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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии  
საქართველოს სამედიცინო სიახლენი

## GEORGIAN MEDICAL NEWS

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**GMN: Georgian Medical News** is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

**GMN: Медицинские новости Грузии** - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

**GMN: Georgian Medical News** – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებშიდან.

### WEBSITE

[www.geomednews.com](http://www.geomednews.com)

## К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman (Кириллица)**, для текста на грузинском языке следует использовать **AcadNusx**. Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - <http://www.spinesurgery.ru/files/publish.pdf> и [http://www.nlm.nih.gov/bsd/uniform\\_requirements.html](http://www.nlm.nih.gov/bsd/uniform_requirements.html) В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректур авторам не высылаются, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

**При нарушении указанных правил статьи не рассматриваются.**

## REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or computer-printed on a single side of standard typing paper, with the left margin of 3 centimeters width, and 1.5 spacing between the lines, typeface - **Times New Roman (Cyrillic)**, print size - 12 (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: [http://www.nlm.nih.gov/bsd/uniform\\_requirements.html](http://www.nlm.nih.gov/bsd/uniform_requirements.html)  
[http://www.icmje.org/urm\\_full.pdf](http://www.icmje.org/urm_full.pdf)

In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

**Articles that Fail to Meet the Aforementioned  
Requirements are not Assigned to be Reviewed.**

## ავტორთა საქურაღებოლ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დაიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx**. შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრაფიების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შედეგების ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფხიხლებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

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## JOINT LESIONS – COMMON EXTRACUTANEOUS MANIFESTATION IN JUVENILE LOCALIZED SCLERODERMA

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### Abstract.

**Aim of the study:** To determine the frequency of joint lesions (JnL) in children with juvenile localized scleroderma and its possible correlation with autoantibodies and markers of fibrosis.

**Materials and methods:** 500 children with JLS (370 girls and 130 boys) were studied retrospectively for the joint lesion, using standard physical examination, ultrasound examination (UIS) X-ray, MRI. In 190 patients we investigated antinuclear antibodies (antinuclear factor (ANF), rheumatoid factor (RF), antitopoisomerase 1 and anticentomere antibodies, antibodies to DNA, autoantibodies to collagen (Cab) types I-IV, cryoglobulins (CG), serum fibronectine (FN) and hyaluronic acid (HA) levels.

**Results:** JLS patients were divided into 4 groups: 124 patients with circumscribed morphea, 259- linear scleroderma, 93- generalized morphea, pansclerotic in 1 patient, mixed morphea – 23 patients.

JnL were noticed in 175 patients (35%), among them the majority 151 patient (86%) with linear and unilateral forms of JLS. JnL were presented by joint pain in 47% of patients, limitation of joint movement in 60% of affected patients, mostly due to periarticular induration or tissue fibrosis. UIS showed joint effusions – in 16% of JnL, sinovitis and tenosynovitis in 45%. In 12 children joint space narrowing was detected by X ray, in 2- articular erosions. MRI was performed in 97 patients with limitation of joint movement, active synovitis, tenosynovitis found in 80 children. In 1 girl with unilateral scleroderma MRI with contrasting visualised avascular osteonecrosis of tibia.

The absolute percentage of positive values detected autoantibodies and fibrosis markers was higher in children with JnL. ANF was detected in 56 % and RF in 28,4 % of patients with JnL, while scleroderma specific antibodies and ds-DNA were detected in small percentage of JnL patients and in none without it. The levels of CG, FN, HA and Cab were elevated in patients with JnL. Cab of type I and type II were detected in most cases of JnL patients (71% and 62 % correspondingly).

**Conclusion:** JnL occurs in 35% of JLS patients, predominantly in linear and unilateral forms of the disease. Detection of autoantibodies and fibrosis markers in 27-56% of JnL cases demonstrates the activity of autoimmune inflammation and justifies early systemic immunosuppressive therapy in JLS.

**Key words.** Juvenile localized scleroderma, joint lesions, X-ray, MRI, ultrasound investigation, autoantibodies, markers of fibrosis.

