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The Journal of Pediatric Academy is the official publication of the Kayseri Child Health Association.

The Journal of Pediatric Academy which was established in 2020 is an international, unbiased double-blinded peer-reviewed, open-access electronic and only-online published journal in the English language. The Journal of Pediatric Academy is published 3 times a year (April, August and December) and accepts original research articles, invited review articles, clinical reports, and case reports in all areas of pediatric research, which summarize recent developments about a particular subject based on standards of excellence and expertise.

The Journal of Pediatric Academy does not expect any fees for publication. All articles are available on the website of journal for all readers.

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J. Pediatr. Acad. (JPA) was established in 2020 as open access and peer-reviewed journal that accepts articles in English. J. Pediatr. Acad. (JPA) is published 3 times a year. Articles submitted should not have been previously published or be currently under consideration for publication any place else and should report original unpublished research results. The journal does not expect any fees for publication. All articles are available on the website of the journal for all readers.

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Journal of Pediatric Academy (JPA) reports on major advances in the diagnosis and treatment of diseases in children. Each issue presents informative original research articles, review articles, case reports, image corners, and letters to the editor from leading clinicians and investigators worldwide.

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Unstructured Abstract and Keywords: Limit of the abstracts are given in the table. It must be factual and comprehensive. Limit the use of abbreviations and acronyms, and avoid general statements (eg, "the significance of the results is discussed"). List three to five keywords or phrases.

Text: Organize the manuscript into four main headings: Introduction, Materials and Methods, Results, and Discussion. Define abbreviations at first mention in the text and each table and figure. If a brand name is cited, supply the manufacturer's name and address (city and state/country). All forms of support, including pharmaceutical industry support, must be acknowledged in the Acknowledgment section.

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Manuscript Types

JPA publishes the types of articles briefly described below.

Editorial Comment:

Editorial comments aim to provide a brief critical commentary by reviewers with expertise or with a high reputation on the topic of the research article published in the journal. The authors are selected and invited by the journal to provide such comments. The text should contain 1500 words or fewer. it includes 5 figures and/or tables or fewer and 15 references or fewer.

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This is the most important type of article since it provides new information based on original research. The main text of original articles should be structured with an Introduction, Methods, Results, Discussion, Conclusion, and References subheadings. Please see **Table 1** for limitations for Research Articles.

Statistical analysis is usually necessary to support conclusions. Statistical analyses must be conducted by international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information on statistical analyses should be provided with a separate subheading under the Materials and Methods section and the statistical software that was used during the process must be specified.

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Invited reviews prepared by authors who have extensive knowledge of a particular field and whose scientific background has been translated into a large volume of publications with a high citation potential are welcomed. Submissions from such authors may also be invited by the journal. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies.

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For educational purposes, the journal publishes original, interesting, and high-quality clinical images having a brief explanation (maximum 500 words excluding references but including figure legends) and of educational significance. The figure legend should contain no more than 100 words. It can be signed by no more than 5 authors and can have no more than 5 references and 3 figures or tables. Any information that might identify the patient or hospital, including the date, should be removed from the image. An abstract is not required with this type of manuscript. The main text of clinical images should be structured with the following subheadings: Case, and References.

Letters To The Editor:

Letters to the editor should pertain to articles published within the Journal of Pediatric Academy or highlight important new clinical or laboratory insights. The text should contain 1000 words or fewer.

Table 1
Limitations for each manuscript type

Manuscript Type	Word Limit	Abstract Word Limit	Reference Limit	Table Limit	Figure Limit
Editorial comment	1500	No abstract	15	2	5
Original Article	3500	300	50	6	6
Invited Review	5000	350	100	6	10
Case Report	1500	200	15	2	5
Image corner	500	No abstract	5	-	3
Letter to the Editor	1000	No abstract	5	1	1

References:

The authors are responsible for the accuracy of the references. Key the references (double-spaced) at the end of the manuscript. Cite the references in the text in the order of appearance.

In-text Citations:

Assign a number to each reference within the text as you cite it. **The citations are identified by Arabic numbers in superscript**. The number must be used even if the author(s) is named in the text.

