed criteria by Schwartz et al.     | Predominantly in middle-aged females, chronic urticarial exanthema, angioedema, arthritis, ocular inflammation, glomerulonephritis, abdominal pain, angioedema, obstructive pulmonary disease | Low complement levels, anti-C1q antibodies | Corticosteroids, immunosuppressants | Chronic, prognosis depending on systemic organ involvement (pulmonary, renal, cardiac), mortality low | Vasculitis/vasculopathy                  |
| Kawasaki disease (mucocutaneous lymph node syndrome) [18, 75–77] | Prevalence unknown, incidence ranges from 3.7/100,000 (Australia) to 243/100,000 (Japan) for children <5 years and increased in previous years, estimate < 1/100,000 | Unknown, but genetic predisposition suspected (much more common in Asia), probably infectious trigger (seasonal peaks) causing small and medium vessel vasculitis | American Heart Association (AHA) guidelines, but primarily clinical diagnosis, as incomplete presentation is common | Predominantly young children until the age of 4 years affected with male predominance; conjunctivitis, exanthema, GI symptoms, fever, oropharynx involvement, lymphadenopathy, cracked lips, erythema of hand and feet, coronary aneurysm | Elevated CRP, ESR, leukocytosis, thrombocytosis | Intravenous immunoglobulins, high dose aspirin | Self-limited, good prognosis if treated, but coronary artery abnormalities occur in 25% if left untreated, leading cause of acquired heart disease in children in developed countries | Vasculitis/vasculopathy                  |
| Disease                                                                 | Prevalence                                      | Genetics/pathogenesis | Diagnostic criteria                  | Clinical features                                                                                       | Laboratory findings                              | Therapy                                      | Prognosis/Complications                      | Classification                   |
|------------------------------------------------------------------------|-------------------------------------------------|-----------------------|--------------------------------------|--------------------------------------------------------------------------------------------------------|-----------------------------------------------|-------------------------------------------|---------------------------------------------|---------------------------------------------|
| Leukocytoclastic/cutaneous small vessel/hypersensitivity vasculitis    | Prevalence unknown, incidence 45–1,000,000,000 – | Unknown; more than 50% idiopathic, other possible causes include malignancy, autoimmune diseases, drugs (antibiotics, NSAIDs), neutrophilic inflammation in postcapillary venules | Chapel Hill criteria (histopathological) | Limited cutaneous variant with palpable purpura and lesions (often on lower extremity), or systemic organ involvement possible (most commonly renal) | Anemia, leukocytosis, elevated renal enzymes | Corticosteroids, immunosuppressants | Variable, commonly remitting-relapsing with treatment, overall survival good | Vasculitis/vasculopathy                  |
| Microscopic polyangiitis (microscopic polyarteritis) [58, 59, 81, 82]  | 25.1/1,000,000 (France) 94/1,000,000 (Sweden) → 6/100,000 | Unknown; possibly related to MHC II genes; environmental (silica) and autoimmune influence discussed; small vessel, necrotizing vasculitis with few or no immune deposits, primarily affecting kidneys and lungs | Chapel Hill criteria (histopathological) | Males slightly more commonly affected than females, onset primarily in elderly (age ≥ 60 years). Dyspnea, cough, hemoptysis, rapidly progressive glomerulonephritis, palpable purpura, GI symptoms, peripheral neuropathy | MPO-ANCA, microscopic hematuria | Corticosteroids, immunosuppressants (rituximab, cyclophosphamide) | Remitting-relapsing with treatment, poor prognosis without therapy, complications include end-stage renal disease, cardiovascular involvement, malignancy, and infections | Vasculitis/vasculopathy                  |
| Behçet’s disease [41, 83–85]                                           | Estimated prevalence in Scandinavia: 2/100,000, Europe: 10.5/100,000, Mediterranean: 188/100,000, Others: 15.7/100,000, Not rare in Turkey (80–370/100,000), estimate 5/10,000 | Association with HLA-B51; most common along the ancient silk road; infectious or environmental triggers; systemic occlusive vasculitis discussed | Many different criteria exist (e.g., New International Criteria of Behçet’s Disease) | Peak of disease onset in third decade of life (any age possible), recurrent eye inflammation (iritis/uveitis), oral and genital ulcers, skin manifestations (erythema nodosum, etc.), arthralgia, thrombosis, neurological symptoms, cardiac involvement | Pathergy-phenomenon, leukocytosis | Corticosteroids, colchicine, immunosuppressants, biologicals, small molecules, anticoagulants | Chronic disease with remitting-relapsing course, increased mortality in case of arterial and neurological involvement, possible cause of blindness | Vasculitis/vasculopathy                  |
| Disease                                      | Prevalence                                      | Genetics/pathogenesis                                                                 | Diagnostic criteria                                                                 | Clinical features                                                                 | Laboratory findings                                                                 | Therapy                                                                 | Prognosis/Complications                                           | Classification       |
|----------------------------------------------|-------------------------------------------------|----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|------------------------------------------------------------------------|---------------------------------------------------------------------|---------------------|
| Erythema induratum (Bazin disease, nodular vasculitis) [86, 87] | Unknown, estimate < 1/1,000,000                  | Unknown; type III or type IV hypersensitivity reaction suspected; associated with drugs (propylthiouracil), infectious (tuberculosis, hepatitis) or non-infectious diseases (leukemia, RA); diffuse panniculitis with neutrophilic vasculitis | Chapel Hill criteria (histopathological)                                              | Female predominance, recurrent nodules, usually on posterior lower legs, with local ulceration and drainage, heal with scarring and post-inflammatory hyperpigmentation | Depending on underlying cause                                          | Treatment of underlying cause, potassium iodide, NSAIDs; corticosteroids, immunosuppressants | Chronic, relapses are common                                      | Vasculitis/vasculopathy |
| Polyarteritis nodosa (Kussmaul-Maier disease) [58, 59, 88, 89] | 307/1,000,000 (France) 31/1,000,000 (Sweden) → 3.1/100,000                           | Early-onset polyarteritis nodosa; mutations in CECR1, leading to deficiency in adenosine deaminase 2 (DADA2); other forms: idiopathic, cutaneous, and infection-associated (HBV); medium vessel, necrotizing vasculitis with segmental, mixed inflammatory infiltrates at branching points and microaneurysms (often in hepatic, renal, and mesenteric arteries), that spares the lung | Male predominance, malaise, weight loss, fever, arthralgia, ulcers, livedo racemosa, myalgia, mononeuritis multiplex, purpura, GI symptoms, kidney infarctions, orchitis, hearing loss; no pulmonary involvement! | ESR and CRP elevated, leukocytosis, anemia, occasionally, hyperesoinophilia, hepatitis serology, liver enzymes, ANCA negative | Corticosteroids, immunosuppressant, biologicals (TNFα), antivirals, NSAIDs | Variable; chronic, acute, remitting-relapsing (10–20%) course possible; potentially life-threatening, remission can be achieved in many cases, good survival rate if treated early | Vasculitis/vasculopathy |
| Disease                                                                 | Prevalence                          | Genetics/pathogenesis                                                                 | Diagnostic criteria                                                                 | Clinical features                                                                 | Laboratory findings                                                                 | Therapy                        | Prognosis/Complications               | Classification               |
|------------------------------------------------------------------------|-------------------------------------|----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|---------------------------------|----------------------------------------|-----------------------------|
| Primary central nervous system vasculitis (PACNS/primary angiitis of the CNS) [90–93] | Prevalence unknown, incidence: 2.4/1,000,000 estimate < 1/1,000,000 | Different infectious agents suggested as triggers, segmental inflammation of CNS vessels | Proposed criteria by Calabrese and Mallek, histological criteria by Alrawi et al. | Disease most common in white males age ≥ 50 years, depending on localization different symptoms occur: headache, stroke, dementia, chronic meningitis, personality changes | Because of lack of systemic disease, inflammatory markers in blood are normal, but cerebrospinal fluid should be investigated | Corticosteroids + immunosuppressants (e.g., cyclophosphamide) | Chronic, controllable with medication, relapses common, fatal in the past, current mortality ~15% | Vasculitis/vasculopathy          |
| Henoch-Schönlein purpura (IgA vasculitis) [21, 94, 95]                 | Incidence 3–26.7/100,000 in children, 0.8–1.8/100,000 in adults, estimate 1/100,000 | Unknown; several reports describe relationship to different HLA genes and MEFV gene mutations; infectious agent suggested in children (seasonal peak in fall and winter), in adults linked to cancer; small-vessel leukocytoclastic vasculitis | ACR criteria, criteria by Michet et al., EULAR pediatric criteria | Predominantly male children affected, purpuric rash, abdominal pain, joint pain, edema, renal involvement | Increased ESR, CRP, leukocytosis, anemia, proteinuria | NSAIDs, corticosteroids, immunoglobulins, immunosuppressants | Usually self-limited, but remitting-relapsing course possible, poor prognosis in case of renal involvement, worse prognosis in adults | Vasculitis/vasculopathy          |
