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Diagnosis, management, and monitoring of interleukin-1 mediated diseases in Central and Eastern Europe: real-world data

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Abstract

Background Global healthcare disparities, stemming from organizational differences in healthcare systems, lead to variable availability and funding, resulting in a gap between recommended and implemented practices for interleukin (IL)-1-mediated autoinflammatory diseases. We aimed to assess diagnostic, treatment and follow-up options for these diseases in Central and Eastern European countries, comparing them with the 2021 recommendations of the European Alliance of Associations for Rheumatology (EULAR)/American College of Rheumatology (ACR).

Methods In 2023, a structured collaborative effort was organized with representatives from 10 Central and Eastern European countries to address autoinflammatory diseases. The discussion focused on potential strategies to achieve the goals mentioned above.

Results Almost all the participating countries have specialized centers for the diagnosis and treatment of autoinflammatory diseases and the care is provided either by rheumatologists and/or clinical immunologists. Genetic testing is available in all countries, but there is variation in the types of tests offered. Massive parallel sequencing panels for autoinflammatory diseases are available in all countries, with waiting periods for results ranging from 3 to 6 months in most cases. The availability of disease-specific laboratory assessments, such as S100 proteins, is limited. IL-1 inhibitors are available in all countries, but there are differences in practices regarding the licensing and reimbursement of anakinra and canakinumab based on specific indications or diagnoses. The age at which the transition process begins varies, but in most countries, it typically starts around the age of 18 or beyond and in majority of the participating countries there is no structured transition program.

Conclusions Adherence to the 2021 EULAR/ACR recommendations for IL-1-mediated autoinflammatory diseases is achievable in Central and Eastern European countries. Determining the prevalence and incidence of these diseases in this region remains a persistent challenge for future research efforts, with the overarching goal of identifying new patients with autoinflammatory diseases.

Keywords Autoinflammatory diseases, Interleukin-1 mediated diseases, Diagnosis, Treatment, Monitoring, Patient-reported outcomes, Transition

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Background

Autoinflammatory diseases represent a categorized set of conditions marked by excessive and inappropriate (dysregulated) activation of the innate immune system [1]. Most of these diseases fall under the umbrella of IL-1-mediated conditions; however, other types of mechanism have also been described and characterized [2]. In the dynamic landscape of these rare diseases, there is a pressing need to standardize care to align with the latest insights into diagnosis, treatment, and follow-up on a global scale. To address these considerations, a task force was assembled with the mandate of forming standardized guidelines for the diagnosis, treatment and long-term monitoring of people struggling with these diseases, with the overarching objective of improving quality of life and disease outcomes worldwide [3].

It is acknowledged that the availability of healthcare and allocated funds vary across different regions of the world, shaped by organizational differences in health systems between countries. These variations manifest themselves in various approaches to the diagnosis, treatment and monitoring of patients with IL-1-mediated autoinflammatory diseases worldwide. Consequently, there is a gap between recommended practices and current clinical implementation. Our objective was to explore the diagnostic, treatment, and follow-up possibilities for patients with these diseases in Central and Eastern European countries, comparing them against the recently endorsed 2021 European Alliance of Associations for Rheumatology (EULAR)/American College of Rheumatology (ACR) recommendations that aim to steer the diagnostic evaluation, treatment, and monitoring of patients with IL-1-mediated autoinflammatory diseases, that is, cryopyrin-associated periodic syndromes (CAPS), tumor necrosis factor receptor-associated periodic syndrome (TRAPS), mevalonate kinase deficiency (MKD) and deficiency of the IL-1 receptor antagonist (DIRA). In our deliberations, we also considered familial Mediterranean fever (FMF), which is the most prevalent disease mediated by IL-1, considering the recommendations published in 2016 [4].

