REVIEWS

Secondary fibromyalgia in children with immune-inflammatory rheumatic diseases

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Patients with immune-inflammatory rheumatic diseases (IIRDs) often present with non-inflammatory musculoskeletal pain associated with nociceptive dysfunction, central sensitization, and secondary fibromyalgia (FM). In recent years, an increasing number of publications have appeared dealing with FM in rheumatoid arthritis and systemic connective tissue diseases in adult patients, while this problem is little discussed in pediatric rheumatology, partly due to the differences between the existing diagnostic criteria in children and adults, which complicate the diagnosis of juvenile secondary FM. The consequence of this is often the unfounded prescription or switching of synthetic disease-modifying antirheumatic drugs (DMARDs) or biologic DMARDs in patients who do not require intensified antirheumatic therapy, but rather psychotherapy and psychopharmacotherapy, as well as the wider use of physical and rehabilitation medicine methods.

In a brief narrative review, we tried to trace the investigation of FM in a rheumatological clinic, including children with IIRD, from a historical perspective, to summarize current literature data on this problem and to point out possible solutions.

Keywords: *fibromyalgia; immune-inflammatory rheumatic diseases; juvenile idiopathic arthritis; systemic lupus erythematosus with juvenile onset; chronic pain.*

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For reference: *Santimov AV, Grechanyi SV, Novik GA. Secondary fibromyalgia in children with immune-inflammatory rheumatic diseases. Sovremennaya Revmatologiya=Modern Rheumatology Journal. 2024;18(3):99–106.* ***DOI:*** *10.14412/1996-7012-2024-3-99-106*

In 2023, G. Tran and A. Gough [1] published an article describing the current state of the problem of the treatment of fibromyalgia (FM) in a rheumatology clinic as "an elephant in the clinic room". This is a slightly modified English idiom "Elephant in the room", denoting an obvious problem that cannot be overlooked, but which no one wants to admit. The authors note that in most rheumatology clinics, patients suffering from FM receive medical care that is far from optimal, although doctors understand that this disease is an important cause of pain and maladjustment. At the same time, G. Tran and A. Gough emphasize that approximately one third of patients with rheumatoid arthritis (RA) and other inflammatory arthropathies fail to achieve adequate pain control when using basic anti-inflammatory drugs and synthetic disease-modifying antirheumatic drugs (DMARDs), and wonder how many patients are unreasonably prescribed DMARDs or have DMARDs replaced because of comorbid FM?

A similar problem exists in pediatric rheumatology – it is the problem of juvenile FM, secondary to immuno-inflammatory rheumatic diseases (IIRDs). Children face the same difficulties as adult patients due to inability of doctors to recognize FM, which leads to inadequate therapy and a significant deterioration in the quality of life. However, in both Russian and world literature, the problem of FM secondary to IIRDs in children has received little attention.

FM attracted the attention of the medical community in the first half of the twentieth century. In those years, this condition was most often referred to as "fibrositis", the term proposed in 1904 by W.R. Gowers [2] in an article on lumbago. It was considered, that fibrositis is a disease characterized by widespread pain, in which painful and touch–sensitive small nodules are formed in the connective tissue. W.R. Gowers assumed the presence of inflammatory changes in the connective tissue structures of the back muscles, which was not subsequently confirmed. In 1947, W.R. Caven [3] noted that fibrositis, one of the most common causes of back pain, is associated with muscle spasm and is not inflammatory in nature. The author emphasized the significant differences between this disease and osteoarthritis, RA and acute rheumatic fever and pointed out that fibrositis is more common in young adults. However, he mentioned that he had also observed some cases of this disease in children, in particular in a child of 8 years old. Over time and with the accumulation of new knowledge, the diagnosis of fibrositis was divided into two modern diagnoses – myofascial pain syndrome, identified by J. Travell and S.H. Rinzler [4] in 1952, and fibromyalgia (FM), the diagnostic criteria of which were first proposed by M. Yunus et al. [5] in 1981. Moreover, M. Yunus et al. used the term "primary fibromyalgia", emphasizing that this is a non-inflammatory condition, that it is not accompanied by concomitant disorders that can explain the cause of pain, and that the results of all laboratory and X-ray examinations should be within the normal range. "Fibrositis", as noted by the authors, may be secondary to injury, various rheumatic diseases, such as osteoarthritis and RA, systemic connective tissue diseases and non-rheumatic diseases such as hypothyroidism and malignant neoplasms. In this case, according to the authors, the term "secondary fibrositis" can be used. It is interesting to note that although the authors equated the new term "fibromyalgia" with the old "fibrositis", for the primary condition they used mainly the name "primary fibromyalgia", and for the secondary – exclusively "secondary fibrositis". In 1985 M.B. Yunus and A.T. Masi [6] rejected the term "fibrositis" and mentioned it only in a historical context, preferring the term "primary fibromyalgia syndrome", thus identifying it as a separate nosology in the absence of other conditions associated with symptoms similar to FM; the terms "secondary fibrosis" or "secondary fibromyalgia" were not mentioned at all. Thus, since the first half of the 1980s, the term "fibrositis", both primary and secondary, has gradually gone down in history, and the name "secondary fibromyalgia" replaced it, though not at once, especially in pediatric rheumatology. The

