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REVIEW

Pediatric rheumatology in Turkey

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Abstract
Pediatric Rheumatology is an emerging specialty in Turkey with increasing number of available centers and specialists all over the country. In this paper, we sought to provide an overview on pediatric rheumatology service in our country, as well as to assess the principle published literature from Turkey in this field. A systematic literature search has been performed to achieve the significance and the impact of this manuscript. The most relevant used databases (PubMed/MEDLINE, Web of Science, SCOPUS) for peer-reviewed studies and reviews in English language published during the last 5 years were screened. In the first part of the manuscript, we tried to give more details on the history of pediatric rheumatology in Turkey. In further text, we put an accent over the most common rheumatologic conditions among children in Turkey, including Familial Mediterranean fever, juvenile idiopathic arthritis, juvenile spondyloarthropathies, and childhood vasculitides. Despite the considerable literature from Turkey on pediatric rheumatic diseases, a need for unique strategies that would guide the management of rheumatic diseases in childhood remains open. The cultural and historical inheritance together with geographical position make the Turkey a suitable ground for investigations in filed of auto-inflammation and all other inflammatory conditions. Prospective, multicentric studies especially among rheumatologic conditions common in this part of the world would give us more relevant data and open new horizons in diseases' management. International collaborations and databases should be highly encouraged and supported, to make the care of pediatric rheumatic disease uniform.

Keywords Familial Mediterranean fever · Juvenile idiopathic arthritis · Spondyloarthropathies · Pediatric rheumatology · Turkey

Introduction

Pediatric Rheumatology is a relatively young specialty in Turkey with increasing number of specialists and centers across the country. With this paper, we aimed to recapitulate pediatric rheumatology service as well as to assess the principle published literature from Turkey.

First part of manuscript consists of details on the history of pediatric rheumatology and its way to be accepted as separated specialization in pediatrics. Further text includes details on the most common rheumatologic conditions among children in Turkey, including familial Mediterranean fever (FMF), juvenile idiopathic arthritis (JIA), juvenile spondyloarthropathies (JSpA) and childhood vasculitides. We could not avoid mentioning some less frequent conditions, such as childhood Behcet's disease and connective tissue disorders due to recently published relevant studies with scientific significance. Apart from more recent papers, some major publications from the past have been added to maintain the chronology of the review.

This is the first review including data on both historical pathway of pediatric rheumatology and the most relevant published literature from Turkey. It gives overall view on the development of this sophisticated branch of pediatrics that has been accepted as independent specialization during the last 7 years. Additionally, this review unifies the most significant data from the literature, giving a general insight in scientific place of Turkey in field of pediatric rheumatology.

Search strategy

Recommendations of guidelines for conducting a narrative literature review have been followed during the search of the literature [1]. A systematic literature search has been

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performed to optimize the relevance and the impact of this manuscript. The most relevant databases (PubMed/MEDLINE, Web of Science, SCOPUS) were searched for peer-reviewed studies and reviews published in English language. Preference was given to the sources published within the past 5 years. Due to nature of the review, some main reports with historical significance published before the mentioned period of time have been included, as well.

Search was performed for the following words: childhood familial Mediterranean fever, FMF, MEFV, juvenile idiopathic arthritis, juvenile spondyloarthropathies, enthesitis-related arthritis, childhood vasculitis, pediatric Behcet's disease, juvenile systemic lupus erythematosus, juvenile scleroderma. All papers were re-evaluated and only those published by Turkish authors and international studies in which Turkish experts participated were elected. Brief reports, letters, editorials and all unpublished data presented in the form of abstracts of biomedical congresses were excluded. The junior author performed the initial selection of the papers. Then senior author re-evaluated selected papers and made a final decision on election of manuscripts that would be reported and discussed in the review.