| Takayasu arteritis [96–100]                                             | 2.82–100,000 (Korea) 4.7/1,000,000 (UK) 22.1,000,000 (Norway) 12.8/1,000,000 (Turkey) 1.7/100,000 | Different candidate genes: HLA variants, FCGR2A/FCGR3A, IL 12B; more frequent in Asia, aortic, and large vessel vasculitis | ACR criteria | Female predominance, fever, fatigue, weight loss, headache, differences in blood pressure of extremities, "pulseless disease" | Elevated CRP, ESR MMP-3 levels, PTX-3 | Corticosteroids, immunosuppressants, biologicals (TNF, IL-6) | Chronic, good overall survival, cardiovascular disease is most common cause of death (infarction, thrombosis, etc.) | Vasculitis/vasculopathy          |
### Table 2 (continued)

| Disease                                                | Prevalence                                                                 | Genetics/ pathogenesis                                                                 | Diagnostic criteria                                                                 | Clinical features                                                                                   | Laboratory findings                                                                 | Therapy                                                                 | Prognosis/ Complications                                                                 | Classification         |
|--------------------------------------------------------|---------------------------------------------------------------------------|----------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|------------------------|
| Granulomatosis with polyangiitis (GPA, formerly Wegener granulomatosis) [29, 58, 59, 101] | 160/1,000,000 (Sweden) 23.7/1,000,000 (France) → 9.2/100,000               | Different genes suspected: HLA variants, SER-PINA1; infectious, environmental (decreasing north–south gradient), and drug-induced triggers suspected; ANCA-associated, small vessel vasculitis | ACR criteria, Chapel Hill criteria (histopathological) | Malaise, myalgia, arthralgia, anorexia, weight loss, fever, oral ulcers, ear/nose/throat manifestations typical: eye manifestations (scleritis/ uveitis, etc.), nasal discharge, epistaxis, upper airway obstructive disease | Elevated inflammatory markers, positive ANCA (proteinase 3 in 80%), urine analysis | Corticosteroids, immunosuppressants (rituximab, cyclophosphamide, azathioprine) | Chronic; relapses are very common, infections are main cause of death | Vasculitis/ vasculopathy |
| Adult-onset Still’s disease (AOSD, Wissler’s syndrome) [4–6, 102, 103] | 3.4 – 6.9/100,000 (Norway) 6.77/100,000 (Turkey) 3.9/100,000 (Japan) → 5.3/100,000 | Unknown; possibly related to MIF, HLA antigens, MEFV; different triggers suspected (infections, malignancies, medications, vaccinations) | Yamaguchi criteria, Fautrel criteria | Females slightly more affected; disease onset often at age 17–35 years, fever, maculopapular rash, arthralgia/ arthritis (most commonly big joint), lymphadenopathy, hepatosplenomegaly, pleuritis, pericarditis, pneumonitis, eye involvement, abdominal pain, myalgia, alopecia, sore throat, weight loss, cranial nerve palsies | Leukocytosis, anemia, hypoalbuminemia, elevated liver enzymes, elevated ESR and CRP, ANA, ACPA and RF usually negative, elevated ferritin, mild proteinuria, increased IgE or elevated β2-microglobulin | NSAIDs, corticosteroids, DMARDs, immunosuppressants, biologicals (IL-1, IL-6) | Variable; 1/3 self-limiting, 1/3 relapsing, 1/3 chronic; overall survival good, complications include MAS | Arthritis/ arthropathy |
| Disease                                                                 | Prevalence                          | Genetics/ pathogenesis                                                                 | Diagnostic criteria                                                                 | Clinical features                                                                 | Laboratory findings                     | Therapy                       | Prognosis/ Complications                       | Classification               |
|------------------------------------------------------------------------|-------------------------------------|----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|------------------------------------------|------------------------------------------|-----------------------------------------------|-----------------------------|
| Progressive pseudorheumatoid arthropathy of childhood (PPAC/ PPD/ PPRD/ SEDT-PA) [104–109] | Maybe not rare, but misdiagnosed as JIA; estimated prevalence < 1/1,000,000 | Autosomal recessive; different mutations in WISP3; possible founder effect in Turkey; WISP mediates cell growth and differentiation in chondrocytes | Clinical and radiographic diagnosis with genetic confirmation                        | Disease onset usually in childhood (age 3–8 years), progressive joint stiffness, contractures, swelling of finger joints, osteopenia, slow linear growth, short stature, osteopenia, arthritis, difficulty in walking, genu valgum, hip pain, adult height usually below 3rd percentile, normal intelligence | No signs of systemic inflammation | Symptomatic: NSAIDs | Chronic, overall prognosis good because systemic organ involvement is absent | Arthritis/ arthropathy          |
| Familial articular chondrocalcinosis (CPPD deposition disease/CCAL1 and CCAL2) [110–114] | Unknown, estimate < 1/1,000,000 | Most cases autosomal dominant with variable penetrance; CCAL2: mutations in ANKH; CCAL1: chromosome 8 suspected, but gene not yet identified; increased extracellular pyrophosphate levels and formation of CPPD | Clinical and radiographic diagnosis                                                   | Disease onset in early childhood with calcium crystal joint deposition; arthritis/arthralgia, most commonly in knee and other big joints | Inflammatory markers may be elevated | Symptomatic: Corticosteroids, colchicine, NSAIDs | Chronic, usually not life-threatening, but high morbidity | Arthritis/ arthropathy          |
| Pigmented villonodular synovitis [25, 115–118]                        | Incidence: 1.8/1,000,000 (USA), estimate < 1/1,000,000 | Unknown; possible association with trauma/surgery, lipometabolism; inflammatory process or benign, tumor-like process suggested | Radiographic or histopathological diagnosis                                           | Peak of disease onset age 20–40 years, pain/swelling of joints (mainly knee or hip, rarely temporomandibular joint) with “locking phenomenon”; fatigue | Elevated ESR and CRP possible | Surgical synovectomy, radiotherapy, immunotherapy | Chronic or remitting-relapsing, locally aggressive and frequent relapses | Arthritis/ arthropathy          |
| Disease | Prevalence | Genetics/pathogenesis | Diagnostic criteria | Clinical features | Laboratory findings | Therapy | Prognosis/Complications | Classification |
|---------|------------|-----------------------|---------------------|-------------------|-------------------|---------|-------------------------|---------------|
| Felty syndrome (splenomegaly-neutropenia-rheumatoid arthritis syndrome) [119–122] | 1% of RA = estimated prevalence 1/10,000 | HLA-DR4 association (78%), autoantibodies against neutrophil extracellular chromatin traps (NETs), anti-GCSF antibodies | Clinical diagnosis | More common in females, chronic symmetric arthritis with severe joint destruction (often knee, wrist ankle, MCP, PIP), hepatosplenomegaly, lymphadenopathy, episcleritis, pleuritis, vasculitis, weight loss | Anemia, neutropenia, infections, ANA, RF | Corticosteroids, DMARDs, biologicals, G-CSF, splenectomy | Chronic, increased mortality due to infections | Arthritis/arthropathy |
| RS3PE (remitting seronegative symmetrical synovitis with pitting edema) [3, 32, 123, 124] | Unknown, prevalence in Japan 0.09% (90/100,000 = 1/1,111) for > 50 years (not rare among elderly), estimate 1/100,000 | Unknown; associated with other rheumatic conditions, infections, and neoplasms (associated malignancy rate 7% in Asia and 31% in Western countries), VEGF may play a role in pathogenesis | Proposed diagnostic criteria by Karmacharya et al. | Usually older males affected, symmetrical synovitis of hands and ankles, sudden onset polyarthritis, pitting edema (especially hands or feet) | Elevated acute phase reactants, usually RF and autoantibodies negative | Usually excellent response to corticosteroids, DMARDs rarely used, treatment of underlying malignancy if present | Good, remission can usually be achieved with corticosteroid use only, poor prognosis if malignancy-associated | Arthritis/arthropathy |
| Multicentric reticulohistiocytosis [37, 125–127] | Unknown, ~ 300 cases in literature, estimate < 1/100,000 | Unknown; different triggers suspected (malignancies, autoimmune diseases, infections/tuberculosis); crucial workup for neoplasms necessary; macrophages, cytokines, and osteoclastic activity seem to play a role in pathogenesis | Histopathological diagnosis | Mainly Caucasian females (3:1) with peak of onset in 4th decade, symmetric erosive polyarthritis or spondylitis with axial involvement (most affected joints: distal interphalangeal joints) with typical papulonodular skin lesions, organ involvement possible (heart, lung), arthritis often precedes skin involvement by years | Elevated ESR, CRP, anemia, hyperlipidemia; different autoantibodies may be positive | NSAIDs, corticosteroids, DMARDs, bisphosphonates, treatment of underlying malignancy if present | Variable, may progress rapidly into arthritis mutilans, but most patients achieve remission spontaneously within 10 years | Arthritis/arthropathy |