Table 1. Diagnostic criteria for juvenile primary FM 1985 [6]

Major criteria
1. Generalized musculoskeletal pain in 3 or more localizations for 3 or more months
2. Absence of another disease that explains the pain
3. Normal results of laboratory tests
4. ≥5 or more typical tender points
Minor criteria
1. Chronic anxiety
2. Increased fatigue
3. Sleep disorders
4. Chronic headaches
5. Irritable bowel syndrome
6. Subjective edema of soft tissues
7. Numbness
8. Modulation of pain by physical activity
9. Modulation of pain by weather factors
10. Modulation of pain by anxiety or stress
The diagnosis is valid in the presence of 4 major and 3 minor criteria or in the presence of the first 3 major criteria, 4 tender points and 5 minor criteria.

Table 2. Tender points in FM, according to the 1990 ACR criteria [7]

1. Occiput: points of attachment of the suboccipital muscles
2. Lower cervical region: on the anterior side of the intervertebral spaces of the 5th, 6th, 7th cervical vertebrae
3. Trapezius muscle: in the middle of its upper border
4. Supraspinatus muscle: at the place of its attachment, above the scapular spine at the medial edge on either side
5. Second rib: in the area of the second costochondral joint
6. Lateral epicondyle of the humerus: 2 cm distally to the epicondyle
7. Buttock: in the upper-outer quadrant, in the anterior muscular fold
8. Greater trochanter: behind the trochanter epicondyle
9. Knee joint: in the area of the medial fat pad, proximally to the articular line

above-mentioned article by M.B. Yunus and A.T. Masi in 1985 [6] was completely devoted to the study of the features of FM in children, and it was the first article in which diagnostic criteria for juvenile primary FM syndrome were formulated. These criteria remained the only ones in pediatric practice for more than 30 years, and all these years the concept of "primary fibromyalgia" prevailed in pediatric rheumatology. The diagnostic criteria of M.B. Yunus and A.T. Masi proposed in 1985 are still often used by pediatric rheumatologists for the diagnosis of primary FM in real clinical practice (Table 1).

M.B. Yanus and A.T. Masi initially proposed to evaluate 31 tender points, however, after publication in 1990 ACR (American College of Rheumatology) criteria for the diagnosis of FM in adult patients [7], most rheumatologists use 18 tender points indicated there, or rather, 9 symmetrical pairs of points (Table 2).

The ACR criteria of 1990 assumed the presence of ≥11 of possible 18 tender points in a patient with a history of widespread pain ≥3 months and emphasized that the presence of other diseases does not exclude the diagnosis of FM, and in the article by F. Wolfe et al. [7], in which these criteria were first described, the features of primary and secondary FM in adult patients were discussed in detail, and it was noted that FM is often found in other rheumatic diseases. However, these criteria have never been validated in the pediatric population. In 2010 ACR proposed new criteria for the clinical diagnosis of FM in adults (Table. 3) [8].

The advantages of the ACR criteria of 2010 compared to the criteria of M.B. Yunus and A.T. Masi of 1985 and the ACR criteria of 1990 include an assessment of the severity of the main symptoms of FM (sleep disorders, fatigue, cognitive disorders) and additional somatic symptoms, ease and quickness of use, the possibility of retrospective diagnosis in patients who do not have a sufficient number of FM symptoms at present, but had them earlier, as well as the exclusion of the tender point survey, which was previously criticized because of its subjectivity and frequent inconsistency in the application [9]. However, a clause reappeared in the 2010 ACR criteria requiring the exclusion of another disorder explaining pain, and thus making it difficult to use the term "secondary fibromyalgia", which was not mentioned in the article by F. Wolfe et al. [7], who published these criteria, and the presence of IIRDs was one of the criteria for excluding patients from this study. According to the authors, the limitation of the study was that they did not test the proposed FM criteria in patients with other rheumatic diseases. They recommended to do it in the future.