Example: In his study, Babbott[11] found that….

New sources are numbered consecutively as they occur in the text. If a source is repeated, so is the number originally assigned to it.

When multiple references are cited at the same place in the text, use commas without spaces to separate non-inclusive numbers.

Example: Multiple studies have indicated….[1,3,9,16]

If multiple references cited at the same place in the text are inclusive, use a hyphen to join the first and last numbers.

Example: Multiple studies have indicated that….[7-10]

Placement of the citation numbers is generally at the end of the sentence, unless there are two individual sets of citations in each sentence. Generally reference numbers should be placed outside of periods and commas, inside of colons and semicolons.

Cite unpublished data—such as papers submitted but not yet accepted for publication and personal communications, including e-mail communications—in parentheses in the text. If there are more than three authors, name only the first three authors and then use et al. Refer to the List of Journals Indexed in Index Medicus for abbreviations of journal names, or access the list at http://www.nlm.nih.gov/tsd/serials/lji.html. Sample references are given below:

Journal Article:

1. Ang KK, Price RE, Stephens LC, et al. The tolerance of primate spinal cord to re-irradiation. *Int J Radiat Oncol Biol Phys*. 1993;25:459–464.

Journal Article published in non-English Languages:

2. Altuntaş N, Çelebi DT, Koçak M, Andıran N. Yenidoğan bebeklerde direkt coombs testi taraması ve pozitifliğinin morbidite üzerine, etkisi; tek merkezd eneyimi. *Pam Tıp Derg* 2015;8:39-44. (in Turkish)

Book Chapter:

3. Dimery IW. Chemotherapy in head and neck cancer. In: Myerhoff WI, Rice DH, eds. Otolaryngology: head and neck surgery, 2nd ed. Philadelphia: WB Saunders, 1992:1027–1045.

Entire Book:

4. Virchow R. Cellular Pathology. Philadelphia: JB Lippincott, 1863.

Software:

5. Epi Info [computer program]. Version 6. Atlanta, GA: Centers for Disease Control and Prevention; 1994.

Online Journals:

6. Friedman SA. Preeclampsia: a review of the role of prostaglandins. Obstet Gynecol [serial online]. January 1988;71:22–37. Available from: BRS Information Technologies, McLean, VA. Accessed December 15, 1990.

Database:

7. CANCERNET-PDQ [database online]. Bethesda, MD: National Cancer Institute; 1996. Updated March 29, 1996.

World Wide Web:

8. Gostin LO. Drug use and HIV/AIDS [JAMA HIV/AIDS Web site]. June 1, 1996. Available at: http://www.ama-assn.org/special/hiv/ethics. Accessed June 26, 1997.

URL (Uniform Resource Locator)

9. (J. M. Kramer, K. Kramer [jmkramer@umich.edu], e-mail, March 6, 1996).

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Contents

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Clinical Guidance

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Erciyes Clinical Guideline for Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with COVID-19

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Abstract

Multisystem Inflammatory Syndrome in Children (MIS-C) is an inflammatory response to prior SARS-CoV-2 infection. Clinical features of MIS-C could resemble those seen in other diseases, including Kawasaki Disease, Hemophagocytic Lymphohistiocytosis, and cardiovascular shock. The pathogenesis is unclear; however, it is thought to develop 4 to 6 weeks after infection. This guideline aims to provide a framework for physicians to use to evaluate patients and manage those diagnosed with MIS-C.

Keywords: Pediatric, COVID-19, MIS-C, guideline

Introduction and Purpose

SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) causes acute and post-acute illness in the pediatric population. One of the post-acute illnesses is Multisystem Inflammatory Syndrome in Children (MIS-C). MIS-C most consistently presents with prolonged fever and GI complaints (abdominal pain, vomiting, and diarrhea). Additional features include rash, extremity swelling, conjunctivitis, and lymphadenopathy similar to Kawasaki Disease. The most concerning feature of MIS-C is progression to cardiovascular abnormalities (myocarditis, coronary aneurysms, ventricular dysfunction) and potentially shock. Children with MIS-C rarely exhibit respiratory complaints, and death is rare.