| Disease                                                                 | Prevalence                  | Genetics/ pathogenesis                                                                 | Diagnostic criteria                                                                 | Clinical features                                                                 | Laboratory findings                      | Therapy                                      | Prognosis/ Complications                  | Classification                             |
|------------------------------------------------------------------------|----------------------------|----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|-------------------------------------------|---------------------------------------------|--------------------------------------------|--------------------------------------------|
| Chronic non-bacterial osteomyelitis (CNO)/ CRMO/SAPHO                  | Estimated prevalence 40/100,000 | No clear association with HLA-B27, possibly related to other genes connected to autoinflammatory disorders, autoimmune process or infection/molecular mimicry (P. acnes) suspected | Inclusion and exclusion criteria by Benhamou et al., Kahn et al.                     | Slight female preponderance, onset often in children or middle-aged adults; inflammatory, painful, sterile (sometimes P. acnes-positive) osteitis (often in anterior chest wall or axial skeleton) with variety of different skin diseases (most commonly palmoplantar pustulosis), onset can be many years before or after bone and articular involvement (often sacroiliac or sternoclavicular joints) | Elevated CRP and ESR (sometimes), different non-specific autoantibodies, sometimes P. acnes | NSAIDs, corticosteroids, bisphosphonates, antimicrobial treatment, DMARDs, biologicals | Chronic disease, complications or disease-associated death rare | Arthritis/ arthropathy                      |
| Systemic-onset juvenile idiopathic arthritis (Still’s disease)          | Estimated prevalence 10.5/100,000 | Association with MEFV and MIF-173 polymorphism; IL-6 and IL-1 play a major role         | ILAR classification criteria for JIA                                                 | Systemic inflammation (spiking fever > 39 °C, skin rash, hepatosplenomegaly, lymphadenopathy, serositis, arthritis) | High levels of serum ferritin, marked polymorphonuclear leukocytosis, thrombocytosis, elevated ESR/CRP | NSAIDs, corticosteroids, DMARDs, biologicals (IL-1, IL-6) | Variable, chronic, self-limiting or remitting-relapsing, ~50% complete recovery, risk of MAS | Arthritis/ arthropathy                      |
| Whipple’s disease                                                      | Unknown, *Tropheryma whipple* can be found in ~ 10% (Europe)/20% (Africa) of fecal samples in healthy population, estimate < 1/1,000,000 | HLA-B27 involvement discussed; infection with *Tropheryma whipplei*, predominantly male patients and patients with immune modulatory conditions (alcohol, abuse, chronic disease) affected | Histopathological diagnosis or PCR                                                  | Predominantly males affected, intermittent polyarthritis and gastrointestinal symptoms, any other organ can be affected (neurology, cardiovascular, lungs, eyes, skin), fever, weight loss, abdominal pain, malabsorption, headaches, diarrhea | Elevated ESR, CRP, anemia, thrombocytosis, reduced IgM and IgA, leukocytosis, RF, anti-CCP-AB may be present | Antibiotics, corticosteroids, DMARDs, biologicals (IL-1) | Chronic, lethal if untreated, increased mortality in case of neurological involvement or occurrence of immune reconstitution inflammatory syndrome (IRIS; ~ 10%) | Arthritis/ arthropathy                      |
| Disease                                      | Prevalence                                      | Genetics/pathogenesis                                                                 | Diagnostic criteria                  | Clinical features                                                                 | Laboratory findings                     | Therapy                                      | Prognosis/Complications                  | Classification                  |
|----------------------------------------------|-------------------------------------------------|----------------------------------------------------------------------------------------|--------------------------------------|----------------------------------------------------------------------------------|------------------------------------------|---------------------------------------------|------------------------------------------|------------------------------------------|
| Osteochondritis dissecans                   | Incidence 6.09/100,000 Estimated 15–29/100,000 → 22/100,000 | Unknown; osteonecrosis of subchondral bone; vascular disruption, multiple microtrauma, and genetic predisposition suggested | Radiographic diagnosis               | Predominantly in physically active male children or adolescents. Pain (worsening with exercise), swelling, joint locking, most often in the knee, but any joint can be affected | Usually inflammatory markers normal       | Supportive: NSAIDs, surgery                | Chronic, prognosis depends on stability of lesion and patient age | Arthritis/arthropathy                    |
| Blau syndrome (familial)/early onset sarcoidosis (sporadic)/pediatric granulomatous arthritis [9, 153–158] | Unknown, incidence: 0.29/100,000 (Denmark), estimated < 1/1,000,000 | Autosomal dominant, sporadic form, gonosomal mosaicism in NOD2/CARD15; NF-κB activation and excessive inflammatory cytokine production | Clinical diagnosis, genetic testing, skin biopsy | Skin rash in first year of life, later boggy polyarthritis, uveitis, non-caseating epithelioid and giant cell granulomas; fever, lymphadenopathy, neuropathy, renal/hepatic/lung/cardiovascular involvement | Leukocytosis, thrombocytosis, elevated ESR, CRP acute-phase reactants, ACE normal | NSAIDs, corticosteroids, immunosuppressants, biologicals, systemic hypertension usually responds to ACE-inhibitors | Chronic, prognosis depends on systemic involvement, severe ocular and articular morbidity | Autoinflammatory syndrome |
| CAPS (familial cold autoinflammatory syndrome/ familial cold urticaria, Muckle-Wells syndrome, CINCA syndrome/NOMID/IOMID) [38, 39, 159–161] | 1–2/1,000,000 in US and 1–2/360,000 (=4.6/1,000,000) in France estimated → 3.05/1,000,000 | Autosomal dominant, gain of function mutation in NLRP3/CIAS1 leads to caspase-1 and inflammasome activation with increased IL-1β secretion; mosaicism possible, usually de novo | Eurofever clinical diagnostic/classification | Intermittent fever, urticarial rash, chronic inflammation, typical facies in CINCA (frontal bossing, saddle back nose), CNS manifestations, chronic polyarthriti, conjunctivitis, papilledema | Elevation of acute phase reactants, leukocytosis, chronic anemia; SAA biomarker for development of AA-amyloidosis | Biologics (IL-1) | Chronic, prognosis significantly improved since availability of anti-IL-1-treatment (65–85% complete remission with Anakinra) | Autoinflammatory syndrome |
| Disease                                      | Prevalence                                      | Genetics/pathogenesis                                                                 | Diagnostic criteria                                                                 | Clinical features                                                                 | Laboratory findings               | Therapy                                      | Prognosis/Complications                           | Classification                        |
|---------------------------------------------|-------------------------------------------------|---------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|----------------------------------|---------------------------------------------|---------------------------------------------|---------------------------------------------|
| Familial Mediterranean fever (familial paroxysmal polyserositis) [38, 162–166] | Prevalence highly differs geographically; in eastern Mediterranean 1/500 – 1/1000, Turkey 1/150 – 1/10,000, Ashkenazi Jews 1/73,000 Estimate 1/10,000 | Autosomal recessive, mutation in MEFV leading to abnormal function of inflammasome; environmental factors also seem to play a role; as patients from the eastern Mediterranean often have a milder phenotype | Multiple criteria: Eurofever clinical diagnostic/classification criteria, Tel-Hashomer, Yalcinkaya-Ozen and Livneh-criteria | Disease onset usually in childhood, 90% before age of 20 years, recurrent fever and serositis, myalgia, arthralgia, abdominal pain, vomiting, chest pain, rash, prodromal phase with unspecific symptoms (restlessness, anxiety, irritability), rapid onset of symptoms lasting for at least 12 h | Elevated acute phase reactants | Colchicine, anti-IL-1 | Chronic, remission and fewer relapses can be achieved by therapy, complications include amyloidosis (strongest predictor seems to be country of residence) and MAS | Autoinflammatory syndrome                  |
| Mevalonate kinase deficiency (hyperimmunoglobulinemia D with periodic fever, HIDS) [38, 167–170] | Unknown, incidence in Germany: 0.39/1,000,000 estimate < 1/1,000,000 | Autosomal recessive, mutations in MVK (homozygosity or, most often, compound heterozygosity), MVK essential for cholesterol synthesis; increased production of IL-1β; possible founder effect in the Netherlands | Eurofever clinical diagnostic/classification criteria | Recurrent fever episodes starting in infancy (most common before end of 1st year of life), fever lasts 4–6 days and can be provoked by physical and psychological stress, lymphadenopathy, splenomegaly, arthralgia, GI symptoms, skin rash, sometimes oral and vaginal aphthous ulcers, neurological symptoms | Elevated ESR, CRP, leukocytosis, elevated IgD (> 100 IU/mL), IgA in blood, elevated mevalonic acid in urine | HMG-CoA-reductase inhibitors, corticosteroids, immunosuppressants, biologicals (II-1) | Chronic, complications include infections, amyloidosis, peritonitis with abdominal adhesions, MAS, and joint contractions | Autoinflammatory syndrome |