For the first time in the pediatric population, the 2010 ACR criteria were used in 2016 by T.V. Ting et al. [10] to diagnose juvenile primary FM in adolescent girls in comparison with the criteria of M.B. Yunus and A.T. Masi of 1985. [6] as the "gold standard". It was shown that the 2010 ACR criteria for the diagnosis of FM in adults had sensitivity of 89.4% and specificity of 87.5% and may be applicable in adolescents. The authors also noted that it would be useful to test these criteria in patients with secondary juvenile FM.

In 2016, the ACR criteria for the diagnosis of FM in adults were once again revised [11], but they were not validated in the pediatric population. In the new ACR criteria, in comparison with the 2010 ACR criteria, there appeared a definition of generalized pain (pain currently present in at least 4 of the 5 areas of the body: left arm, right arm, left leg, right leg, axially), which allowed minimizing the risk of hyperdiagnosis of FM in localized pain syndromes. And most importantly, the new criteria contained a direct statement that the diagnosis of FM can be made regardless of the presence of other diagnoses and does not exclude the existence of other clinically significant diseases in the patient (the initial 1990 ACR criteria stated that the absence of other disease capable of explaining pain was necessary to establish the diagnosis of FM).

In 2019, L.M. Arnold et al.[12] proposed their own set of criteria for the diagnosis of FM in adults. In accordance with these criteria, the diagnosis of FM can be established in the presence of widespread pain, determined as pain in 6 out of 9 localizations (left arm, right arm, left leg, right leg, head, chest, abdomen, lower back, including buttocks; upper back, including neck) in combination with severe/moderate sleep disorders or fatigue for at least 3 months, and the presence of another pain disorder or related symptoms does not exclude the diagnosis of FM.

Table 3. Diagnostic criteria for FM 2010 ACR [8]

1. The absence of another disorder that can explain the pain 2. The presence of symptoms for at least 3 months 3. Widespread pain index is >7, and the symptom severity scale is >5; or widespread pain index is from 3 to 6, and the symptom severity scale is >9
Widespread pain index is the number of areas of the body (out of 19 possible locations) in which the patient experiences pain: neck, upper back, lower back, chest, abdomen, left jaw, right jaw, left shoulder, right shoulder, upper left arm, upper right arm, lower left arms, lower right arm, left buttock, right buttock, upper left leg, upper right leg, lower left leg, lower right leg.
Symptom severity scale evaluates the severity of fatigue in the patient, feelings of fatigue after waking up in the morning, cognitive symptoms on a 3-point scale for each (0 – do not bother, 1 – expressed slightly, 2 – expressed moderately, 3 – serious persistent problems that disrupt vital activity)
The *severity of somatic symptoms* is also assessed on a 3-point scale: muscle pain, irritable bowel syndrome, fatigue, thinking or memory disorders, muscle weakness, headache, abdominal pain, numbness/tingling, dizziness, sleep disorders, depression, constipation, pain in the upper abdomen, nausea, nervousness, chest pain, blurred vision, fever, diarrhea, dry mouth, itching, lack of air, Raynaud's phenomenon, tinnitus, vomiting, heartburn, mouth ulcers, loss/change of taste, cramps, dry eyes, shortness of breath, loss of appetite, rash, photosensitivity, hearing impairment, slight bruising, hair loss, frequent/painful urination (0 – no symptoms, 1 – a small number of symptoms, 2 – a moderate number of symptoms, 3 – a large number of symptoms).
The overall score on the symptom severity scale can range from 0 to 12 points.

In 2019, F. Wolfe [13], the chief author of all previously published ACR criteria (1990, 2010 and 2016), in a letter to the editorial board of The Journal of Pain, sharply criticized the criteria proposed by L.M. Arnold et al. for oversimplifying them. He regarded these criteria as a step back in the study of FM, which would lead to an increase in the number of unreliable diagnoses. In addition, the new criteria were not validated in the pediatric population. However, the undoubted advantage of the work of L.M. Arnold et al. in 2019 is the recognition that the diagnosis of FM does not exclude the presence of other clinically significant diseases, but, on the contrary, it assumes the existence of characteristic comorbid conditions, including various IIRDs.