Methods

Under the auspices of the European Society for Pediatric Rheumatology (PReS) and the European Reference Network for Rare Immunodeficiency, Autoinflammatory, and Autoimmune Diseases (ERN-RITA), a collaborative effort was initiated, involving representatives from 10 Central and Eastern European countries: Croatia, Czech Republic, Hungary, Latvia, Lithuania, Poland, Romania, Serbia, Slovakia, and Slovenia. Among the participating centers, four are full members of ERN-RITA (located in Croatia, the Czech Republic, Hungary, and Slovenia), and two are affiliated partners (Latvia, Lithuania). Among the participating centers, four are full members of ERN-RITA (located in Croatia, the Czech Republic, Hungary, and Slovenia), and two are affiliated partners (Latvia, Lithuania). Representatives from centers in Central and Eastern Europe specializing in autoinflammatory diseases, that are part of the ERN-RITA network—or, where no such centers exist, from centers that diagnose and treat these patients—were selected for a structured discussion aimed at capturing current clinical practices in diagnosing, treating, and monitoring patients with IL-1-mediated diseases. Following the discussion, they participated in a survey. The questionnaire was developed through expert consensus discussions, based on the 2021 EULAR/ACR recommendations [3]. The recommendations were reformulated into questions to assess the extent to which they are followed in everyday clinical practice and to identify gaps between guidelines and real-world implementation. The questionnaire was designed in a semi-structured format and is included in the supplement. In alignment with the 2021 EULAR/ACR recommendations [3], the questionnaire's inquiries were categorized into six groups: overarching principles, diagnosis, treatment, monitoring, patient-reported outcomes, and transition. Information collected through the questionnaire was analyzed and subsequently presented using descriptive statistics.

Results

A summary of the key findings is presented in Table 1.

Overarching principles

Within the overarching principles, the 2021 EULAR/ACR recommendations advocate for the formation of multidisciplinary teams responsible for the diagnosis, treatment and long-term management [3]. Therefore, we investigated the presence of specialized centers in Central and Eastern European countries dedicated to diagnosing and treating autoinflammatory diseases, particularly those with experience in the management of patients with complex, atypical, rare, and severe autoinflammatory conditions. Additionally, we explored the availability of an expert panel that could provide assistance in both diagnosis and treatment. Except for Latvia and Lithuania, in all countries inspected there are specialized centers for diagnosing and treating auto-inflammatory diseases with multidisciplinary teams that take care of patients with autoinflammatory conditions. In all countries, there is the option to reach panels, available within hospitals, as well as national and international expert groups specializing in autoinflammatory diseases.

Table 1 Overview of the critical aspects related to the diagnosis and monitoring of IL-1-mediated autoinflammatory diseases in Central and Eastern European countries

Country	Expert centers	Number of recognized expert centers*	MPS panels	Waiting time for MPS panel results	S100 proteins	Waiting time for the first visit	Patient-reported outcomes	Organized transition
Croatia	Yes	1	Yes	3–6 months	Yes	0–1 month	PGA PPGA	Yes
Czech Republic	Yes	1	Yes	3–12 months	Yes	1–3 months	AIDAI, QoL	No
Hungary	Yes	1	Yes	1–3 months	Yes	1–3 months	AIDAI ADDI PGA PPGA QoL Missing school days	No
Latvia	No	0	Yes	1–3 months	Yes	1–3 months	AIDAI ADDI PGA PPGA QoL	Yes
Lithuania	No	0	Yes	3–6 months	No	0–1 month	AIDAI PGA PPGA QoL Missing school days	No
Poland	Yes	1	Yes	6–12 months	Yes	0–1 month	AIDAI ADDI QoL Missing school days	No
Romania	Yes	0	Yes	1–3 months	No	1–3 months	AIDAI PGA PPGA QoL	Yes
Serbia	Yes	0	Yes	3–6 months	No	0–1 month	AIDAI ADDI PGA PPGA	Yes
Slovakia	Yes	0	Yes	3–6 months	Yes	0–1 month	AIDAI QoL Missing school days	Yes
Slovenia	Yes	1	Yes	1–3 months	No	1–3 months	PGA PPGA	No

ADAI autoinflammatory diseases activity index, *AIDAI* autoinflammatory diseases damage index, *MPS* massive parallel sequencing, *PGA* global assessment scales for physicians, *PPGA* global assessment scales for patients/parents, *QoL* health-related quality of life, *SAA* serum amyloid A protein. *Note: To ensure a uniform definition and avoid varying interpretations, recognized expert centers are defined as full members of European Reference Network for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases (ERN-RITA) specializing in the field of autoinflammatory diseases

Diagnosis

The most significant variations among Central and Eastern European countries are evident in the diagnostic capabilities available. All participating countries have the possibility of genetic diagnostics, although there are considerable differences in the types of tests that are available.