This guideline was developed by a multi-specialty team of Erciyes University Department of Pediatrics clinicians to assist with evaluating and treating pediatric patients (< 18 years old) who present to Erciyes University with confirmed or suspected MIS-C secondary to infection with SARS-CoV-2.

This guideline is not for the management of acute SARS-CoV-2 infection. This guideline does not address isolation precautions, transport, airway, and treatment of suspected active SARS-CoV-2 infection.

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This guideline is intended as a general guide, should be applied, and interpreted with caution, and is likely to change over time. As this guideline was developed for Erciyes University patients, any use of this document by other clinicians or facilities should be based on the individual clinical circumstances of their patients and the resources available to the patient's treating clinicians.

BOX 1 POSSIBLE SYMPTOMS AND FINDINGS FOR MIS-C

(In the evaluation of the cases in terms of MIS-C, the following must be questioned)

- Presence of findings consistent with ACTIVE COVID-19 in the patient and/or in the close contacts
- A history of illness compatible with COVID-19 in the patient and/or close contacts in the last six weeks

- Systemic inflammation findings:
  - Fever
  - Myalgia
  - Bone pain in extremities
  - Tachycardia
  - Hypotension
  - Hypoperfusion or hyperperfusion
  - Lymphadenopathy
- Respiratory:
  - Chest pain
  - Respiratory distress
- Neurologic:
  - Headache
  - Altered mental status/confusion
  - Meningismus
  - Convulsion
  - Focal neurological deficit
- Gastrointestinal:
  - Nausea / vomiting
  - Diarrhea
  - Abdominal pain
- Skin and mucosal changes:
  - Rash (polymorphous exanthem, erythroderma, erythematous macules, and/or papules)
  - Swollen hands and feet
  - Bilateral non-purulent conjunctivitis
  - Mucous membrane changes (erythematous mucous membranes, strawberry tongue)
  - Peeling of skin

BOX 2 INITIAL WORK-UP FOR SUSPECTED MIS-C (LABORATORY AND RADIOLOGICAL)

- SARS-CoV-2 PCR: Nasal oropharyngeal combined swab sample (if suspected of an active disease, a total of 3 consecutive samples should be sent daily from patients)
- COVID-19 Rapid Antibody Test: The test should be seen before IVIG treatment. If this is not possible, the sample should be kept for testing before IVIG. Antibody testing is not obligatory in children with positive PCR positivity in the past.
- SARS-CoV-2 Rapid Antigen Test (if available)

- Complete blood count with differential, basic renal and liver function panel, blood gas with lactate, lactate dehydrogenase
- Acute phase reactants: C-reactive protein, erythrocyte sedimentation rate, ferritin, procalcitonin
- Coagulation tests: Prothrombin time, active partial thromboplastin time, fibrinogen, D-dimer
- Cardiac enzymes: CK, CK-MB, troponin, BNP
- Urinalysis with microscopy
- Blood culture, respiratory viral PCR panel, rapid influenza, and RSV tests
- If concern for viral co-infection; Cytomegalovirus, Epstein-Barr virus, Parvovirus, Adenovirus PCRs

- Chest X-Ray→If there is an abnormality, consider thorax CT
- If there is an abdominal finding→Abdominal X-ray and/or abdominal USG
- Electrocardiogram (ECG)
- Transthoracic echocardiogram focused on ventricular function and coronary arteries
- An echocardiogram should be performed urgently if there is a suspicion of cardiac involvement. Otherwise, it can be done in the first 6 hours.