In our 2019-2023 publications [14-18] devoted to the psychosomatic aspects of chronic non-inflammatory pain in juvenile idiopathic arthritis (JIA), we deliberately avoided the term "fibromyalgia" (although, in fact, it was specifically about patients with JIA and secondary FM), since at the time of our research in both Russian and world literature we did not find any references to FM as a disease comorbid with juvenile onset IIRDs. Instead of the concept of "secondary fibromyalgia", we used the widespread term "chronic pain syndrome", which is opposed by A.E. Karateev [19]. T.A. Lisitsyna et al. [20] in a publication devoted to the study of chronic pain and depression in adult patients with RA, did not use the term "fibromyalgia" either emphasizing the existence of non-inflammatory mechanisms that support chronic pain in patients with RA, and its association with psychosocial stress and anxiety-depressive disorders. A.E. Karateev and E.L. Nasonov [21] mention secondary FM as one of the characteristic manifestations of central sensitization in RA and psoriatic arthritis. E.S. Filatova and A.M. Lila [22] showed that chronic pain in RA and ankylosing spondylitis in some patients may be mixed, and includes both inflammatory and neurogenic mechanisms (neuropathic and nociplastic). Yu.A. Olyunin [23] in an article on chronic musculoskeletal pain cited FM as an example of primary chronic pain of unknown etiology, but did not use this term in relation to chronic pain, comorbid with IIRDs. N.A. Melikova et al. [24] published for the first time in the Russian Federation the results of a study on the prevalence and features of the course of FM in RA: 24 (43.6%) of 55 patients with active RA met the ACR 2016 diagnostic criteria of FM; they had pain of high intensity and prevalence, accompanied by neuropathic descriptors and significantly worsening the quality of life. According to earlier foreign studies, the prevalence of FM in RA ranges from 12% to 48% [25-27]. Such a high incidence of FM in patients with RA in comparison with the general population significantly increases the likelihood of a secondary nature of FM in relation to RA and not just its comorbidity [28].

In 2022, M.S. Tesher et al. [29] clearly identified chronic non-inflammatory musculoskeletal pain in patients with JIA as FM. The study included 129 patients with JIA observed in four North American rheumatology centers, their age was 11-17 years (median – 14 years), among them there were 99 (77%) female patients, 96 (74%) white patients. All subtypes of JIA were present: polyarticular (n=44, 34%), oligoarticular (n=37, 29%), enthesitis-related (n=14, 11%), psoriatic (n=12, 9%), systemic (n=5.5%), undifferentiated/unspecified (n=16, 12%). Out of 129 patients included in the study 11 (8.5%) patients met the ACR 2010 diagnostic criteria for FM (1 boy and 10 girls). The ethnic characteristics of the prevalence of FM in JIA were not established. Diagnostic criteria for FM were more often met by patients with enthesitis-related and undifferentiated arthritis (FM was observed in 21% of cases), but FM was not found in systemic and oligoarthricular subtypes of JIA, which is fully consistent with the results of our earlier study, in which chronic non-inflammatory pain syndrome in JIA was also statistically significantly more often detected in patients with enthesitis-related and undifferentiated subtypes of JIA and less often in patients with oligoarthritis [30]. According to M.S. Tesher et al. [29], JIA patients who met the FM criteria had greater pain intensity and much more pronounced functional disadaptation (as well as JIA patients with chronic pain syndrome in our work in 2020 [16]) and higher indicators of pain catastrophization than JIA patients who did not meet the FM criteria. In our study, the indicators of pain catastrophization were not evaluated, however, in JIA patients with chronic pain syndrome, both in the younger and older age subgroups, the overall level of anxiety and its individual components, such as generalized, social, and separation anxiety, turned out to be significantly higher. These patients also had a higher level of depression, which did not differ in the active and inactive phases of the disease [16]. In the study of M.S. Tesher et al. [29] patients with JIA who met the FM criteria had greater disease activity than patients who did not meet these criteria, whereas in our study [16], on the contrary, in most cases

patients with JIA and persisting chronic pain syndrome against the background of the adequate therapy, had no active inflammatory process according to clinical, laboratory and X-ray examinations, which reflects the complex relationship between inflammatory and non-inflammatory pain that may be present in this disease.