### Introduction.

Juvenile scleroderma is a rare disease of childhood. It includes two main clinical entities, juvenile systemic sclerosis (JSS) and juvenile localized scleroderma (JLS). Both have a common pathophysiology, with an initial inflammatory phase of the

disease associated with endothelial dysfunction, and a later fibrotic phase with skin thickness. In JSS many organs may be affected - vascular system (Raynaud phenomenon), cutaneous (skin thickening), gastrointestinal tract, pulmonary, cardiac and musculoskeletal system, while in JLS the process of fibrosis involves mainly the skin and subcutaneous tissues. It is known that JLS is 4-7 times more common than the systemic form, its estimated incidence 3.4–27 per 100.000 or 4–27 new cases per million children per year reported [1-3]. The average age of disease onset is 7.3-8.3 years, and there is a slight female predominance with a reported female: male ratio of 2.4:1. The diagnosis of JLS is often delayed with a median time from disease onset to diagnosis of 11 to 13 months [3,4]. JLS is usually divided into five general subtypes: circumscribed morphea (superficial and deep), linear scleroderma (trunk/extremity and head), generalized morphea, pansclerotic morphea, and mixed subtype according to pediatric classificational criteria [5,6].

Structures other than the skin may be involved in JLS, as subcutaneous tissue, muscles, joints, and even bones [4]. Children with JLS may develop severe deformities, including extremity length discrepancies, muscle atrophy, joint contractures, and facial atrophy, odontostomatologic deformities [7,8]. Approximately from 20 - 40% of patients present extracutaneous manifestations, above the latter are nervous system involvement with frequent epileptic seizures, headaches, cranial nerves impairment and uveitis. [4,9]. These complications are mainly permanent and persist into adulthood. The disease is associated with considerable morbidity due functional limitations and disability, produces a negative impact on quality of life [10-12].

Joint lesion's (JnL) mostly develop in linear and deep subtypes of JLS (Figure 1). Moreover in unilateral subtype, which usually begins in childhood, joints are involved and results in articular contractures and severe deformities of extremities (Figures 2 and 3).

The origin of JnL in JLS may be of different types: caused by scleroderma changes (induration or fibrosis) of skin and periarticular tissues, arthritis itself, avascular necrosis of joints and bones [9,13,14]. Modern techniques such as ultrasound and magnetic resonance, infrared thermography, above X-ray, are used now in pediatric rheumatology to describe structural articular lesions at the early stage of JLS [15-18].

The pathogenesis of scleroderma and JnL is complex and incompletely understood. Vascular injury, autoimmune dysfunction and connective tissue remodeling with excessive collagen production are the main pathways of the disease. The exact pathogenesis is unclear; however, translational peripheral blood and skin studies in LS support a predominance of CD4+ T cells, macrophages, fibroblasts, and TH1- and IFN $\gamma$ -associated





**Figure 1.** Induration, oedema, fibrosis of skin over the ankle of 5-year-old girl with JLS.



**Figure 2.** Unilateral subtype of juvenile localized scleroderma, typical skin induration and fibrosis of the right leg, contractures in the right hip, knee, ankle in 11-year-old girl with JLS.



**Figure 3.** Atrophy, deformation skin sclerosis, contractures of wrist and interphalangeal joints of the left hand in 8-year-old boy.

chemokines/cytokines [19]. Significant elevation of circulating CD4+ IFN $\gamma$  + T cells (TH1) was detected during active disease [20], along with IFN $\gamma$ -related proteins CXCL9 [monokine induced by gamma interferon (MIG)] and CXCL10 [interferon gamma-induced protein 10 (IP-10)] [21,22]. Skin biopsy shows lesions within the perivascular lymphocytic infiltrate of the papillary and reticular dermis with the presence both CXCL9 and CXCL10, CD4+TH cells and macrophages. Recent data showed elevated levels of Interferon-Gamma-Inducible Protein -10. Tumor Necrosis Factor and autoantibodies to myelin basic protein in all clinical subtypes of LS [19,23-25]. Additionally modern research of pathway of endothelial dysfunction revealed that signaling from diseased endothelial cells was predicted to promote fibrosis, identified potential disease-propagating endothelial cell clusters with upregulated pathways in LS skin, highlighting their importance in disease progression [26].

Potential interaction between lymphocytes and macrophages via IFN $\gamma$  chemokine signaling may synergistically promote fibroblasts to increase collagen expression in LS, leading to increased collagen deposition, and fibrosis [21,23]. Fibroblasts are involved in the excessive production of collagen, markers for fibroblasts include vimentin 31, fibroblast-specific protein 1,64 and platelet-derived growth factor receptor beta 65. They can be monitored in LS patients and predict disease progression [14].