Abbreviations: BNP, brain natriuretic peptide; CT, computed tomography; COVID-19, Coronavirus Disease 2019; CK, creatinine kinase; CK-MB, creatine kinase-MB; IVIG, intravenous immune globulin; MIS-C, Multisystem Inflammatory Syndrome in Children; PCR, polymerase chain reaction; RSV, respiratory syncytial virus; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; USG, ultrasonography

BOX 3 CASE-BASED ADDITIONAL EVALUATIONS

- Cases evaluated for MIS-C should be followed up separately from other cases
- In all evaluation processes, hospital isolation rules for COVID-19 cases should be obtained
- Head Imaging - consider if focal neurologic deficit, altered mental status, seizure, or severe headache with or without meningeal signs. The first choice should be cranial MRI, and the second is CT
- Imaging should be performed with contrast if renal functions are normal. If a thorax CT scan is planned for COVID-19, a non-contrast scan should be done. In these cases, the radiology department should be informed before.
- Cerebrospinal fluid (CSF) studies - if there is a neurological finding and lumbar puncture indicated;
  - Opening pressure
  - Cell count
  - Glucose, protein, sodium, and chloride
  - Culture (aerobic blood culture bottle)
  - Infectious meningitis/encephalitis PCR panel
- Any rash should be photographed and documented
- In the presence of diarrhea, rotavirus, and adenovirus rapid antigen tests, gastrointestinal pathogen PCR panel
- Triglycerides after 12 hours of fasting in suspected hemophagocytosis
- Serology and blood culture for brucellosis in the presence of fever and/or joint complaints lasting for ≥7 days
- Thoracic USG should be requested if pleural fluid is suspected
- While making the differential diagnosis of cases with known primary or secondary immunodeficiency, appropriate antibiotic treatments should be started within the indications without any delay. Cefepime or piperacillin-tazobactam intravenous can be started in the first step in patients with febrile neutropenia whose focus of fever is unclear. A glycopeptide or antifungal drug may be added to the initial treatment regimen according to the additional characteristics of the cases

Abbreviations: CT, computed tomography; COVID-19, Coronavirus Disease 2019; MRI, magnetic resonance imaging; MIS-C, multisystem Inflammatory Syndrome in Children; PCR, polymerase chain reaction; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; USG, ultrasonography

BOX 4 DIFFERENTIAL DIAGNOSIS OF MIS-C

- Kawasaki Disease
- Brucellosis
- Bacterial infection / sepsis / septic shock
- Staphylococcal and streptococcal toxin-related diseases
- Vasculitis
- Viral infections (CMV, EBV, adenoviruses)
- Myocarditis (Non-SARS-CoV-2 viral agents)
- Drug hypersensitivity reactions
- Systemic juvenile idiopathic arthritis
- Other autoinflammatory diseases can cause macrophage activation syndrome
- Hematological malignancies