History of pediatric rheumatology in Turkey

The way of pediatric rheumatology in Turkey was long, with first steps taken during the 1985–1990 years. In the 1987, Imamoglu and Ozen [2] evaluated the epidemiology of the rheumatic heart disease in elementary schoolchildren in Turkey. In the mentioned time period, pediatric cardiologist and occasionally pediatric nephrologists were dealing with pediatric rheumatologic patients since the pediatric rheumatology has not been recognized as a separated branch in pediatrics. It was a quite confusing situation for both doctors and patients, who had difficulties in choosing the right department for admission. In some centers, adult rheumatologists were responsible for management of patients with juvenile idiopathic arthritis. In that time period, professor Ozdogan (one of the founders of pediatric rheumatology in Turkey) and her team were treating juvenile patients with arthritis (JIA) at the Division for rheumatology at the Department of Internal medicine. Ozdogan et al. [3] in 1986 reported that sulphasalazine is an effective and relatively safe drug in management of JIA.

Afterward, Ozdogan et al. [4] reported the first cohort of JIA from Turkey. In 1997, again Ozdogan et al. [5] pointed out the association between vasculitis and FMF, describing the vasculitis as a first disease sign in certain FMF patients.

In 2001, the first multicentric study from Turkey supported by the Pediatric Rheumatology International Trials Organization (PRINTO) has been carried out. The cross-cultural adaptation and validation of the Childhood Health Assessment Questionnaire (CHAQ) into the Turkish language has been performed. Turkish version of the CHAQ has been found to be a valid tool for the functional, physical and psychosocial assessment of JIA patients [6]. This opened a door for further multicentric studies and significant international collaboration supported by PRINTO.

The Turkish Pediatric Rheumatology Association was founded in 2002, with Nil Arisoy, Huri Ozdogan, Seza Ozen, Ozgur Kasapcopur, Aysin Bakkaloglu, Nesrin Besbas and Rezan Topaloglu representing the core-founding members. In 2007, Turkey was the host of the 14th Pediatric Rheumatology European Society (PReS) Congress, which opened possibilities for international collaborations and increased interest in field of pediatric rheumatology (Fig. 1).

The officially first Department of Pediatric Rheumatology in Turkey was founded at Istanbul University, Cerrahpasa Medical School in 2010. Consequently, in 2011, the pediatric rheumatology was accepted as separated subspecialization in pediatrics and the educational program was established. The first fellow in pediatric rheumatology was selected according to the score on the national exam for pediatric fellowships in 2012. Ever since, the number of fellows in pediatric rheumatology increased to 38 (Fig. 1).

Currently, there are a total of 21 pediatric rheumatology centers all over the country: 11 departments at university hospitals and 9 departments at education and research hospitals providing tertiary health care. There is one governmental

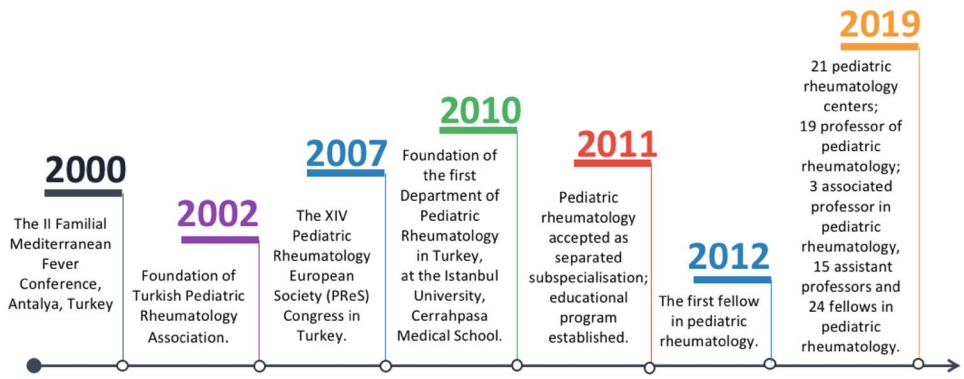

Fig. 1 History of pediatric rheumatology in Turkey

hospital with one specialist in pediatric rheumatology providing secondary health care.