Antinuclear antibodies (ANA), rheumatoid factor (RF), anti-double-stranded DNA antibodies and anti-histone antibodies were detected in LS [27,28]. Thus, according to some authors, ANA is detected in 46-80%, antinuclear antibodies – in 50%, antihistone antibodies (AHAs) – in 47%, rheumatoid factor (RF)– in 26% of adult patients with LS [29]. AHAs were found in 32%–39% of the LS patients, and anti-dsDNA in 29%–30% of the LS patients, authors propose the use of them combined as a marker for higher risk of muscle and joint morbidity [30]. Anti-topoisomerase I antibodies were also detected in LS [31]. ANA positivity has been associated with extracutaneous involvement. ANAs and AHAs were more prevalent among children with linear morphea, where their presence is associated with greater lesion burden and functional impairment [27,28]. There are some data stating that antinuclear factor directly correlates with joint lesions [27].

Patients with rheumatic conditions often have mixed cryoglobulins, composed of class M and rheumatoid factor immunoglobulins, class G polyclonal immunoglobulins and fibronectin. The level of cryoglobulins also correlates with clinical and laboratory activity of scleroderma.

The extracellular matrix of skin, tendon and bone tissue is composed mainly of type I collagen, and of type III collagen to a lesser extent. Type II collagen is mostly located in the articular cartilage, collagen IV – in basal cell membranes. Elevated levels of autoantibodies to types I-V collagens were detected in LS patients [32]. Anti-collagen type V are considered by some authors as a marker of early systemic sclerosis [33].

Fibrosis in scleroderma is a result of monocyte overproduction, an intensive secretion of monokines, such as fibronectin and interleukin-1 are stimulated. Fibronectin has a high affinity to the native and denatured collagen. Some data suggests that in scleroderma level of fibronectin and hyaluronic acid are increased and could be used as biomarkers of fibrosis [23,34].

JnL is the most frequent extracutaneous finding in JLS, patients who developed arthritis often have a positive rheumatoid factor (RF), and sometimes an elevated erythrocyte sedimentation rate (ESR) and circulating antibodies [4,7].

**Aim of the study.** To determine the frequency of joint lesions in children with juvenile localized scleroderma and its possible correlation with autoantibodies and markers of fibrosis.

### Materials and Methods.

JnL were studied retrospectively in 500 children with JLS, who were under supervision at the specialized rheumatology department of I.M. Sechenov First

Moscow Medical University for a five – year period from 2013-2024. The surveyed group consisted of children from 3 to 17 years of age, including 370 girls and 130 boys (F\M ratio 2,8:1). Patients with JLS were divided into groups based on the clinical forms of the disease in accordance with the preliminary classification criteria [5]. At the time of examination, the patients with different clinical forms of the disease had dissimilar disease duration and activity.

A history of joint manifestations was obtained by standard physical examination, ultrasound examination (UIS) X-ray, MRI. In 190 patients we investigated antinuclear antibodies (antinuclear factor (ANF), rheumatoid factor (RF), antitopoisomerase 1 and anticentomere antibodies, antibodies to DNA, autoantibodies to collagen (Cab) types I-IV, cryoglobulins (CG), serum fibronectine (FN) and hyalyronic acid (HA) levels. Levels of Scl-70 and anti-centromere antibodies were measured by enzyme immunoassay test using kit “Anti-Scl-70 Orgentec”, (Germany). ANF was determined by indirect immunofluorescence. RF was determined by ELISA test with the normal values of <20 IU/mL, and anti- DNA was determined by ELISA test with the reference value of <20 IU/mL. Unconjugated concentration of FN was measured by ELISA (“Fibronectin Technoclone”, Austria). Normal values of unconjugated FN are 70 to 148 mg/ml according to the manufacturer’s recommendations. The concentration of HA in blood serum was measured by ELISA testing using “HA Testkit Corgenix”, (USA). The level of HA in children was considered to be high when its concentration exceeded 30 ng/ml in accordance with the recommendations of the manufacturer. The presence of cryoglobulins in blood serum was determined with “Solar” PV 1251C (Solar, Belarus) spectrophotometer at a wavelength of 500 nm in accordance with the optical fluid density difference in a buffer solution (pH 8.6), incubated for 1 hour at the temperature of 4°C and then at 37°C. The normal values are up to 0.06 optical density. Determination of type I-IV collagen antibodies in blood serum was performed with ELISA method. The test was considered positive if the negative control value exceeded. To interpret the results of the research the concept of “positive” was introduced for this test. The results were thought to be “positive” if they showed exceeding reference values in the tests with quantitative expression, presence of Scl-70 and anticentromere antibodies in blood serum, antinuclear factor titer of 1:80 or higher.