M.I. Kaleda et al. [31] for the first time in the Russian-language scientific literature, used the term "fibromyalgia" in the context of chronic non-inflammatory musculoskeletal pain in IIRD with juvenile onset on the example of systemic lupus erythematosus (SLE), however, the prevalence and features of the course of secondary FM have never been studied either in SLE with juvenile onset or in other IIRDs in children in the Russian population.

According to the SLE registry of the Spanish Society of Rheumatology, FM was less common in SLE with juvenile onset than in SLE with adult onset: in 11 (2.4%) of 484 children and in 224 (6.7%) of 3428 adult patients [32], however, in different studies of SLE with adult onset, the prevalence of FM varied from 5% to 65% [33-35]. Moreover, in the study of E. Elefante et al. [35] the frequency of FM in patients with low SLE activity was significantly higher than in patients with high disease activity (12% and 5.9%, respectively). Most of SLE patients with FM assessed their condition as significantly more severe than the attending physician, which clearly illustrates catastrophization of pain - another problem that often leads to the erroneous interpretation of patient complaints as manifestations of exacerbation of SLE. Several studies assessed the effects of pain, fatigue, anxiety and depression on the course of SLE with juvenile onset [36, 37] and it was shown that the high severity of fatigue and depression, as well as pain, anxiety and coping difficulties, are predictors of a deterioration in the health-related quality of life in children with SLE at follow-up, despite the absence of signs of SLE activity. However, the authors did not evaluate whether these patients met the diagnostic criteria of FM, and did not discuss the possibility of having secondary FM, which, given the combination of pain, fatigue, anxiety and depression, seems very likely. So, J.T. Jones et al. [37] revealed clinically significant pain that did not correlate with the activity of the disease in 40% of 50 SLE patients with juvenile onset without comorbid pathology and with low disease activity.

We did not find any publications devoted to the analysis of prevalence FM in other systemic connective tissue diseases with juvenile onset, as well as in systemic vasculitis in children. In adult patients, the prevalence of FM in primary Sjogren's syndrome, according to various authors, ranges from 12% to 31% [38-40], in Behcet's disease – from 3.3% to 29.2% [40-42], in systemic sclerosis – from 6.67% to 30.3% [42, 43], in primary anti-phospholipid syndrome – 16.7% [44].

Studies on the occurrence of FM in idiopathic inflammatory myopathies (IIM) have not been conducted so far, even in adult patients, there are only isolated clinical observations [40, 45]. At the same time, this topic is of particular interest in connection with frequent objective difficulties in differential diagnosis of FM and IIM. G. Sambataro et al. [46] published the results of a study of myositis-specific (MSA) and myositis-associated (MAA) antibodies in 233 adult patients with FM without clinical signs of IIRDs at the time of inclusion in the study, who were followed-up for at least 1 year. Antinuclear antibodies were present in 56 (24%) patients, but the result was considered positive if the titer was ≥1:80, the titer ≥1:320 was registered only in 7 (3%) patients. MSA/MAA were detected in 33 (14.1%) patients, MSA – in 21 (9%), of which antibodies to Mi2 were detected significantly more often (5.1%). Various MAAs were present in 14 (6%) cases with approximately equal frequency. In addition, 7 (3%) patients with FM were positive for rheumatoid factor, 4 (1.7%) for anti-Ro-antibodies, and 1 (0.4%) patient for anti-La-antibodies, 1 (0.4%) patient for double-stranded DNA and 1 (0.4%) patient for anti-neutrophil cytoplasmic antibodies (ANCA) to proteinase 3 (PR3). Seropositivity for various antibodies was not associated with any clinical features at the time of inclusion in the study. As a result, 12 (5.2%) patients were diagnosed with IIRD, 5 of them had primary Sjogren's syndrome (none of these patients complained of xerostomia or xerophthalmia at the first visit) and 7 (3%) of the 233 patients with an initial diagnosis of FM had IIM, which indicates the need for periodic examination of patients with an established diagnosis of primary FM for IIRDs.