Emerging number of specialists, increasing number of relevant local studies and contributions in international collaborations place Turkey into central position when talking about rheumatology in general, including pediatric rheumatology as its relatively young, developing branch.

Familial Mediterranean fever (FMF)

Familial Mediterranean fever (FMF) is an auto-inflammatory condition characterized by recurrent episodes of fever accompanied with inflammation of serous membranes, caused by the *MEFV* gene mutation. The autosomal recessive heredity pattern of the disease makes its frequency higher in regions with increased consanguinity rate [7, 8]. The prevalence of FMF in Turkey is generally known to be 1/1000 [8]. However, its prevalence differs among different regions. Increased FMF prevalence was reported in Central Anatolia and Black Sea regions of Turkey [9]. The high disease frequency consequently leads to increased burden of FMF patients in primary and secondary health care centers. This gave rise to proposal of diagnostic criteria for childhood FMF. Yalcinkaya et al. [10] showed the high sensitivity and specificity of proposed criteria for diagnosis of FMF in childhood. These criteria were shown to be practical to use on an everyday basis with a note that diagnosis of FMF is still clinical one [10].

Apart from genetic basis of the disease, there are some indicia on epigenetic factors that modify the disease phenotype. In addition, the high frequency of *MEFV* gene mutation carriers in the healthy Turkish population (20%) should be kept on mind during the interpretation of the genetic analysis results [11, 12]. There are some studies showing that age at disease onset could predict the clinical course and disease prognosis. In other words, late disease onset is associated with milder clinical presentations and less disease complications [13, 14].

A report on colchicine as a new approach in FMF treatment in 1972 opened a new ear in disease control and prevention of disease complications (namely, amyloidosis) [15]. In 1997, Saatci et al. [16] reported a pediatric FMF cohort including 425 patients with and 180 patients without amyloidosis. Authors pointed out the presence of a familial history of amyloidosis and potential genetic predisposition as the most important risk factors in the development of amyloidosis [16].

Colchicine remains the mainstone of FMF treatment with majority of patients showing good response. However, there are still 5–10% patients who are considered colchicine-resistant [7, 17]. The definition of colchicine resistance is a matter of debate with variety of criteria being used [17]. Usage of both clinical and laboratory criteria for definition of colchicine resistance is recommended to recognize all the resistant patients [17]. FMF patients who were unresponsive to colchicine or who had developed amyloidosis brought about new treatment strategies. In a certain number of international and local Turkish studies, anti IL-1 agents have been reported as effective and safe treatment options for colchicine-resistant FMF patients and for FMF-related renal amyloidosis [18–24].

Despite the significant burden of FMF patients in Turkey, the better drug compliance, increased awareness and availability of biological agents lead to decreased percentage of amyloidosis as a major disease complication. In a recently published cohort of 708 childhood FMF patients, only 2 of them (0.3%) developed amyloidosis [7]. These promising results show the significant improvement in management of children with FMF and marked reduction in development of amyloidosis as a main disease complication.

The first international conference of FMF has been held in 1997 in Israel, followed by the 2nd FMF conference (today known a International Conference of Systemic Auto-Inflammatory Diseases (ISSAID)), which was held in Antalya (Turkey) in 2000. Huri Ozdogan, Nil Arisoy and Hasan Yazici headed the conference. Current Editor-in-Chief of The Rheumatology International Journal, Mr. Armen Y. Gasparyan, participated to the conference as a young scientist (Fig. 2). Since then, the ISSAID is held biannually raising awareness, promoting researches and bridging experts in the field of FMF and autoinflammation.