Statistical analysis of the results was performed with the use of Statistica 6.0 software. The quantitative indices were presented as mean values ± standard deviation and range of

values. Quality indices were presented as an absolute number of observations and proportion (in %) of the total number. The validity of differences in the compared values was determined by Student’s t-test for interval variables. The differences were considered statistically significant at p<0.01.

### Results.

According to the clinical form of JLS the patients were divided into 4 groups :124 patients with circumscribed morphea, 259-linear scleroderma, 93– generalized morphea, pansclerotic in 1 patient, mixed morphea – in 23patients (Table 1).

Mean age of the disease onset was seven years and six months (range 18 months – 15.5 years).

As the Table 1 shows, the vast majority of surveyed patient were children with severe forms of JLS - linear scleroderma of limbs, generalized morphea (unilateral form) and pansclerotic scleroderma. JnL were noticed in 175 patients (35%), among them the majority 151 patient (86%) with linear and unilateral forms of JLS. (Figure 4) In linear scleroderma of head joint contracture of temporo-mandibular joint was only in 1 case, with prolonged disease duration, for more than 10 years.

JnL were presented by joint pain in 47% of patients, limitation of joint movement in 60% of affected patients, mostly due to periarticular induration or tissue fibrosis. UIS showed joint effusions – in 16% of JnL, sinovitis and tenosinivitis in 45% (Figure 5).

X- ray was done in 102 patients. Radiologic abnormalities in knee, hip, ankle and wrist joints were seen 8 patients with linear JSL,5 with unilateral generalised morphea and 1- pansclerotic morphea. In 12 children joint space narrowing was detected, in 2- articular erosions. Patients with articular erosions had

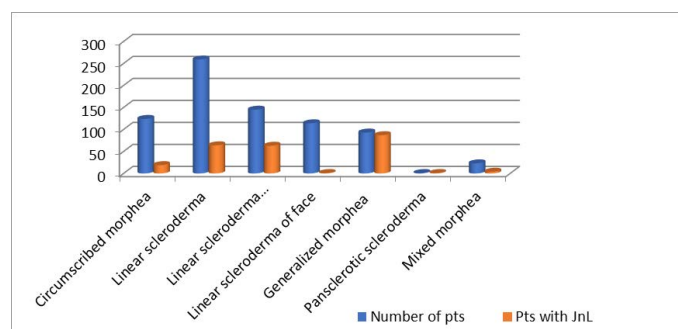


Figure 4. Distribution of patients with JnL by scleroderma subtypes.

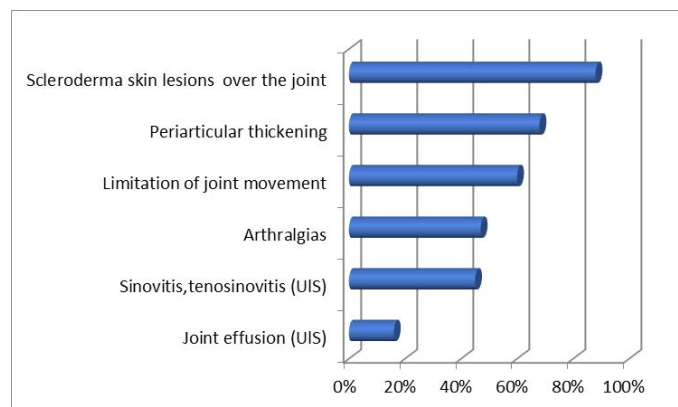


Figure 5. Manifestations of joint lesions.