BOX 5 *CASE DEFINITIONS*

Criteria	CDC	WHO	ERCİYES
Fever	• Documented > 38.0°C and lasting ≥ 24 hr, or; • Declared fever lasting ≥24 hrs	• ≥ 3 day lasting fever	• Documented or declared fever lasting ≥24 hrs
Inflammation	≥1 abnormal marker of inflammation; • CRP ↑ • Sedimentation ↑ • Procalcitonin ↑ • Fibrinogen ↑ • D-dimer ↑ • Ferritin ↑ • LDH ↑ • IL-6 ↑ • Neutrophilia, lymphopenia • Hypoalbuminemia	≥1 abnormal marker of inflammation; • CRP ↑ • Sedimentation ↑ • Procalcitonin ↑	≥1 abnormal marker of inflammation; • CRP ↑ • Sedimentation ↑ • Procalcitonin ↑ • Fibrinogen ↑ • D-dimer ↑ • Ferritin ↑ • Lymphopenia
Multi-system involvement	► **Hospitalization AND** ≥ 2 systems involvement; • Cardiovascular: Hypotension or shock, elevated troponin and BNP, arrhythmia, abnormal ECHO finding • Respiratory: Pneumonia, ARDS, emboli • Renal: Acute kidney injury • Neurologic: Seizures, encephalitis, aseptic meningitis • Hematologic: Coagulopathy • GIS: Nausea/vomiting, diarrhea, abdominal pain, ileus, bleeding, elevated liver enzymes • Skin/mucosa: Erythema, mucositis, rash	► **≥ 2 systems** involvement; • Rash, bilateral nonpurulent conjunctivitis, mucocutaneous inflammation • Hypotension or shock • Cardiac dysfunction, pericarditis, valvulitis, or coronary abnormalities (elevated troponin or BNP values) • Coagulopathy • Acute GIS symptoms (diarrhea, vomiting, or abdominal pain)	► **≥ 2 systems** involvement; • Skin: Mucositis, conjunctivitis, erythroderma, polymorphic rash • Cardiovascular: Hypotension, shock, troponin ↑, BNP ↑, arrhythmia, abnormal ECHO findings (pericarditis, valvulitis, decreased EF, coronary abnormalities) • Respiratory: Pneumonia, ARDS • Renal: Acute renal injury, renal insufficiency • Gastrointestinal: Diarrhea, vomiting/ nausea, abdominal pain, elevated liver enzymes • Neurologic: Seizures, neurological deficit, meningitis • Hematologic: Coagulopathy
Evidence of COVID-19	• PCR; • Antigen test; • Serology positive; or • Likely contact with patients with COVID-19	• PCR; • Antigen test; • Serology positive; or • Likely contact with patients with COVID-19 in the last 4 weeks	• PCR; • Antigen test; • Serology positive; or • Likely contact with patients with COVID-19 in the last 4-8 weeks
Exclusion	No alternative plausible diagnoses	No other apparent microbial cause of inflammation	No alternative plausible diagnoses
DIAGNOSIS	Fever + inflammation + multisystem involvement + hospitalization + evidence of COVID-19 + no alternative plausible diagnoses	Fever + inflammation + multisystem involvement + evidence of COVID-19 + No other apparent microbial cause of inflammation	Fever + inflammation + multisystem involvement + evidence of COVID-19 + no alternative plausible diagnoses

Abbreviations: ARDS, acute respiratory distress syndrome; BNP, brain natriuretic peptide; CRP, C-reactive protein; COVID-19, Coronavirus Disease 2019; ECHO, echocardiogram; EF, ejection fraction; GIS, gastrointestinal system; LDH, lactate dehydrogenase; PCR, polymerase chain reaction; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2.

BOX 6 CLASSIFICATION OF CLINICAL SEVERITY*

	MILD	MODERATE	SEVERE
Vital signs (instead of fever)	Normal	Abnormal	Abnormal
Vasoactive requirement** (Vasoactive-inotropic score)	None	≤ 10	> 10
Respiratory support	None	Oxygen	• High-flow O2 support (> 1 lt/kg) **OR** • Non-invasive or invasive ventilatory support
Organ injury	• None	• Mild/limited	• Moderate or severe
Cardiac involvement***	• None **OR** • Mild valvular insufficiency without elevated a cardiac marker (troponin and/or BNP)	• No clinical finding • No hypotension or arrhythmia **AND** • At least one criteria; • Troponin ≥ 2x upper normal limit • Mild abnormalities in ECHO • Elevated BNP	• At least one clinical finding; • Hypotension, arrhythmia, tachycardia, poor perfusion **OR** • Abnormalities in ECHO • Moderate to severe ventricular dysfunction
Mental status (Evaluated in the absence of fever)	Normal	Normal	Altered

*There is no generally accepted classification of disease severity yet. Clinical severity can be determined based on the criteria given here or additional findings and clinical course. Since not all systems may be equally involved in cases, clinical grading should be made according to the system most affected.

** Vasoactive-Inotropic Score (VIS) Calculation;

VIS= dopamine dose (µg/kg/min) +
dobutamine dose (µg/kg/min) +
100 x epinephrine dose (µg/kg/min) +
10 x milrinone dose (µg/kg/min) +
10,000 x vasopressin dose (U/kg/min) +
100 x norepinephrine dose (µg/kg/min)

*** While assessing the severity of cardiac involvement, ECHO findings and laboratory (BNP or pro-BNP and troponin) results should be evaluated together. BNP and pro-BNP are acute phase reactants, and unless other ECHO, laboratory, or clinical findings are accompanied, the elevation of these markers should not be considered as cardiac involvement alone.