Juvenile idiopathic arthritis (JIA)

Juvenile idiopathic arthritis (JIA) is the most commonly seen chronic rheumatic disease in childhood, representing one of the most common conditions followed up at pediatric rheumatology departments [25]. The exact disease prevalence and incidence are still unclear, due to the lack of uniform classification and variability of disease frequencies across the different regions [26, 27]. A study from Turkey reported a prevalence of chronic arthritis in childhood as 64 in 100.000 [26, 27]. Distribution of JIA subtypes differs between different geographical regions. First, Ozdogan et al. [4] analyzed clinical characteristics of 147 Turkish patients with JIA in the time period between 1980 and 1988. They reported a male predominance (1.3:1), low frequency of early onset pauciarticular disease (16%), chronic anterior uveitis (7%) and positive antinuclear antigens (6%). The striking one is high incidence of secondary amyloidosis (10%) [4]. In another cohort reported in 2017 including 378 JIA patients from Turkey, enthesitis-related arthritis and oligoarticular JIA patients represented the majority (both seen in 23% of patients).

Fig. 2 The II Familial Mediterranean fever international conference, May 2000, Antalya, Turkey

The other disease forms were less frequent: systemic in 9.2%, rheumatoid factor (RF) positive poliarticular JIA in 9.5%, RF negative poliarticular JIA in 2.6% and psoriatic arthritis in 1.3%. A fact that there was no patient with amyloidosis in cohort of 378 JIA patients was encouraging [27].

The aetiopathogenesis of the disease is unclear with different theories, supporting the immunogenic mechanisms, infections and genetic factors as potential triggers [25]. However, some recent studies have reported the *Laccase* (multicopper oxidoreductase) domain-containing 1 (LACC1; MIM 613,409) as a potentially causative gene in rare familial forms of JIA [28]. These genetic studies open new perspectives in aetiopathogenesis of the JIA, especially in familiar cases and in regions with increased consanguinity. Systemic juvenile idiopathic arthritis (sJIA) is distinguished from other JIA subtypes by unique systemic clinical features and treatment responses that are similar to auto-inflammatory diseases. Auto-inflammatory characteristics of the disease provoked discussions on disease nature and classification [29, 30]. The other important characteristic of this disease form is a possibility for development of macrophage activating syndrome (MAS), which represents the life-threatening condition. The prevalence of MAS has been reported as 10% of sJIA patients [26]. Barut et al. [26] reported ten cases of MAS secondary to sJIA between June 2013–May 2014. They conclude that diagnosis of MAS should be considered in patients with sudden deterioration of general condition, resistant fever and signs of systemic inflammation in children with active rheumatic disease. Complete recovery can be provided with timely efficient treatment, as early as the diagnosis of MAS has been established [31].

Treatment of juvenile idiopathic arthritis

Despite the emerging developments and discovering of many novel treatment options, some basic principles have not changed in JIA treatment. Glucocorticoids have been effectively used in JIA treatment for almost 60 years. Although systemic glucocorticoid use decreased with the introduction of biologic drugs, glucocorticoid in combination with non-steroidal anti-inflammatory drugs (NSAIDs) and conventional-synthetic disease modifying anti-rheumatic drugs (csDMARDs) still represent the treatment of choice in JIA [30]. Methotrexate represents the most commonly used csDMARD, followed by leflunomide and sulphasalazine [25]. Roughly, systemic glucocorticoids represent the "bridging therapy" for JIA patients waiting for the therapeutic effect of csDMARDs [31]. On the other hand, the glucocorticoids' adverse effects should be kept on mind, especially for young patients in the phase of intensive growth and development. Therefore, the benefits and risks of glucocorticoid therapy should be continuously balanced throughout the treatment [31]. Intraarticular injections represent a practical way for glucocorticoids usage, decreasing the risk for systemic adverse effects. Oligoarticular JIA is the JIA subtype with most frequently application of intraarticular steroids: methylprednisolone acetate for small joints and triamcinolone acetate for large joints [25, 31].