| Disease                                                                 | Prevalence                                                                 | Genetics/pathogenesis                                                                 | Diagnostic criteria                                                                 | Clinical features                                                                 | Laboratory findings                                                                 | Therapy                                      | Prognosis/Complications               | Classification                       |
|------------------------------------------------------------------------|----------------------------------------------------------------------------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------|---------------------------------|----------------------------------|----------------------------------|
| Nakajo-Nishimura syndrome (NNS) [171–173]                             | Unknown, 28 reported cases in Japan until 2010 (19 males, 9 females), estimate < 1/1,000,000 | Autosomal recessive, mutation in PSMB8; probably common founder; reduced proteasome activity and accumulation of ubiquitinated and oxidized proteins, leading to increased cytokine levels | Distinctive clinical diagnostic criteria for NNS                               | Onset usually at age of 2 months—8 years with pernio-like rash, rash often appears in first winter after birth and reappears every year. Symptoms worsen with cold stimuli; periodic high fever, skin rash, myositis, hepatosplenomegaly, partial lipomuscular atrophy, joint contracture (mainly in upper body), hyperhidrosis, short stature, low IQ, lymphadenopathy described; characteristic thin facial appearance, elongated clubbed fingers | Constantly elevated ESR, CRP, chronic anemia, hypergammaglobulinemia, elevated IgG and IgE, positive ANA described | Corticosteroids, kallikrein, dapsone | Chronic and often lethal, most patients die of cardiac or respiratory failure | Autoinflammatory syndrome           |
| PAPA syndrome (pyogenic arthritis-pyoderma gangrenosum acne syndrome) [28, 39, 174–177] | Only few patients from five families worldwide reported (34 until 2006), estimate < 1/1,000,000 | Autosomal dominant, missense mutation in PSTPIP1/CD2BP1, which causes hyperphosphorylation of PSTPIP1 protein and induction of inflammasome | Clinical diagnosis with genetic confirmation                                      | Recurrent sterile arthritis, fever, pustulosis, abdominal pain, hidradenitis, acne, pyoderma gangrenosum, ulcerations | Elevated ESR, CRP, IL-1β | Corticosteroids, biologicals (IL-1β) | Chronic or remitting-relapsing       | Autoinflammatory syndrome           |
| Disease                                      | Prevalence                                                                 | Genetics/pathogenesis                                                                 | Diagnostic criteria                                                                 | Clinical features                                                                 | Laboratory findings                                                                 | Therapy                                                                                      | Prognosis/Complications                                                                 | Classification |
|---------------------------------------------|---------------------------------------------------------------------------|----------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|---------------|
| PFAPA syndrome (periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis; Marshall syndrome with periodic fever) [178–182] | Unknown, incidence 2.3/10,000 in children up to 5 years (Norway), probably not so rare; estimate < 1/10,000 | Unknown; many patients have heterozygous MEFV mutation; familial occurrence; polygenetic cause suspected, IL-1 and vitamin D may play a role in pathogenesis | Diagnostic criteria by Marshall/Thomas; Cantarini et al. | Disease onset usually in early infancy; slight male predominance; episodes last 5 days and recur every 28 days; prodromal: aphthous stomatitis, malaise, fatigue, irritability, headache; then sudden onset of high fever, pharyngitis, lymphadenopathy, chills, cough, headache, abdominal pain, nausea, diarrhea, rash; patients are remarkably healthy between episodes | Leukocytosis and elevated ESR in episodes | Corticosteroids, surgery (tonsillectomy), omeptide, anakinra, colchicine | Good prognosis, self-limited within 4–5 years, normal development | Autoinflammatory syndrome |
| Schnitzler syndrome (chronic urticaria with gammopathy) [183–186] | Unknown, ~ 250 reported patients, mainly from western Europe, estimate < 1/100,000 | Unknown; involvement of IL-1β and IL-6 suspected | Strasbourg diagnostic criteria | Slight female predominance (1.6:1), disease onset in adulthood (mean age 51 years), recurrent urticarial rash (most constant symptom), fever, muscle/bone/joint pain, lymphadenopathy | Monoclonal IgM (rarely IgG) gammopathy, elevated ESR, κ-light chain, leukocytosis | Anakinra (IL-1) rapidly controls symptoms (diagnosis should be reconsidered if ineffective), canakinumab, colchicine, NSAIDs, pefloxacin, hydroxychloroquine | Chronic, spontaneous remission and relapses common, complications include amyloidosis and overt lymphoproliferation | Autoinflammatory syndrome |
| Macrophage activation syndrome [187–192] | Seen in about 10% of patients with systemic onset JIA. Prevalence unknown, estimate < 1/1,000,000 | Excessive activation of T-lymphocytes and macrophages. Possible association with impaired NK cell cytotoxicity due to PRF1 mutation | HLH-2004 diagnostic guidelines/2016 criteria for MAS complicating systemic JIA | Fever, hepatosplenomegaly, cytopenias, coagulopathy, liver dysfunction, neurological symptoms, lymphadenopathy, skin rash, jaundice, edema | Cytopenia, elevated transaminases + ferritin, low NK cell activity, elevates sIL2-R | Corticosteroids, Cyclosporine, Biologicals, IL-1 receptor blockade | Mortality in one retrospective study 8% (higher mortality in adults) | Autoinflammatory syndrome |
Table 2 (continued)

| Disease                                                                 | Prevalence                                                                 | Genetics/pathogenesis                                                                 | Diagnostic criteria                                                                 | Clinical features                                                                 | Laboratory findings                                      | Therapy                                                                 | Prognosis/Complications                                  | Classification                  |
|------------------------------------------------------------------------|----------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------|------------------------------------------------------------------------|-------------------------------------------------------------|---------------------------------|
| Majeed syndrome (chronic recurrent multifocal osteomyelitis) [193–195] | Unknown, only 4 families/14 patients with Middle Eastern origin reported, estimate < 1/1,000,000 | Autosomal recessive, mutation in LPIN2, which plays a role in fat metabolism and, possibly, mitosis | Clinical diagnosis, genetic testing                                                 | Inflammation of bone and skin, resulting in growth disturbances and joint contractures; recurrent high fevers, severe pain; frequently associated with cutaneous inflammatory syndromes (e.g., psoriasis, Sweet syndrome) | Dyserythropoietic anemia with microcytosis, elevated ESR          | Blood transfusions, NSAIDs, corticosteroids, biologicals (IL1 β) | Chronic, osteomyelitis probably life-long, anemia is prominent in childhood | Autoinflammatory syndrome                                    |
| TRAPS (tumor necrosis factor receptor 1 associated periodic syndrome; familial Hibernian fever) [38, 39, 196–198] | Unknown, incidence 1/1,785,714 for children < 16 (Germany); most patients are European Caucasian, estimate 1/1,000,000 | Autosomal dominant with variable penetrance, mutations in TNFRSF1A; different hypotheses on pathophysiology, including intracellular trafficking, receptor shedding, or induction of apoptosis, leading to increase in cytokines; triggers include stress, menstrual cycle, fatigue, infections, exercise, vaccinations | Eurofever clinical diagnostic/classification criteria | Disease onset usually in infancy or childhood, attacks last around 11 days, on average 70 symptomatic days a year with high fever, limb pain, abdominal pain, rash, cervical lymphadenopathy, periorbital edema | Elevated ESR, CRP, leukocytosis, thrombocytosis, anemia, hyperγ-globulinemia; SAA levels correlate with disease activity | NSAIDs, corticosteroids, biologicals (most promising is anti-IL-1) | Often remitting-relapsing, but chronic course possible; complications include amyloidosis and MAS | Autoinflammatory syndrome                                    |
| Necrotizing autoimmune myopathy (anti-HMG-CoA myopathy) [199, 200]    | Unknown, estimate < 1/1,000,000                                            | Unknown; immune-mediated muscle fiber necrosis without inflammation due to statin use, other drugs, malignancies, or connective tissue diseases | Histopathological diagnosis                                                        | Female predominance (73%), myalgia, dysphagia, weight loss, fatigue, ILD, arthralgia, Raynaud’s phenomenon | Anti-SRP antibodies present in 16%, anti-HMGCR antibodies seem to be specific and present in ~ 60% of patients previously exposed to statins; CRP and CK elevated | Statin withdrawal, corticosteroids, DMARDs                | Variable, good prognosis in case of treatable underlying cause, but chronic in most cases | Myositis/myopathy                                           |