According to the 2021 EULAR/ACR recommendations, if accessible, the next-generation sequencing (NGS) platform should be used for genetic testing to establish a genetic diagnosis [3]. NGS panels (referred to as massive parallel sequencing panels for autoinflammatory diseases) are available in all participating countries. In all of these countries, massive parallel sequencing panels cover not only monogenic autoinflammatory diseases, but also primary immunodeficiencies, disorders of immune regulation, and various other conditions. Serbia does not have access to the whole exome sequencing (WES), and in Romania access is limited, whereas all other countries do have this capability. However, whole genome

sequencing is accessible in a restricted number of countries, specifically Slovakia, Slovenia, Hungary, and Romania. Sanger sequencing is not an option for diagnosing autoinflammatory diseases in Croatia, Serbia, and Latvia. In most countries, the waiting period for massive parallel sequencing panel results ranges from 3 to 6 months. Unfortunately, the results are not available in any country in less than a month. The expenses of genetic analysis are covered by public health insurance in most countries, including Poland, Czech Republic, Slovakia, Croatia, Slovenia, Serbia, Hungary, Latvia and Lithuania. An exception is noted in Romania, where patients and foundations mostly cover the expenses for genetic analysis. Currently, public health insurance can cover genetic analysis for a limited number of patients and with a much longer waiting time (up to 12 months). Additionally, under specific conditions in Poland and Hungary, patients are responsible for covering the costs of testing.

There is an even greater difference in the availability of disease-specific laboratory tests. According to the 2021 EULAR/ACR recommendations, the clinical examination of systemic inflammation should encompass C-reactive protein, erythrocyte sedimentation rate, and complete blood count with differential count [3]. If accessible, the evaluation of the serum amyloid A protein (SAA) and S100 proteins is also recommended [3]. Nowadays, the assessment of circulating calprotectin can be conducted using high-throughput clinical chemistry platforms, delivering swift and cost-effective results for healthcare practitioners. However, measuring serum calprotectin (S100 A8/A9) as part of routine clinical practice is feasible in only a limited number of countries. The status with respect to SAA is significantly more favorable, as it can be measured regularly in all countries except Croatia. Urinary mevalonic acid levels can be assessed in all countries except Romania. The determination of mevalonate kinase enzyme activity and measurement of IL-1 in serum is not possible in any of the countries analyzed in Central and Eastern Europe, while the measurement of IL-18 is possible in Poland from January 2024.

Treatment

IL-1 blocking therapy has become the preferred treatment and the introduction of a therapeutic trial with IL-1 blocking treatment is considered when there is a strong clinical suspicion of a diagnosis involving CAPS, TRAPS, MKD, or DIRA [3]. Regarding FMF, the initiation of colchicine treatment should begin immediately after a clinical diagnosis [4]. Patients who are adherent but do not respond to the maximum tolerated dose of colchicine can be classified as non-responders, warranting consideration of alternative biological treatments for these individuals. Anakinra and canakinumab are approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Both drugs are accessible to treat the diseases mentioned in all Central and Eastern European countries, except Latvia, where canakinumab is not available. Rilonacept, only approved by the FDA, is not available in any European country.

However, there exists a disparity among individual countries in their practices in licensing and reimbursement for anakinra and canakinumab based on specific indications or diagnoses. Anakinra is licensed and/or covered by health insurance or the state for treating FMF, CAPS, and TRAPS in all surveyed countries except Serbia. Canakinumab is licensed and/or reimbursed for these conditions in all countries except Lithuania, where it is available but not reimbursed, and Latvia, where it is not available. In addition, in some countries, the expenses for this treatment are not covered by health insurance.

Follow-up specificities

Although monitoring patients more than twice a year is feasible in all countries, there is a substantial disparity in the waiting time for the initial examination. In half of the countries surveyed, the waiting period is within one month, while in the others, it ranges from one to three months.

Patient-reported outcomes

In addition to objective laboratory measurements, patient-reported outcomes and disease assessment tools can prove valuable in monitoring disease symptoms. Patient- or physician-reported outcomes may encompass evaluations of health-related quality of life (QoL) [5], disease activity (such as the autoinflammatory diseases activity index [AIDAI] for CAPS, TRAPS, and MKD) [6], global assessment scales for physicians and patients/parents (PGA, PPGA) [7], and the evaluation of disease-related organ damage (such as the autoinflammatory disease damage index [ADDI]) [8]. Questions related to performance at school and on the job, as well as recording missed school/work days, contribute to the evaluation of the burden of the disease and inform adjustments to the treatment plan.

The Czech Republic, Croatia and Slovenia distinguish themselves from other countries by employing the least number of patient-reported outcomes and disease assessment tools in their routine practice. Conversely, in Hungary, all the aforementioned tools are employed.