**Table 1.** Joint lesions in different clinical subtypes of juvenile localized scleroderma.

Clinical subtypes of juvenile localized scleroderma		Number of patients (% of the whole )	Patients with Joint lesions (% of the clinical subtype)
<b>JLS (N=500) Male -130 Female – 370</b>	<b>Circumscribed morphea</b>	<b>124 (24%)</b>	<b>19(15)</b>
	-superficial	79	6 (7,5)
	- deep	45	13 (28)
	<b>Linear scleroderma</b>	<b>259 (51,8)</b>	<b>64 (24,7)</b>
	- trunk\limbs	145	63 (43,4)
	- head	114	1(0,8)
	<b>Generalized morphea (unilateral form)</b>	<b>93 (19,5)</b>	<b>87 (93)</b>
	<b>Pansclerotic scleroderma</b>	<b>1 (0,2)</b>	<b>1 (100)</b>
	<b>Mixed morphea</b>	<b>23 (4,5)</b>	<b>4 (17,3)</b>
<b>Total number</b>	<b>500</b>	<b>175 (35)</b>	

**Table 2.** Serum antibodies profile in JSL (N=190) patients with and without JnL.

Feature	The range of absolute value	Mean level (M±m) JLS pts (N=190)	% Of positive in JLS pts with JnL (group I N=125)	% Of positive in JLS pts without JnL (group II N=65)	P	
Antinuclear antibodies* (titer)	1:80 -1:640	-	56	3,2	p<0,01	
Rheumatoid factor* (IU/ml)	11-125	82,4±60,3	28,4	2,1	p<0,01	
ds-DNA (IU/ml)	0-62	34,5±36,2	2,5	-		
Anti Scl-70 antibodies	-	-	8,5	-		
Anti-centromere B antibodies	-	-	0,5	-		
Crioglobulines (optical density unit)*	0,037- 0,216	0,051 ± 0,037	27,6	5,2	p<0,01	
Collagen antibodies (mkg/ml)	I type*	0,297-0,893	0,405±0,112	71	11,5	p<0,01
	II type*	0,330-1,129	0,551±0,161	62	12	p<0,01
	III type *	0,287-0,681	0,370±0,108	58	8	p<0,01
	IV* type	0,151-0,577	0,300±0,085	51	5	p<0,01
Serum fibronectin * (mg/ml)	68-264	124,8±41,9	46,5	14	p<0,01	
Hyaluronic acid* (ng/ml)	5,4 -68,4	15,7±16,7	23,7	8,5	p<0,01	

**Note**\*- difference between groups statistically valid (p<0,01).

prolonged disease duration (more than 7 years) and were treated inadequate.

MRI was performed in 97 patients with limitation of joint movement, active synovitis, tenosynovitis found in 80 children. In 1 girl with unilateral scleroderma MRI with contrasting visualised avascular osteonecrosis of tibia.

Data on serum antibodies profile and markers of fibrosis are summarized in Table 2.

The analysis of the data suggests that patients in both groups were “positive” for most of the required tests, except scleroderma-specific antibodies. At the same time, the absolute percentage of positive values was higher in the group I – children with JnL (differences are statistically valid).

Our data shows that ANF was detected in 56 % and RF in 28,4 % of patients with JnL.

In our series scleroderma-specific antibodies and ds-DNA were detected in small percentage of JnL patients and in none without it. It is no wonder, because these antibodies are mainly found in JSS.

Surprisingly, the levels of CG and Cab were elevated in patients with JnL. CG was the third most frequently detected element (27,6%) in JLS with JnL, while its detection rate was less than 5,2% in patients without JnL. Increased level of CG in JnL patients confirms the role of immune mechanisms in the pathogenesis of this clinical form [23]. Similar to it, the levels of FN and HA in serum had a higher detection rate in children with

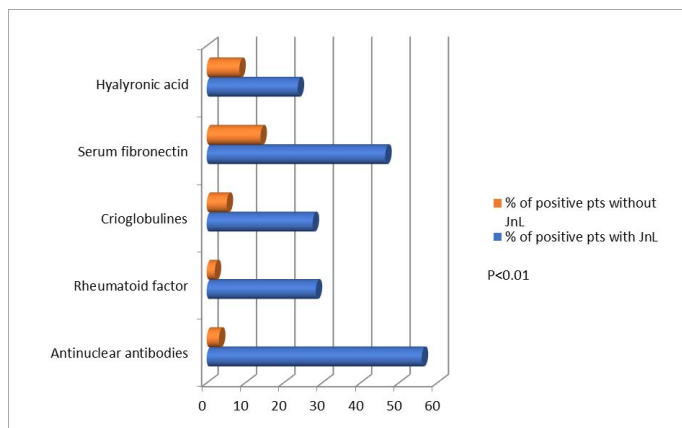
articular manifestations. Analyses of the detection of four classes of Cab revealed that in the group of JnL Cab were detected significantly more often than in the group without JnL (Figure 7). Cab to of type I and type II were detected in most cases of JnL patients (71% and 62 % correspondingly). This seems reasonable because type I and type II collagens are involved in the construction of skin, tendons, and articular cartilage and are affected by the pathological scleroderma process.