| Disease                                                                 | Prevalence                                                                 | Genetics/pathogenesis                                                                 | Diagnostic criteria                                                                 | Clinical features                                                                 | Laboratory findings                                                                 | Therapy                                                                 | Prognosis/Complications                                                                 | Classification                                                                 |
|------------------------------------------------------------------------|---------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Antisynthetase syndrome [201–204]                                      | Unknown, 20–25% of patients diagnosed with PM/DM; prevalence of PM/DM approx. 15/100,000 → 3.4/100,000 | Unknown; antibodies against anti-threonyl-tRNA-synthetase; relationship to exposure to airborne particles discussed | Clinical diagnosis + antibody findings                                               | Females 2–3 times more often affected than males, at presentation often only RA-like arthritis, then inflammatory myopathy, interstitial lung disease, fever, Raynaud’s, Gottron’s papules, mechanic’s hands | Anti-Jo-1, anti-P17/PL12, many other antibodies possibly positive | Corticosteroids, immunosuppressants (rituximab), DMARDs | Chronic, overall survival good but decreased in case of lung involvement | Myositis/myopathy                                                                   |
| Myopathic form of carnitine palmitoyltransferase II (CPT II) deficiency [205, 206] | Unknown, more than 300 published cases, one of the most common disorders of oxidative fatty acid metabolism, prevalence probably higher than suspected, estimate < 1/100,000 | Autosomal recessive, mutation in CPTII; CPT is involved in the transportation of long chain fatty acids in mitochondria; impaired energy metabolism; frequent triggers are physical stress and exposure to cold | Enzyme measurement, genetic testing                                                 | Disease onset in adolescence or adulthood, males more commonly and more severely affected, myalgia, rhabdomyolysis, muscle weakness, pain, lipid accumulation in muscle | Elevated CK, BUN, myoglobinuria, hepatic steatosis | Avoidance of triggers (fasting, prolonged exercise), low fat and high carbohydrate diet, carnitine | Chronic, but good prognosis; rhabdomyolysis can lead to renal failure | Myositis/myopathy                                                                   |
| Dermatomyositis/Polymyositis [207–210]                                 | 10–13/100,000 (Japan) 8.7/100,000 (Norway) 7–10/100,000 (Brazil) → 9.6/100,000 | Unknown; humoral-mediated inflammation in DM, cell-mediated (CD8+ T-cells) in FM, often associated with other autoimmune diseases and malignancies | Histopathological diagnosis                                                         | Predominantly females, myalgia, arthritis, dyspnea, dysphagia, muscle weakness, rash (not in PM), myocarditis, Gottron’s papules | Different myositis-specific autoantibodies can be found: anti-Jo-1, NXP2/MJ antibody, anti-155/140 antibodies, anti-MDA5, MI-2-antibodies | Corticosteroids, immunosuppressants | Variable, most patients improve over time with treatment, prognosis depends on associated diseases (malignancies) | Myositis/myopathy                                                                   |
| Disease                                      | Prevalence                        | Genetics/pathogenesis                                                                 | Diagnostic criteria                                                                 | Clinical features                          | Laboratory findings          | Therapy                              | Prognosis/Complications               | Classification               |
|----------------------------------------------|-----------------------------------|---------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|--------------------------------------------|-----------------------------|--------------------------------------|--------------------------------------|----------------------------------------|
| Inclusion body myositis [31, 211, 212]       | 33/1,000,000 (Norway) 1.7 – 71/1,000,000 (USA) – 3.7/100,000 (Norway) | Hereditary autosomal recessive form with onset in young adults; mutations in GNE (very rare); sporadic form in elderly, associated with HLA-DR3 and MHC variants; genetic, environmental, aging, and immune-mediated factors probably related to pathogenesis | Histopathological diagnosis               | Predominantly males (2:1) and elderly; slowly progressive muscle weakness (often beginning in wrists or quadriceps muscle), dysphagia | CK may be elevated or normal      | Refractory to immune therapy; can be used tentatively in case of relation to other autoimmune diseases | Chronic and slowly progressing, most patients wheelchair-reliant within 10 years | Myositis/myopathy                     |
| Eosinophilia-myalgia syndrome [213]          | Unknown, 5000–10,000 people affected; predominantly females in the US (epidemic in 1989), estimate < 1/1,000,000 | Unknown; consumption of manufactured L-tryptophan or 5-hydroxytryptophan associated with disease onset; increased TGF-β and IL-4 may be responsible for fibrosis | Clinical diagnosis                        | Rapid onset of severe myalgia, cough, fever, fatigue, joint pain, edema; long-term symptoms include eosinophilic fasciitis, alopecia, CNS involvement, myocarditis, arrhythmias, GI involvement | Elevation of eosinophils, WBC       | Supportive treatment, corticosteroids in acute phase may be used tentatively | Chronic course with systemic organ involvement not uncommon | Myositis/myopathy                     |
| Focal myositis [214, 215]                    | Unknown, estimate < 1/1,000,000 | Unknown; trigger factors poorly understood (e.g., physical trauma)                    | Clinical, radiographic, and histopathological diagnosis | Rapidly growing mass in a single muscle, most commonly in lower limbs, usually painless | Usually no elevated acute phase reactants; CK may be elevated but usually normal | No treatment; moderately active lifestyle and ingestion of simple carbohydrates before exercise recommended | Usually self-limited within few weeks or months; relapses possible but uncommon | Myositis/myopathy                     |
| McArdle’s disease (glycogenosis type 5) [216–219] | Estimated 1:50,000 (US) – 1:40,000 (Spain) – 1:4100,000 (Spain) | Autosomal recessive, mutations in PGM, leading to glycogen phosphorylase deficiency | Enzyme measurement, histopathology, genetic testing | High clinical variability, rapid fatigue, myalgia and cramping with exercise and fast recovering with rest (“second-wind phenomenon”) | Elevated baseline CK, myoglobinuria, rhabdomyolysis | No treatment; corticosteroids in case of inflammation or complications | Chronic, but variable in severity; complications include renal failure and cardiovascular diseases | Myositis/myopathy                     |
| Disease                        | Prevalence                                                                 | Genetics/pathogenesis                          | Diagnostic criteria                          | Clinical features                                      | Laboratory findings                          | Therapy                                    | Prognosis/Complications                  | Classification          |
|-------------------------------|----------------------------------------------------------------------------|-----------------------------------------------|---------------------------------------------|-------------------------------------------------------|--------------------------------------------|------------------------------------------|-------------------------------------------|------------------------------------------|
| Tarui disease (GSD7) [220, 221] | Unknown, more than 100 cases described, Common in Ashkenazi-Jews, estimate < 1/1,000,000 | Autosomal recessive, mutations in PFKM, leading to muscle phosphofructokinase deficiency | Histopathological diagnosis, genetic testing | Exercise intolerance, myalgia, cramps, cardiomyopathy  | Myoglobinuria, hemolytic anemia, hyperuricemia, hyperCKemia, reticulocytosis | No treatment; avoid extensive exercise | Chronic; complications include renal and cardiac involvement | Myositis/myopathy |
| Camurati-Engelmann disease (progressive diaphyseal dysplasia) [26, 222, 223] | Unknown, estimate < 1/1,000,000                                          | Autosomal dominant, mutations in TGFβ1, resulting in increased growth factor signaling | Genetic testing, clinical findings + radiographic images | Hyperostosis of long bones and skull, severe limb pain, muscle atrophy, wide-based waddling gait, progressive joint contractures, hearing loss, absence of subcutaneous fat | Increased levels of TGF-β1 | Corticosteroids, NSAIDs, bisphosphonates, all with variable outcomes; experimental: anti-TGFβ (e.g., losartan) | Chronic; patients may become wheelchair-reliant | Bone disorder |
| Fibrodysplasia ossificans progressiva (Munchmeyer’s disease) [224, 225] | 0.36/1,000,000 (Spain) 1.36/1,000,000 (France) estimated worldwide prevalence (literature): 1/2,000,000 → 0.74/1,000,000 | Autosomal dominant (most cases de novo), mutation in ACVR1, leading to enhanced BMP signaling with fibroproliferation, angiogenesis, enchondral ossification; risk seems to be increased with older age of mother and father, fathers often exposed to chemicals | Clinical, radiographic, histopathological diagnosis | Heterotopic ossification, tumor-like swellings and short, malformed great toes (early sign), cervical spine fusions, osteochondroma, hearing loss | Usually normal, although ESR and AF may be elevated | Short-term muscle relaxants, NSAIDs, Cox-2-inhibitors, corticosteroids, bisphosphonates; operations should be avoided (triggers new flare ups and bone growth) | Chronic, progressive, and lethal within approximately 40 years, most patients wheelchair-reliant at the end of second decade of life | Bone disorder |