Transition

According to the 2021 EULAR/ACR recommendations, long-term monitoring objectives must prioritize

the implementation of a transition program for adolescents to transition to adult specialist care [3]. However, the data indicate that there is no structured transition program for patients with IL-1-mediated autoinflammatory diseases in half of the countries surveyed. The age at which the transition process begins varies, but in the majority of countries, it typically begins later, around the age of 18 years or beyond. This is the situation in Poland, Czech Republic, Croatia, Slovenia, Latvia, and Lithuania. In Slovakia, the transition process begins around the age of 15, while in Serbia and Romania it begins at approximately 16 years of age. In Hungary, the transition process begins with the first visit.

In Slovakia, Croatia, Serbia, and Romania, the responsibility for the care of patients with autoinflammatory diseases transitioning into adulthood falls under the purview of adult rheumatologists and immunologists, or rheumatologists in Lithuania, or immunologists in Poland, and rheumatologists, immunologists, internists, and general practitioners in Latvia. Consequently, pediatricians no longer have the option to treat and monitor these patients. Only in the Czech Republic, Slovenia and Hungary is there the option for pediatricians to continue monitoring their patients with autoinflammatory diseases as they transition into adulthood. In Slovakia, in the case of rheumatologists a transition process should be completed by reaching the age of 19 years (if the patient is in the care of immunologists, he can continue under the care in adulthood without the transition).

Difference between centers within the ERN-RITA network and centers outside the ERN-RITA network

Differences between centers within and outside the ERN-RITA network are minimal. In countries with ERN-RITA centers, the main advantage is greater access to disease-specific laboratory tests. However, medication availability is determined by national regulations rather than ERN-RITA affiliation.

Discussion

Central and Eastern European countries have experienced significant social and economic changes, bringing their economies and societies closer aligned with the standards of Western and Northern Europe. These reforms, leading to the social and economic convergence of the Central and Eastern European region with the rest of the European Union, were not without challenges. They entailed notable social costs, including widespread emigration from the region, inadequate social safety nets, and limited support for the elderly and disadvantaged [9, 10]. Financial development in Central and Eastern European countries has witnessed significant advancements and variations throughout the region. Three decades after the downfall of communism, Central and Eastern European countries are still grappling with the challenge of securing ample public resources for healthcare and striving to reach the level of Western European countries in achieving universal health coverage. This involves providing equal access to essential healthcare without imposing financial hardship on patients [11, 12].

Given these circumstances, we ponder how these countries handle the challenges associated with autoinflammatory diseases, a group of relatively newly defined conditions that often involve high costs in terms of diagnosis and treatment. Our goal was to investigate the diagnostic, treatment, and follow-up options for patients with the most prevalent subset of these diseases—specifically, IL-1 mediated autoinflammatory diseases—in Central and Eastern European countries. This involved a comparison with the recently approved 2021 EULAR/ACR recommendations [3].

Following our research, we observed that in all examined countries, patients undergo diagnosis, treatment, and follow-up in accordance with the 2021 EULAR/ACR recommendations.

Considering the financial challenges facing healthcare systems in many of these countries, it is in fact surprising that genetic diagnostics for autoinflammatory diseases are accessible in all the mentioned countries. Furthermore, the costs are covered by public health insurance in most of them. However, it should be noted that the waiting period for the results of genetic analyzes is somewhat extended, typically up to 6 months.

In contrast to genetic analyzes, availability of inflammatory biomarkers is restricted in central and Eastern Europe. Traditionally, assessments of systemic inflammation have been based on historical measures such as CRP, ESR, and, when available, SAA. In certain research contexts, some investigators have used S100 proteins as sensitive markers [13]. SAA is commonly used in clinical practice in these countries, while serum S100 proteins are rarely accessible.

A significant challenge in daily clinical practice is the limited availability of disease-specific tests. Genetic analysis results often take a long time, and each newly identified de novo variant requires molecular confirmation to establish a causal relationship between genotype and phenotype [14]. With the increasing number of sequencing studies, the number of variants requiring functional validation continues to grow, making it impractical to test all of them due to the high costs and the limited availability of specialized laboratories. To address this challenge, it is crucial to encourage the formation of consortia, such

as the Clinical Genome Resource, which includes the Monogenic Autoinflammatory Diseases Gene Curation Expert Panel, to systematically evaluate the validity of genes implicated in autoinflammatory diseases [15].