Summing it up, the levels of autoantibodies and markers of fibrosis were significantly higher in the patients with JnL.

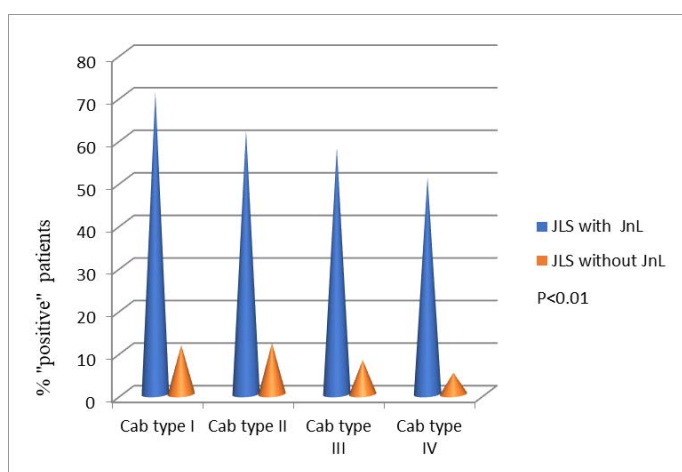
## Discussion.

The frequent occurrence of JnL in JSL has been previously reported both in adults and children. In the present series of 500 JSL children, JnL were detected in 175 patients (35%), among them the majority 151 patient (86%) with linear and unilateral forms of JLS.

Common occurrence of JnL is mentioned by the other authors, who point out joint involvement as specific feature of childhood localized scleroderma [4,7-9]. Our data from one pediatric rheumatology center prove it. Only 47 % of affected children complained of joint pain or had tenderness or pain on joint motion. Flexion contractures of joints with disability were the main complain. JnL also were presented by limitation of joint movement in 60% of affected patients, mostly due to periarticular induration or tissue fibrosis round the joint.



**Figure 6.** Levels of autoantibodies and markers of fibrosis in LS patient with and without JnL.



**Figure 7.** Detection rate of antibodies to type I-IV collagens in patients with JnL and without JnL.

UIS showed joint effusions – in 16% of JnL, sinovitis and tenosynovitis in 45%. While joint space narrowing by X-ray was detected in 12, articular erosions - in 2 children. MRI joint abnormalities were seen in 82% of examined children with JnL. In 1 girl with unilateral scleroderma MRI with contrasting detected avascular osteonecrosis of tibia. The literature is now emphasising the need for early instrumental identification of articular involvement in JLS [15,17].

In our series the levels of detected autoantibodies and markers of fibrosis were significantly higher in the patients with JnL. The obtained data are agreed with the results of the international multicenter studies of children, in which the proportion of ANF detection in children with juvenile systemic sclerosis (JSS) ranges from 81% to 97% [4] and it amounts to 42.3% in patients with JLS [28,35]. RF has been detected, as low titre, in 16 % of the patients who had JLS, and significantly correlated with the presence of arthritis [23].

Despite modern biomarkers of scleroderma inflammation [19], the detection of autoantibodies and markers of fibrosis in JLS patients in our series is additional evidence of systemic autoimmune and collagen synthesis disturbances in these patients. Our data in coherence with the other studies [21,22] determines the target points for the treatment with corticosteroids (CS) and immunosuppressants JLS accompanied by JnL. According to

it we believe that JLS with JnL of numerous joints could be considered as systemic form of scleroderma. Especially, it is true for the unilateral form JLS, that usually starts in childhood and lead to disability and impaired quality of life [36].

Contractures in JLS are mainly reversible thanks to reversibility of odema and induration stages of scleroderma under treatment with CS and methotrexate (MTX). Only few of our patients had irreversible arthritis with joint space narrowing and erosions. In JSS clinicians rarely doubt the wisdom of including CS and cytotoxic drugs in the therapy. In contrast, the treatment of JLS is believed to have successful outcomes with the local use of immunosuppressive agents. There are a lot of studies (in particular randomized, placebo-controlled) that prove effectiveness of CS, MTX, Mycophenolate mofetil in JLS, including joint contractures [37-39].