The emergence of biological agents represents the revolution in pediatric rheumatology, due to markedly better clinical course and decreased complications [25]. Biological agents, namely anti TNF-α agents (infliximab, etanercept, adalimumab), anti IL-1 agents (anakinra, canakinumab) and anti IL-6 agents (tocilizumab) have been used efficiently and safely in patients with JIA [23, 25, 32, 33].

Rehabilitation

Exercise-based rehabilitation represents inseparable modality of JIA treatment. There are some relevant studies accentuating the role of physical exercise and its ability to improve the quality of life of JIA patients [34, 35]. Bayraktar et al. [36] recently showed that 8-week water-running program improves anaerobic exercise capacity in children with JIA. It seems that psychosocial factors sometimes remain underestimated in JIA patients. This was a reason for Unal et al. [37] to propose a multidimensional questionnaire for the assessment of biopsychosocial outcome among JIA patients. However, further validation of this tool in independent cohort is needed to confirm its utility. Demirkaya et al. [38] recently performed a validation of the Turkish version of the Juvenile Arthritis Multidimensional Assessment Report (JAMAR). They found the Turkish version of JAMAR to be valid and suitable for use in routine clinical practice and scientific research [38].

Juvenile spondyloarthropathies (JSpA)

Juvenile spondyloarthropathies (JSpA) represent a seronegative rheumatologic disorder dominantly seen in males before 16 years of age, characterized by enthesitis, oligoarthritis of lower extremities and HLA B27 positivity. The axial involvement is not seen as frequent as expected, comparing to adults [39]. This disease group encompasses a wide spectrum from enthesitis-related arthritis (ERA) to ankylosing spondylitis as its most serious presentation, mostly seen in adults. In the past, a certain percentage of patients followed up as oligoarticular JIA "type 2" were likely to have spondyloarthritis. In 2001, ILAR suggested new classification criteria accepting ERA as JIA subtype [40].

According to Demirkaya et al. [41], enthesitis-related arthritis encompasses about 18.9% of all JIA patients in Turkey. Different classification criteria have been proposed for the classification of JSpA, none of them shown to have optimal sensitivity and specificity [27, 39, 40]. Our study group performed an evaluation of predetermined classification and diagnostic criteria for JSpA. Additionally, we have proposed new set of criteria for the diagnosis and classification of JSpA. However, neither the predetermined criteria nor the proposed new set of criteria have been shown to be totally adequate and efficacious [41, 42] (Table 1).

There is an important topic that has been pointed out recently, regarding the frequency and characteristics of JSpA among FMF patients. Recent studies demonstrated that pediatric patients with coexistence of FMF and sacroiliitis have higher inflammatory markers but less frequent spinal involvement and HLA-B27 positivity from patients with isolated JSpA [43]. Similarly, Ozer et al. [44] reported that apart from acute monoarthritis of the lower extremities, the chronic arthritis should be kept on mind among FMF patients. The JSpA should be considered in FMF patients with oligoarthritis, inflammatory back pain and enthesopathy complaints with onset over 6 years. However, it is still a matter of debate whether the FMF triggers the JSpA or sacroiliitis represents an isolated feature of FMF. Further multicentric studies would reveal more clear data and possibly answer the question.

Makay et al. [45] pointed out the association between the body mass index and disease activity in patients with enteritis-related arthritis. According to the results of their study, increased body mass index and obesity influence the response to treatment and disease activity in patients with JSpA. Those findings open new horizons in management and treatment of JSpA patients.