S. Haliloglu et al. [40] studied the prevalence of FM in adult patients with various rheumatic diseases. It was found that FM was less common in gout – only in 1 (1.4%) of 71 patients and was most often observed in systemic vasculitis – in 5 (25%) of 20 patients. F. Alibaz-Oner et al. [47] analyzed the prevalence of FM in Takayasu arteritis in 55 adult patients: 7 (12%) of them corresponded to the ACR 2010 criteria of FM. R.A. Hajj-Ali et al. [48] diagnosed FM in 13 (23.6%) of 55 adult patients suffering from granulomatosis with polyangiitis. In addition, 22% of these patients had depression, 29% had significant sleep disorders, and 76.4% – fatigue, and in 49.1% of patients, fatigue significantly limited everyday activity.

C. van Eeden et al. [49] assessed the frequency of chronic fatigue and FM in 52 adult patients with ANCA-associated vasculitis in remission, 27 of them (19 with granulomatosis with polyangiitis, 4 with microscopic polyangiitis and 4 with eosinophilic granulomatosis with polyangiitis) met the diagnostic criteria of chronic fatigue syndrome, and 10 (37%) of these 27 patients met the 2016 ACR FM diagnostic criteria. The severity of fatigue did not depend on the subtype of ANCA-associated vasculitis, but in patients with ANCA to myeloperoxidase (MPO) it was significantly higher than in patients with PR3-ANCA. Patients with MPO-ANCA also had greater pain intensity and a greater number of cases of comorbid FM (n=7) than patients with PR3-ANCA (n=3), in addition, they turned out to be more similar in terms of anxiety, depression and sleep disorders to patients from the comparison group suffering from primary FM. This may be due to the chronic course which is characteristic of vasculitis associated with MPO-ANCA, in contrast to the acute but recurrent course of vasculitis associated with PR3-ANCA. Knowledge of the differences underlying the mechanisms of fatigue development in two different serotypes of ANCA-associated vasculitis is important not only for the choice of their personalized therapy, but also for a better understanding of the pathogenesis of chronic fatigue and FM in IIRDs.

Given the almost complete lack of research of FM in IIRDs in children, with the exception of a few works on JIA and SLE with juvenile onset, which appeared only in recent years, it seems very interesting to publish the results of the study by G. Alayli et al. conducted in 2011. [50]. These authors studied the prevalence of juvenile FM in children with familial Mediterranean fever (FMF): 20 (21.9%) of 91 patients with FMF met the diagnostic criteria of M.B. Yunus and A.T. Masi of 1985 [6] in contrast to only 2 (3.3%) cases of FM among 60 healthy children of the control group. In addition, patients with FMF and FM had depression rates significantly higher and the quality of life significantly

lower than patients with FMF without FM. We have not found more modern studies on FM in children with FMF, as well as in other autoinflammatory diseases, in the literature.

N. Karakus et al. [51] analyzed the prevalence of the Mediterranean fever gene (MEFV) in a Turkish cohort of patients with FM. Heterozygous mutations in the MEFV gene were detected in 44 (23.5%) of 187 patients with FM and only in 22 (11.6%) of 190 healthy children of the control group, and 13 of 44 patients with FM and a mutation in the gene MEFV had R202Q polymorphism, which was not found in any child of the control group with a similar mutation. The results of this study suggest that mutations and polymorphisms of the MEFV gene are positively associated with a predisposition to the development of FM. Further studies in larger populations are required to confirm these findings.

Currently, the question whether and which genetic and epigenetic mechanisms are involved in the development of FM, as well as comorbid chronic pain, anxiety and depression, remains relevant [52, 53]. The true prevalence of mental health disorders in children with FM and IIRDs is still unknown, the possibilities of psychotherapy and psychopharmacotherapy have been little studied, and the potential use of biological DMARDs in their treatment has not been studied at all. In this article, we did not dwell in detail on these important issues, since they have already been identified in our recent publications [54, 55] and the search for answers to them, along with studying the prevalence and features of the course of FM in children with IIRDs, will be the main tasks of our subsequent research. But, as the data provided in this brief narrative review shows, the use of the term "secondary fibromyalgia" in IIRDs with juvenile onset seems quite feasible and timely and will help to draw attention to the problem of chronic non-inflammatory pain in children with IIRDs and improve the results of their personalized therapy.

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Received/Reviewed/Accepted
07.03.2024/05.05.2024/13.05.2024

Conflict of Interest Statement The investigation has not been sponsored. There are no conflicts of interest. The authors are solely responsible for submitting the final version of the manuscript for publication. All the authors have participated in developing the concept of the article and in writing the manuscript. The final version of the manuscript has been approved by all the authors.

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