It should be emphasized that the chronic nature of scleroderma, the prevalence of linear form of the disease in children, complicated by irreversible fibrosclerotic defects of the musculoskeletal system, growth retardation of extremities encourages pediatric rheumatologists to elaborate a unified treatment protocols with CS, MTX, biologics. There are reports of successful treatment with biologics in JLS cases resistant to conventional immunosuppressive therapy, even pansclerotic morphea [40-43]. Experts in JLS prioritize early initiation of CS, cytotoxic drugs and biologics to avoid disability, lag in growth and development in children [44].

### Conclusion.

JnL according to our data occur in 35% of JLS patients, predominantly in linear and unilateral forms of the disease. Detection of autoantibodies and fibrosis markers in 27-56% of JnL cases demonstrates the activity of autoimmune inflammation and justifies systemic immunosuppressive therapy in JLS. The appropriate treatment with systemic immunosuppressants and biologics must be started at early stages of JLS, to prevent joint contractures and severe deformities of legs and hands.

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სახსრის ჩართვა ჩვეულებრივი კანქვეშა გამოვლინებაა არასრულწლოვანთა შეზღუდული სკლეროდერმიაში

კვლევის მიზანი: არასრულწლოვანთა ლოკალიზებული სკლეროდერმიის მქონე ბავშვებში სახსრის დაზიანების სიხშირის (JnL) დადგენა და მისი შესაძლო კორელაცია აუტოანტიისხეულებთან და ფიბროზის მარკერებთან.

მასალები და მეთოდები: 500 ბავშვს არასრულწლოვანთა ლოკალიზებული სკლეროდერმიით (370 გოგონა და 130 ბიჭი) შესწავლილი იქნა სახსრის დაზიანების რეტროსპექტულად, სტანდარტული ფიზიკური გამოკვლევის, ულტრაბგერითი გამოკვლევის, რენტგენის, მაგნიტურ-რეზონანსული გამოკვლევის გამოყენებით. 190 პაციენტში გამოვიკვლიეთ ანტიბირთვული ანტიისხეულები (ანტიბირთვული ფაქტორი, რევმატოიდული ფაქტორი, ანტიტოპოიზომერაზა 1 და ანტიცენტომერული ანტიისხეულები, ანტიისხეულები დნმ-ის მიმართ, აუტოანტიისხეულები კოლაგენის I-IV ტიპის, კრიოგლობულინები, შრატში ფიბრონექტინისა და ჰიალირონის მჟავას დონეები.

შედეგები: არასრულწლოვანთა სკლეროდერმიით დაავადებული პაციენტები დაიყო 4 ჯგუფად: 124 პაციენტი შემოხაზული მორფით, 259-ხაზოვანი სკლეროდერმიით, 93- გენერალიზებული მორფეა, პანსკლეროზული 1 პაციენტში, შერეული მორფეა - 23 პაციენტი.

სახსრების დაზიანება აღინიშნა 175 პაციენტში (35%), მათ შორის უმეტესობა 151 პაციენტი (86%) ხაზოვანი და არასრულწლოვანთა სკლეროდერმიით დაავადებულთა ცალმხრივი ფორმები. სახსრების დაზიანებები გამოვლინდა სახსრის ტკივილით პაციენტთა 47%-ში, სახსრის მოძრაობის შეზღუდვა დაზარალებულთა 60%-ში, უმეტესად პერიარტიკულური ინდურაციის ან ქსოვილის ფიბროზის გამო. ულტრაბგერითი გამოკვლევა აჩვენა სახსრების გამონაყარი - სახსრის დაზიანების 16%-ში, სინოვიტი და ტენოსინივიტი 45%-ში. 12 ბავშვს აღენიშნებოდა სახსრის სივრცის შევიწროება რენტგენის საშუალებით, 2- სასახსრე ეროზიაში. მაგნიტური რეზონანსი ჩატარდა 97 პაციენტში სახსრის მოძრაობის შეზღუდვით, აქტიური სინოვიტით, ტენოსინოვიტით აღმოჩენილი 80 ბავშვში. 1 გოგონაში ცალმხრივი სკლეროდერმიის მაგნიტური რეზონანსით კონტრასტული ვიზუალური ავასკულარული ოსტეონეკროზით.