Table 1 A new set of criteria for classification of juvenile spondyloarthropathies [37, 38]

Major criterion
Oligoarthritis
Enthesopathy
Disease onset after 6 years of age
Inflammatory back pain
Minor criterion
Hip arthritis
Tarsometatarsal arthritis
Male sex
NSAID response
Sacroiliitis (on MRI or radiography)
HLA B27 positivity
Limitation in Schober test (< 4 cm)
Family history of SpA group of disease, dactylitis, psoriasis or presence of IBD
At least 2 major + 3 minor or 3 major variables are needed to establish the diagnosis of JSpA

IBD inflammatory bowel disease, *MRI* magnetic resonance imaging, *NSAID* non-steroidal anti-inflammatory drugs, *SpA* spondyloarthropathies

Childhood vasculitides

Childhood vasculitis encompasses a wide spectrum of different conditions with vessel wall inflammation as a common pathophysiological characteristic. It is important to mention that vasculitides in childhood are separated from those seen in adults. Some forms of vasculitides could be exclusively seen in childhood (e.g., Kawasaki disease). Kawasaki disease is the second most frequent childhood vasculitis, after the Immunoglobulin A vasculitis [46, 47]. Other forms of vasculitis (e.g., Takayasu arteritis, granulomatous poliangitiis) should not be underestimated, despite its rarity in childhood [46]. It is of particular importance to mention the priceless efforts of professor Seza Ozen in establishment of classification criteria for childhood vasculitides [48, 49].

Immunoglobulin A vasculitis is a systemic vasculitis involving small vessels with the deposition of IgA immune complexes. Batu et al. [47] recently investigated differences and similarities between adult and pediatric IgA vasculitis patients. They reported the self-limiting, generally benign course of IgA vasculitis in children and more severe disease form in adults. They emphasized that persistent haematuria represent predictive factor for disease relapse [47].

On the other hand, Kawasaki disease is an exclusive disease of childhood. It is an acute, febrile medium vessel vasculitis, frequently observed in children aged between 6 months and 5 years. Due to tendency for coronary artery involvement, the timely diagnosis and early treatment (first 10 days of the disease onset) are of a high relevance in disease prognosis [46]. A recent study points out the impairment of left ventricular mechanics (especially within the left anterior descending artery territories) in patients with history of Kawasaki disease. Those findings accentuate the importance of long-term follow up for patients with Kawasaki disease [50].

Recently, we have become aware of single gene defects influencing the inflammatory pathway and causing a phenotype often resembling those of vasculitis [51]. Description of monogenic vasculitides has provided novel insights in pathogenesis of vasculitis and of inflammation, in general. Deficiency of adenosine deaminase 2 (DADA2), stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy (SAVI), and haploinsufficiency of A20 (HA20) are some of monogenic vasculitides [51–56]. Recognition of the familial forms of polyarteritis nodosa with central nervous system involvement (namely: DADA2 deficiency), caused by the *CECR1* (Cat eye syndrome critical region protein 1) gene mutation opened new perspectives in management of childhood vasculitides [52–54]. Both principle manuscripts for the DADA2 deficiency include Turkish patients as index cases [52, 53].

There is a noteworthy recently published case report from Turkey on renal amyloidosis in DADA2 patients, who responded well to anti-IL1 treatment (canakinumab) [57]. Authors opened a discussion on etiology of amyloidosis in reported patient (MEFV heterozygosity or DADA2?). It seems that there are still many questions that should be answered, regarding the underlying *MEFV* mutation and auto-inflammation other than FMF. Further multicentric international collaboration would create a platform for the new investigations.

Behcet's disease (BD)

Behçet's disease (BD) is a multisystemic auto-inflammatory condition affecting vessels with different diameters and being classified as variable vasculitis [58]. It has originally been demonstrated in 1937 by Dr. Hulusi Behcet, a Turkish dermatologist from the Istanbul University [59]. The disease is typically appearing in the 2nd to 4th decades of life with low incidence in pediatric population [58]. Uluduz et al. [60] showed that pediatric neuro-BD comprises 3.6% of our whole neuro-BD cohort. Dural venous sinus thrombosis is the main form of neurological involvement in pediatric patients, whereas the adult population has parenchymal disease, suggesting that the pathogenesis of neuro-NB may be different according to the age at disease onset [60].