| Osteomesopyknosis [226]       | Unknown, < 50 cases reported, predominantly from France, estimate < 1/1,000,000 | Autosomal dominant, gene unknown               | Radiographic diagnosis                        | Disease onset and diagnosis usually in adolescence, diffuse back pain | Usually normal | Symptomatic | Benign and good prognosis, normal life expectancy | Bone disorder |
| Disease                  | Prevalence                                      | Genetics/pathogenesis                                                                 | Diagnostic criteria                                                                 | Clinical features                                                                 | Laboratory findings                                      | Therapy                                                                 | Prognosis/Complications                                      | Classification   |
|--------------------------|-------------------------------------------------|---------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|------------------------------------------------------------------------|------------------------------------------------------------------------|------------------------------------------------------------------------|------------------|
| Fabry disease            | Australia 0.85/100,000                           | alpha-galactosidase A deficiency due to mutation in GLA-gene on X-chromosome (X-linked disorder) | Measurement of enzyme activity, genetic testing                                    | Neuropathic pain, hypohidrosis, gastrointestinal symptoms, kidney failure, cardiovascular disease | renal function may be impaired                                       | Enzyme replacement therapy                                           | Chronic. Life expectancy increased with ERT, but limited by cardiovascular and renal function | Bone disorder |
| Farber disease           | Unknown, estimate <1/1,000,000                   | Autosomal-recessive, ASAH1-gene; acid ceramidase deficiency                          | Measurement of enzyme activity; histopathology of granuloma; ceramide accumulation in granuloma | Subcutaneous nodules, joint disease, hoarseness of voice, inflammatory granuloma | Enzyme replacement therapy in progress; Stem cell transplantation       | Enzyme replacement therapy                                           | Chronic and progressive. Death due to respiratory insufficiency caused by pulmonary granulomas | Bone disorder |
| Gaucher’s disease (type 1 in 90% of cases) | Estimated 1–2/100,000 worldwide, 1/850 in Ashkenazi-Jews → 1.5/100,000 | Autosomal recessive, mutations in GBA1; deficiency in lysosomal glucocerebroside leads to accumulation of glucocerebrosid | Measurement of enzyme activity, genetic testing                                    | Age of onset and disease course variable; fatigue, growth retardation, delayed puberty, bone pain, avascular necrosis of bone, gallstones, hepatosplenomegaly, Parkinson’s disease, malignancies (predominantly hematological) | Thrombocytopenia, anemia, monoclonal gammopathy, vitamin D deficiency; biomarkers: chitotriosidase, CCL 18, glucosylsphingosine, ferritine | Lifelong enzyme replacement or substrate reduction therapy | Chronic, reduced life expectancy due to neurological involvement and malignancies | Bone disorder |
| Hypophosphatasia (HP)    | 1/300,000 for severe HP, 1/6370 for moderate HP, Estimate 1/100,000 | Autosomal-recessive or autosomal-dominant; mutations in TNSALP lead to accumulation of pyrophosphate, an inhibitor of mineralization | Laboratory values + radiologic features, confirmed by genetic testing               | Age of onset and disease course very variable; perinatal death, bone deformities, stress fractures, loss of dentition, musculoskeletal pain and weakness | low serum AP, hypercalcemia                                          | Enzyme replacement therapy for pediatric onset hypophosphatasia       | Chronic, mortality and morbidity varies with onset                  | Bone disorder |

Table 2 (continued)
| Disease                          | Prevalence                  | Genetics/pathogenesis                                                                 | Diagnostic criteria                        | Clinical features                                                                 | Laboratory findings | Therapy                                             | Prognosis/Complications                                                                 | Classification   |
|---------------------------------|----------------------------|---------------------------------------------------------------------------------------|---------------------------------------------|-----------------------------------------------------------------------------------|---------------------|-----------------------------------------------------|------------------------------------------------------------------------------------------|------------------|
| Morquio disease                  | 1/323,000 (Denmark)         | Autosomal recessive, mutations in GALNS resulting in N-acetylgalactosamine-6-sul-      | Measurement of enzyme activity, genetic    | Disease onset in childhood; progressive skeletal dysplasia, short trunk dwarfism,   | GAGs in urine       | Enzyme replacement therapy, pain management,       | Chronic, wheelchair-reliance beginning in adolescence, increased mortality due to cervical instability and pulmonary compromise | Bone disorder    |
| (mucopolysaccharidosis type IVa) | 1/599,000 (UK)              | fat sulfatase-deficiency                                                              | testing                                     | spondyloepiphyseal dysplasia with ligamentous laxity, joint pain, preserved        |                     | supportive therapy, surgery                        |                                                                          |                  |
|                                 | 1/1,872,000 (Malaysia)      |                                                                                        |                                             | intelligence, odontoid hypoplasia, pulmonary, cardiac, ophthalmologic, audiologic,  |                     |                                                     |                                                                          |                  |
|                                 | 1/926,000 (Australia)       |                                                                                        |                                             | dental, abdominal and neurologic involvement possible                              |                     |                                                     |                                                                          |                  |
|                                 | → 1.6/1,000,000             |                                                                                        |                                             |                                                                                    |                     |                                                     |                                                                          |                  |
| Melorheostosis                   | ~400 cases reported, estimate 1/1,000,000 | Usually sporadic; somatic LEMD3 mutations suspected as a possible cause; disturbance in bone formation and modeling; possible association with scleroderma and Buschke-Ollendorf syndrome | Radiographic diagnostic criteria (Freyshmidt) | Disease onset in childhood or adolescence; limb deformity, contractures, joint and bone pain, leg length discrepancy, stiffness, hyperostosis (usually long bones in lower extremity) usually in one limb, but may be bilateral, soft tissue involvement (hypertrichosis, fibrosis, erythema) above affected bone | Markers of bone metabolism usually normal (calcium, AP, etc.) | Pain management, bisphosphonates, surgery (relapses common) | Chronic and progressive, morbidity mostly due to pain, stiffness, and reduced range of motion | Bone disorder    |
| (Leri’s disease)                 | [105, 242–244]             |                                                                                        |                                             |                                                                                    |                     |                                                     |                                                                          |                  |

*Table 2 (continued)*
| Disease                                                                 | Prevalence                                                                 | Genetics/pathogenesis                                                                 | Diagnostic criteria                                                                 | Clinical features                                                            | Laboratory findings | Therapy                                                                 | Prognosis/Complications                                           | Classification       |
|------------------------------------------------------------------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|---------------------|-------------------------------------------------------------------------|-------------------------------------------------------------------|---------------------|
| Pachydermoperiostosis (primary hypertrophic osteoarthropathy; Touraine-Solente-Golé syndrome) [23, 24, 245–247] | Unknown, estimate < 1/1,000,000                                            | Autosomal dominant with incomplete penetrance proven, autosomal recessive and X-linked inheritance also suggested, mutations in SLCOA21, HPGD, possibly also related to HLA-B12 or BMP pathway; involvement of testosterone promoting proliferation suspected | Clinical diagnosis                                                                     | Occurs predominantly in males (7:1), disease onset often in puberty, progression for 5–20 years; pachydermia, digital clubbing, periostosis, cranioostearthropathy, congenital heart diseases (especially patent ductus arteriosus), hyperhidrosis, rash, myelofibrosis, gastrointestinal involvement | Unspecific               | NSAI Ds, corticosteroids, colchicine, bisphosphonates, retinoids, plastic surgery | Chronic, progressive for 5–20 years | Bone disorder       |