აუტოანტიისხეულების და ფიბროზის მარკერების გამოვლენილი დადებითი მნიშვნელობების

აბსოლუტური პროცენტი უფრო მაღალი იყო სახსრის დაზიანებით ბავშვებში. ანტიბირთვული ფაქტორი გამოვლინდა სახსრის დაზიანების მქონე პაციენტების 56%-ში და რევმატოიდული ფაქტორი 28,4%-ში, ხოლო სკლეროდერმოსპეციფიკური ანტიისხეულები გამოვლინდა სახსრის დაზიანებით დაავადებულთა მცირე პროცენტში და არცერთში მის გარეშე. სახსრების დაზიანების მქონე პაციენტებში ამალეებული იყო კრიოგლობულინების, ფიბრონექტინის, ჰიალირონის მჟავისა და კოლაგენის მიმართ ანტიისხეულების დონე. I და II ტიპის კოლაგენის ანტიისხეულები გამოვლინდა სახსრის დაზიანებული პაციენტების უმეტეს შემთხვევაში (71% და 62% შესაბამისად).

დასკვნა: სახსრების დაზიანება ხდება არასრულწლოვანთა ლოკალიზებული სკლეროდერმიით დაავადებულთა 35%-ში, უპირატესად დაავადების ხაზოვანი და ცალმხრივი ფორმებით. აუტოანტიისხეულების და ფიბროზის მარკერების გამოვლენა სახსრის დაზიანების შემთხვევების 27-56%-ში ადასტურებს აუტოიმუნური ანთების აქტივობას და ამართლებს ადრეულ სისტემურ იმუნოსუპრესიულ თერაპიას არასრულწლოვანთა ლოკალიზებული სკლეროდერმიაში.

საკვანძო სიტყვები: არასრულწლოვანთა ლოკალიზებული სკლეროდერმია, სახსრების დაზიანებები, რენტგენი, მაგნიტურ-რეზონანსული გამოკვლევა, ულტრაბგერითი გამოკვლევა, აუტოანტიისხეულები, ფიბროზის მარკერები.

**Поражение суставов – частое внекожное проявление при ювенильной ограниченной склеродермии.**

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**Целью работы:** явилась оценка характера поражения суставов (ПС) при, возможная корреляция с уровнем аутоантител и маркеров фиброза.

**Материал и методы исследования:** Проведена ретроспективная оценка ПС у 500 детей с ЮОСД. Использовали физикальный осмотр, ультразвуковое (УЗИ), рентгенологическое, МРТ исследование суставов, лабораторные иммунологические тесты; у 190 определяли аутоантитела- антинуклеарный фактор, ревматоидный фактор, склеродермоспецифические антитела, антитела к коллагенам 4 типов, уровень гиалуроновой кислоты, фибронектина, криоглобулинов.

**Результаты:** Пациенты с JLS были разделены на 4 группы: 124 пациента с бляшечной склеродермией, 259 - линейной склеродермией, 93 - с генерализованной, 1 с пансклеротической, 23 пациента - смешанной формой склеродермии. ПС были отмечены у 175 пациентов (35%), среди них большинство - 151 пациент (86%) с линейной и гемисклеродермией туловища.

ПС проявлялись болью в суставах у 47%, ограничением

движений в суставах у 60% больных, в основном за счет периартикулярной индурации или фиброза тканей. УЗИ показало наличие суставного выпота - в 16% случаев, синовита и теносиновита - в 45%. У 12 детей при рентгенографии выявлено сужение суставной щели, у 2 - суставные эрозии. МРТ выполнена у 97 пациентов с ограничением движений в суставах, активный синовит, теносиновит выявлен у 80 детей. При лабораторном исследовании – уровень аутоантител и маркеров фиброза был выше у детей с ПС, отмечено значительное повышение антител к коллагенам I и II типов. Антинуклеарный фактор был обнаружен у 56 %, ревматоидный - у 28,4 %

пациентов с ПС, склеродермоспецифические антитела были обнаружены у небольшого процента пациентов с ПС и ни у кого без него.

**Выводы:** ПС при ЮОСД встречается у 35% детей, преимущественно при линейной форме гемисклеродермии туловища. Обнаружение аутоантител и маркеров фиброза в 27-56 % случаев больных ЮОСД с ПС свидетельствует об активности аутоиммунного воспаления и обосновывает раннее назначение иммуносупрессивной терапии системно.

**Ключевые слова:** Ювенильная локализованная склеродермия, поражение суставов, рентгенография, МРТ, УЗИ, аутоантитела, маркеры фиброза.