The predominant treatment approach for patients with FMF, CAPS, TRAPS, MKD, and DIRA involves subcutaneous IL-1-targeted biologic therapy, provided it is available [3]. Access to these drugs exhibits substantial variations among different countries around the world. Concerning IL-1 inhibitors, it is worth mentioning that anakinra is accessible in all participating Central and Eastern European countries. Except for Latvia, the same applies to canakinumab. This placed these countries alongside Western European nations. However, for extremely rare IL-1-mediated autoinflammatory diseases such as DIRA, there is an issue of financing the expenses associated with IL-1 inhibitors, despite their availability. To improve the accessibility of IL-1 inhibitors for various indications, particularly in the context of rare diseases, it is essential to involve patients in clinical trials. However, it should be noted that the availability of such trials in Central and Eastern European countries is comparatively restricted compared to Western European nations and the United States.

Monitoring IL-1-mediated autoinflammatory diseases is essential to prevent complications from unchecked inflammation and to enhance the quality of life for both patients and their families. Alongside laboratory tests, patient-reported outcomes and disease assessment tools play a key role in tracking symptoms [5–8]. However, the use of these tools varies significantly, with some countries using very few and others employing a wide range of available tools.

For adolescents with IL-1-mediated autoinflammatory conditions, consistent, age-appropriate care throughout the transition to adult services is vital for maintaining treatment adherence and achieving positive health outcomes [16]. Unfortunately, factors like low readiness, insufficient quality measures, and a lack of focus on adolescent needs mean that nearly half of patients do not experience a smooth transition to adult care [17]. Care pathways also differ across regions; in many Central and Eastern European countries, structured transition processes are in place but often begin late, around age 18. Starting this transition earlier—ideally by age 13 or 14—helps patients become familiar with adult care teams and boosts readiness for the shift [18, 19].

Creating disease-specific guidelines could standardize transition practices, helping adolescents build independence in managing their health and addressing broader life impacts of their conditions. Conversely, few countries allow continued pediatric care into adulthood, raising concerns about the adequacy of adult care for patients with these rare diseases given the limited transition period.

Data on the incidence and prevalence of autoinflammatory diseases in Central and Eastern Europe are regrettably limited. The initial data from these regions were published as far back as 2010 and may have evolved considerably since then [20]. In 2010, only a handful of countries had access to genetic testing, awareness of these diseases was lower, and possibly a considerable number of patients went undetected. It is imperative to gather updated data to assess how the landscape has transformed over the past decade.

Currently, a shared registry named Eurofever is in operation for the compilation of data on patients with autoinflammatory diseases, and enrollment has been ongoing since November 2009 [21]. Leveraging and endorsing existing international registries could contribute to gaining a more comprehensive understanding of the prevalence of these conditions. The use and support of available international registries could help to have a clearer idea of the prevalence of these conditions. Therefore, we advocate for the need to channel additional efforts into establishing registries, laying the foundation for the development of an international and collaborative clinical network. The ultimate objective is to facilitate the identification of new patients with autoinflammatory diseases.

Conclusions

In summary, it can be emphasized that adherence to the 2021 EULAR/ACR recommendations for IL-1-mediated autoinflammatory diseases is feasible in Central and Eastern European countries. Although genetic testing (massive parallel sequencing panels/NGS panels) is universally accessible, prolonged waiting times for panel results are prevalent in many nations. In particular, disease-specific laboratory assessments, such as S100 proteins, face limitations in availability. IL-1 inhibitors are accessible in all countries; however, comprehensive data on the precise number of patients is currently lacking.

Abbreviations

ACR	American College of Rheumatology
ADAI	Autoinflammatory diseases activity index
AIDAI	Autoinflammatory diseases damage index
CAPS	Cryopyrin-associated periodic syndromes
ERN-RITA	European Reference Network for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases
DIRA	Deficiency of the IL-1 receptor antagonist
EULAR	European Alliance of Associations for Rheumatology
MKD	Mevalonate kinase deficiency
MPS	Massive parallel sequencing
PGA	Global assessment scales for physicians
PPGA	Global assessment scales for patients/parents
QoL	Health-related quality of life
PReS	European Society for Pediatric Rheumatology
SAA	Serum amyloid A protein
TRAPS	Tumor necrosis factor receptor-associated periodic syndrome

Supplementary Information

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Additional file 1.

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Authors' contributions
MJ and MS designed the study. MJ and MS analyzed and interpreted the data and wrote the first version of the manuscript. NT, CT, JV, ZZ, BWK, MSp, MJes, SR, VS and PD substantial contributed to acquisition of data. LH, YU and MG revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript

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All data generated or analysed during this study are included in this published article.

Declarations

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