| Mucopolysaccharidosis type 2 (Hunter syndrome) [248–250]               | 0.65/1,000,000 (Sweden) 0.44/1,000,000 (Norway) 0.91/1,000,000 (Denmark) 0.67/1,000,000 (Denmark) → 0.67/1,000,000 (Denmark) | X-linked recessive, mutation in IDS; lysosomal storage disorder: iduronate-2-sulfatase enzyme deficiency | Measurement of enzyme activity, genetic testing                                      | Disease onset in childhood; peau d’orange, cognitive impairment, joint stiffness, contractures, cardiac and respiratory involvement, short stature, carpal tunnel syndrome, hepatosplenomegaly, glaucoma | GAGs in urine      | Enzyme replacement therapy, supportive treatment, pain management | Chronic, often lethal within 20—30 years (cardiovascular involvement limiting), patients with attenuated form may have normal life expectancy | Bone disorder       |
| Caffey disease (infantile cortical hyperostosis, Caffey-Silverman syndrome, Smyth syndrome) [251–253] | Unknown, estimate < 1/1,000,000                                            | Autosomal dominant, heterogeneous mutation in COL1A1 with incomplete penetrance       | Clinical and radiographic diagnosis with genetic confirmation                        | Fever, swelling of soft tissues, hyperostosis of outer cortical surface in first 5 months of life, unusual irritability | Elevated ESR, AP, thrombocytosis, anemia, increased immunoglobulin | Symptomatic: NSAI Ds | Good, usually self-limiting in early childhood, chronic or remitting-relapsing course possible | Connective tissue disease |
| Disease                     | Prevalence | Genetics/pathogenesis | Diagnostic criteria | Clinical features | Laboratory findings | Therapy | Prognosis/Complications | Classification |
|-----------------------------|------------|-----------------------|---------------------|-------------------|---------------------|---------|-------------------------|----------------|
| Ehlers-Danlos syndrome [254–256] | 1/10,000 – 1/25,000= 7/100,000 | Autosomal dominant or autosomal recessive, mutations in COL5A1/COL5A2/ COL5A3/COL3A1 and other, depending on subtype | Villefranche classification | Depending on subtype: joint hyperlaxity and luxation, easy bruising, arthralgia, vascular aneurysm, muscle hypotonia | Normal coagulation status despite easy bruising | Only symptomatic and supportive treatment | Chronic, worst prognosis in vascular subtype, obstetrical complications common | Connective tissue disease |
| Fibrosing mediastinitis [257–259] | Unknown, estimate <1/1,000,000 | Most cases idiopathic, or due to infections (histoplasma, aspergillus) or sarcoidosis; proliferation of fibrous tissue, possibly IgG4-related | Radiographic diagnosis | Often younger people affected; cough, hemoptysis, dyspnea, other symptoms depend on grade of obstruction of surrounding structures | Usually normal | Corticosteroids, local therapies, surgery | Variable, often chronic and progressive, potentially lethal because of invading/displacing growth | Connective tissue disease |
| IgG4-related Disease [260–263] | 6/100,000 (Japan) | Immune mediated, multiple possible risk factors | ACR/EULAR Classification Criteria | Elderly men primarily affected; any organ involvement possible, most often gastrointestinal organs or salivary glands, leading to fibrosis and subsequent organ dysfunction | Serum IgG4 may be elevated | Corticosteroids | Chronic, remitting-relapsing. Usually mild symptoms, only slowly progressing | Connective tissue disease |
| Marfan syndrome [264–266] | 6.5/100,000 (genetically proven patients in Denmark) | Autosomal dominant, mutation in FBN1, resulting in disturbed fibrillin 1 function and altered TGF β regulation, large phenotypic variability | Revised Ghent criteria | Tall stature, joint hypermobility, arachnodactyly, aortic aneurysm, mitral valve prolapse, ectopia lentis, scoliosis, dural ectasia | Usually normal | β–blockers, cardiac and/or orthopedic surgery | Chronic, mortality depends on cardiovascular involvement, life expectancy normal with regular follow-up and treatment | Connective tissue disease |
Table 2 (continued)

| Disease                              | Prevalence                                      | Genetics/pathogenesis                                                                 | Diagnostic criteria                                                                 | Clinical features                                                                                   | Laboratory findings                                                                 | Therapy                                             | Prognosis/Complications                                      | Classification                  |
|--------------------------------------|-------------------------------------------------|----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------|-----------------------------------------------------------------|-----------------------------|
| Shulman disease (eosinophilic fasciitis) [267, 268] | Unknown, estimate < 1/1,000,000                  | Association with HLA-A2 described, many different theories on pathogenesis and possible triggers (e.g., physical exercise) exist | Proposed diagnostic criteria by Pinal-Fernandez et al.                               | Disease onset at any age (mean 4th-5th decade); abrupt onset of painful swelling and thickening of skin and other soft tissues, joint contractures, most often extremities symmetrical involved | Blood eosinophilia, hypergammaglobulinemia, elevated ESR, TIMP-1 possibly marker for disease activity | Corticosteroids, MTX; not all patients require treatment            | Variable, remission usually occurs spontaneously or with therapy | Connective tissue disease                                      |
| Sharp syndrome (mixed connective tissue disease) [269-271] | 3.8/100,000                                     | Unknown, B cells may play a role in pathogenesis                                       | Different diagnostic criteria exist (Sharp’s, Alarcón-Segovia and Villareal, Kasukawa) |                                                                                                     | Anti-ribonucleoprotein antibodies (anti-U1RNP)                                          | NSAIDs, corticosteroids, immunosuppressants                            | Chronic and progressive, may evolve into other connective tissue disease, mortality increased with cardiovascular involvement | Connective tissue disease                                      |
| Systemic sclerosis [30, 44, 45, 272-275] | More common in Europe than Asia, less common in northern countries, highest ever reported prevalence in population of Choctaw Indians in Oklahoma (469/100,000), worldwide → 15–30/100,000 (= 22.5) | Unknown, HLA-association suspected; different pathophysiological factors suspected (vasculopathy, autoimmuneles, fibroblast dysfunction, immune system alteration, silica dust, toxins, infections) | ACR criteria                                                                           | Female predominance (3:1), peak incidence at age 45 – 64 years; skin thickening, Raynaud’s phenomenon, pulmonary fibrosis, PAH, digital ulcers, esophageal hypomobility, arthralgia, myalgia, variable organ involvement | Anti-centromere-AB, anti-topoisomerase-I-AB (Sc70), anti-RNA-polymerase III | Symptomatic and supportive treatment of Raynaud’s phenomenon, digital ulcers, skin, lung, and GI disease | Chronic and progressive, worst prognosis among all connective tissue diseases, mean survival 11–12 years after diagnosis | Connective tissue disease                                      |
| Disease                                                                 | Prevalence                                           | Genetics/ pathogenesis | Diagnostic criteria                                                                 | Clinical features                                                                 | Laboratory findings | Therapy                                                                 | Prognosis/ Complications                                                                 | Classification                  |
|------------------------------------------------------------------------|------------------------------------------------------|------------------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|---------------------|-------------------------------------------------------------------------|------------------------------------------------------------------------------------------|---------------------------------|
| CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal nevi syndrome) [276–279] | Unknown, only a few cases reported, estimate < 1/1,000,000 | Mosaic activating, postzygotic mutation in PIK3CA, causing tissue overgrowth | Clinical diagnostic criteria for PIK3CA-related overgrowth spectrum (Keppler-Noreuil et al., genetic testing) | Vascular malformations, thoracic lipomatous hypertrophy, asymmetric growth, visceral and neurological disorders, linear epidermal nevus, gigantism of hand and feet, macrodactyly, sandal gap toe, renal anomalies | Normal | Clinical trials with mTOR kinase-inhibitors and selective PIK3CA-inhibitors, laser, sclerosing, or surgical treatment | Chronic, severity depends on somatic mosaic, frequent recurrence of lipomatous masses, increased risk of tumors (e.g., Wilms tumor) | Overgrowth syndrome |