The diagnosis of BD in children is challenging, due to rarity of the disease and variable clinical presentations. Different classification criteria have been proposed for the pediatric BD [61–63]. Recently, Batu et al. [62] evaluated the performance of most widely used classification criteria for pediatric BD patients. They found that the pediatric BD classification criteria (PEDBD) have better sensitivity than International Behçet's Study Group (ISG) criteria among pediatric patients. Additionally, they found positive correlation between severity scores and physician global activity, suggesting their use in clinical practice [62]. Apart from clinical clues, Topcuoglu et al. [64] emphasize the relevance of imaging methods in differential diagnosis of pediatric BD.

In contrast to wide range of studies among adult BD patients from Turkey, investigations in pediatric population are insufficient. Multicentric approaches with higher number of patients and engagement of experts in the field are need, to provide a consensus on management of pediatric BD patients.

Connective tissue disorders

Talking about pediatric rheumatology, we cannot avoid mentioning connective tissue disorders as an inevitable part of rheumatology practice. Although pretty rare among children,

Fig. 3 The IV national congress in pediatric rheumatology, April 2018, Bodrum, Turkey

connective tissue disorders represent a significant portion of pediatric rheumatologic patients. Large single-center cohorts of juvenile systemic lupus erythematosus (jSLE), scleroderma (jScl) and dermatomyositis (JDM) from Turkey have been published [65–67]. Artim-Esen B. et al. [68] reported a higher frequency of renal involvement, cutaneous symptoms, oral ulcers, neuropsychiatric manifestations, autoimmune hemolytic anemia and anti-dsDNA positivity among patients with juvenile disease form, comparing to adults. Recently, Batu et al. [69] reported seven jSLE cases with early disease onset ($\leq$5 years of age) and family history suggestive for the autosomal recessive pattern of inheritance. Authors suggest that monogenic causes should be sought in early-onset jSLE patients, with positive family history.

Despite the rarity of juvenile scleroderma, there is a single-center report including 29 patients with systemic sclerosis and 28 with localized scleroderma [66]. Likewise, one Turkish center joined the international collaboration on the juvenile systemic sclerosis with significant contribution [70].

National congress of pediatric rheumatology

The Turkish National Congress in Pediatric Rheumatology is held biannually. This year, the 4th National Congress in Pediatric Rheumatology has been held on 4–7 April 2018 in Bodrum, Turkey. A total of 205 participants were registered. Seventy-nine local speakers and 3 foreign experts gave a talk on relevant topics in pediatric rheumatology. There were 14 sessions, 43 oral and 83 poster presentations. Three renowned experts in rheumatology were honorary guests of the congress: Francesco Zulian from University of Padova, Marco Gattorno from Institute Giannina Gaslini from genoa and Armen Gasparyan from Departments of Rheumatology and Research and Development from Birmingham (Fig. 3). This was an opportunity for young investigators to remain updated, enabling them to be aware of recent advances and possibly introduce new research ideas. In addition, it also provides pediatric rheumatologists an opportunity to interact and to build bridges for future scientific collaboration.

Conclusion

Pediatric rheumatology is an emerging specialty in Turkey with increasing number of available sub-specialists. Increasing number of specialists facilitates the availability of pediatric rheumatology care all over the country. Rising number of centers providing tertiary health care with experts and skilled professionals represents appropriate basis for education and research activities.

Although there is considerable literature from Turkey on pediatric rheumatic diseases, there is a striking need for unique strategies that would guide the management of rheumatic diseases in childhood. Prospective, multicentric studies especially among rheumatologic conditions common in this part of the world (e.g., FMF, sJIA) would give us more relevant data and open new horizons in diseases' management. Lastly, continuous growth of pediatric rheumatology with increasing number of young investigators prioritizing scientific work and forming international collaboration is expected.

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Compliance with ethical standards

Conflict of interest None of the authors of this paper has a conflict of interest, including specific financial interests, relationships and/or affiliations relevant to the subject matter or materials included.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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