| Klippel-Trénaunay-Weber syndrome complex (angio-osteohypertrophic syndrome = Klippel-Trenaunay, special form with AV fistulas = Parkes-Weber syndrome) [280–283] | Unknown, ~ 1000 reported cases in literature, estimated incidence 1/100,000 estimate < 1/1,000,000 | Unknown, multiple different inheritance modes suspected; current candidate genes: VEGF, PIK3CA, AGGF1, INGS, HDAC9; congenital defects in spinal cord, vessels, and mesodermal tissues suspected | Clinical and radiographic diagnosis | Cutaneous capillary malformations (portwine stain), varicous veins, hypertrophy of bone and soft tissue (often resulting in different limb lengths), usually isolated to one extremity (most commonly leg), pain, edema, pruritus; in Parkes-Weber syndrome + AV fistulas | Normal | Symptomatic: compression stockings, laser surgery, treatment of infections, thromboembolic events | Chronic, but rarely cause of death, higher mortality in Parkes-Weber syndrome because of AV fistulas; complications include coagulopathy and thromboembolic events | Overgrowth syndrome |
| Disease                      | Prevalence                                                                 | Genetics/pathogenesis                                                                 | Diagnostic criteria                                                                 | Clinical features                                                                 | Laboratory findings                                    | Therapy                                                                                             | Prognosis/Complications                             | Classification                        |
|------------------------------|----------------------------------------------------------------------------|---------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|--------------------------------------------------------|-----------------------------------------------------------------------------------------------------|------------------------------------------------------|------------------------------------------|
| Proteus syndrome             | Unknown, possibly over-/under-diagnosed because of similarities to other overgrowth spectrum disorders, incidence estimated 1/1,000,000 estimate < 1/1,000,000 | Somatic mosaic activating AKT1 mutation, increased growth in affected cells           | Revised diagnostic criteria (Turner et al., Cohen), genetic testing of affected tissue | Males more commonly affected than females (2:1); overgrowth of different tissues: cerebriform connective tissue nevus, vascular malformations, deep vein thromboses, dysregulated adipose tissue (lipomas), pulmonary abnormalities, asymmetric and disproportionate overgrowth, tumors, facial phenotype, intellectual impairment, seizures | Coagulopathy and DVT possible                     | Supportive: antithrombotic prophylaxis, orthopedic surgeries, psychological support                   | Chronic, premature death in 20% due to respiratory or neurological involvement | Overgrowth syndrome                              |
| Erdheim-Chester disease      | Unknown, ~ 600 reported cases, estimate < 1/1,000,000                     | In more than 50% BRAF-mutations, non-Langerhans cell-histiocytosis with hyperactivation of cytokines | Radiographic and histopathological diagnosis, genetic testing                        | Predominantly males in 5th-7th decade of life; bone involvement nearly always present, CNS involvement (diabetes insipidus, visual disturbances, pyramidal/extra-pyramidal syndromes), other organ involvement possible (cardiac/lung/retroperitoneal/cutaneous, etc.) | Elevated ESR, AP, or CRP, signs of pituitary insufficiency | Interferon, corticosteroids, immunosuppressants, biologicals (TNF, IL-1), BRAF-inhibitors       | Chronic and often lethal, 5-year survival < 70% | Other                                    |
| Disease | Prevalence | Genetics/pathogenesis | Diagnostic criteria | Clinical features | Laboratory findings | Therapy | Prognosis/Complications | Classification |
|---------|------------|-----------------------|--------------------|------------------|--------------------|---------|------------------------|----------------|
| Hyaline fibromatous syndrome (infantile systemic hyalinosis/juvenile hyaline fibromatosis) | Unknown, ~ 150 cases reported (predominantly from Middle East), estimated < 1/1,000,000 | Autosomal recessive, mutations in CMG2/ANTXR2 gene, CMG2 is a transmembrane protein that plays a role in capillary morphogenesis (also binds anthrax toxins); higher carrier frequency in Middle Eastern populations suspected | Demonstration of hyaline deposition in dermis, genetic testing | Subcutaneous skin nodules, gingival hypertrophy, joint contractures, hyaline deposition, osteopenia, infections, protein-losing enteropathy; cognitive development normal | No specific findings depending on complications (e.g., diarrhea) | Symptomatic: surgery, D-penicillamine, physiotherapy, NSAIDs, nutritional therapy | Chronic, variable course, but often lethal within first 2 years of life (infantile form), oldest known patient is 58 years old | Other |
| Sweet syndrome (SS, acute febrile neutrophilic dermatosis) | Unknown, estimated < 1/1,000,000 | Unknown; classic SS (idiopathic), malignancy-associated, and drug-induced histiocytoid SS; commonly related to inflammatory bowel diseases (especially females with Crohn’s disease) | Classic SS: diagnostic criteria by Su and Liu (modified by van den Driesch); drug-induced SS: diagnostic criteria by Walker and Cohen | Slight female predominance, abrupt onset of fever, peripheral neutrophilia, tender erythematous skin lesions, diffuse neutrophilic dermal infiltrate; arthralgia, malaise, headaches, myalgia | Leukocytosis, elevated ESR, CRP | Corticosteroids, potassium iodide, colchicine, immunosuppressants in relapsing cases, treatment of underlying cause if found | Spontaneous or therapy-induced remission, relapses more common in malignancy-associated SS | Other |
| Relapsing polychondritis | 2/100,000 (Hungary) estimated prevalence in literature: 4.5/1,000,000 → 1.2/100,000 | Association with HLA-DR4, 30% of all patients have associated autoimmune or hematological disease (MDS); vasculitis of all sized vessels occurs | Michet’s criteria, McAdams’ criteria, Damiani and Levine criteria | Typically onset in middle-aged adults; recurrent inflammation of cartilage, especially ears, nose, respiratory tract; vasculitis of all sized vessels, aortic or mitral valve disease, joints, eyes and skin possible | Elevated CRP, ANCA may be positive | NSAIDs, corticosteroids, dapsone, colchicine, immunosuppressants, biologicals | Chronic, survival rate variable, but recent studies report good survival rates | Other |
| Disease | Prevalence | Genetics/ pathogenesis | Diagnostic criteria | Clinical features | Laboratory findings | Therapy | Prognosis/ Complications | Classification |
|---------|------------|------------------------|---------------------|-------------------|---------------------|---------|------------------------|----------------|
| Cogan syndrome [307–309] | Unknown, over 250 cases reported, estimate < 1/1,000,000 | Unknown, autoimmune process suggested (additional autoimmune disease diagnosed in ~ 10% of patients), association with cigarette smoking suspected | Clinical diagnostic criteria for typical and atypical Cogan syndrome | Non-syphilitic interstitial keratitis (or other ocular symptoms, then called atypical Cogan), vestibulo-auditory symptoms, fever, weight loss, arthromyalgia, headache | Anemia, leukocytosis, thrombocytosis, elevated ESR or CRP possible | Corticosteroids, DMARDs, immunosuppressants, biologicals; vestibulo-auditory symptoms often unresponsive to treatment | Chronic or remitting-relapsing, complications include persistent hearing loss and cardiovascular involvement with increased mortality | Other |
| Weber-Christian panniculitis (relapsing febrile nodular nonsuppurative panniculitis; idiopathic lobular panniculitis) [310–313] | Unknown, only a few cases reported, estimate < 1/1,000,000 | Unknown, inflammation and necrosis of subcutaneous adipose tissue, mechanism unclear, probably autoimmune | Histopathological diagnosis | Predominantly middle-aged females affected, recurrent subcutaneous inflammatory painful nodules, fever, malaise, arthralgia, hepatosplenomegaly, anorexia, weight loss, ocular inflammation, lung nodules, systemic organ involvement possible | Elevated ESR, anemia, leukocytosis or leucopenia, hypocomplementemia | Corticosteroids, immunosuppressants, biologicals | Chronic, prognosis variable, poor in case of systemic organ involvement | Other |
| Systemic mastocytosis (mast cell disease) [314–318] | 9.59/100,000 (Denmark, including all systemic subtypes) | Somatic gain of function mutation in KIT, KIT is a tyrosine kinase receptor essential for correct mast cell development and function | WHO diagnostic criteria | Abnormal proliferation and accumulation of mast cells cause urticaria pigmentosa, flushing, urticaria, GI symptoms, musculoskeletal pain, headaches, anaphylaxis, weight loss, osteoporosis | Anemia, thrombocytopenia, leukocytosis, eosinophilia, elevated tryptase, unc acid, LDH, bilirubin, ferritin, hypoalbuminemia | Imatinib, symptomatic treatment, interferon-α, corticosteroids, 2-chlorodeoxyadenosine | Chronic, variable progression, may evolve into leukemia | Other |
| Disease | Prevalence | Genetics/pathogenesis | Diagnostic criteria | Clinical features | Laboratory findings | Therapy | Prognosis/Complications | Classification |
|---------|------------|-----------------------|---------------------|-------------------|-------------------|---------|------------------------|----------------|
| Sarcoidosis (Boeck’s sarcoid) [319–321] | 11.16/100,000 (Northern Ireland) 28.13/100,000 (Ireland) → 19.6/100,000 | Associated with different HLA subtypes and BTNL-2, inhaled antigens are considered a possible trigger | Clinical and histopathological diagnosis | Females more often and more severely affected, peak onset in second decade, many patients are asymptomatic or have unspecific symptoms, such as fever, fatigue, weight loss, most commonly affected organ: lung | Elevated acute phase reactants, ACE, s-IL2R | Corticosteroids, immunosuppressants, biologicals | Variable, often self-limiting within 24 months, increased mortality with systemic organ involvement | Other |
Competing interests
The authors declare that they have no competing interests.

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