Abbreviations: BNP, brain natriuretic peptide; ECHO, echocardiogram; pro-BNP, pro-brain natriuretic peptide.

BOX 7 MANAGEMENT BY CLINICAL SEVERITY

(For doses and administration, refer to Box 8)

	MILD	MODERATE	SEVERE
Intravenous immune globulin	+	+	+
Steroid	2 mg/kg/day	10 mg/kg/day	30 mg/kg/day
Anticoagulation[a] (LMWH)	+/-[a]	+	+
GIS prophylaxis with proton pump inhibitor	+	+	+
Immunomodulation[b,c,d] (Anakinra or tocilizumab)[e]	-	Refractory illness (consider high-dose steroid)	+
Antiagregan[f] Aspirin© (ASA)	If there is coronary dilatation and/or thrombocytosis	If there is coronary dilatation and/or thrombocytosis	If there is coronary dilatation and/or thrombocytosis
If Kawasaki Disease criteria meet	ASA[f]	ASA[f]	ASA[f]
Antibiotics[g]	If needed	If needed	If needed

[a]Unless there is a contraindication, **prophylactic** LMWH should be started in cases with a diagnosis of MIS-C. If aspirin is started in the treatment of mild cases and there is no additional risk factor in the case, prophylactic LMWH should be added to the treatment according to the disease course. In the following conditions, LMWH should be given in the **treatment dose**;
- The documented presence of thrombosis or a history of thrombosis (hematology consultation), moderate or severe ventricular dysfunction (EF<35%), coronary artery aneurysm Z score >10, rhythm abnormalities, D-dimer >3000 µg/L, and progressive increase, presence of a central venous catheter, inotropic infusion.

[b]In the presence of hemophagocytosis, the addition of immunomodulators to treatment should be considered.

[c]High-dose steroid therapy can be used before immunomodulator therapy.

[d]An online application should be made to the Ministry of Health for off-label use approval.

[e]The short half-life, availability, and side-effect profile are the advantages of anakinra over tocilizumab.

[f]In the presence of Kawasaki disease features (complete or incomplete) or coronary artery dilatation, it is recommended to add aspirin to the treatment. In cases where the platelet count is >400.000 /mm3, aspirin can be added to the treatment. However, caution should be exercised in the simultaneous use of LMWH and aspirin. There is no generally accepted recommendation regarding the use of LMWH and ASA in treating MIS-C, yet, it should be decided on a case-by-case basis. Aspirin should be avoided in cases with bleeding risk. Platelet value should be kept at >80.000 /mm3 during aspirin therapy. **See box 8 for aspirin dosage.**

[g]If there is a risk of sepsis, septic shock, or a concomitant bacterial infection, antibiotics are started considering the age of the patient and the underlying disease, if any.

Abbreviations: ASA, acetylsalicylic acid; ECHO, echocardiogram; EF, ejection fraction; GIS, gastrointestinal system; LDH, lactate dehydrogenase; LMWH, low molecular weight heparin.

BOX 8 DOSES OF DRUGS USED IN MIS-C TREATMENT, ADMINISTRATION WAYS, AND POINTS TO BE CONSIDERED

Intravenous immune globulin (IVIG)	1 - 2 gr/kg, IV infusion in 12 hours Maximum dose: 100 gr (It should be given according to the ideal weight in obese) In refractory cases, a second dose of IVIG can be given if other treatments are contraindicated	Adverse events; • Infusion reactions • Anaphylaxis • Elevated liver enzymes • Aseptic meningitis • Hemolysis
Steroid (methylprednisolone)	Starting (low dose): 2 mg/kg/day IV, once per day, max: 60 mg/day Moderate cases; 10 mg/kg/day IV once per day, For 1 – 3 days, max: 1 gr/day High dose: 30 mg/kg/day IV, once per day, For 2 – 3 days, max: 1 gr/day	• In obese patients, it should be given according to the ideal weight • It can be given orally when the clinic improves • **The maintenance dose of steroid is 2 mg/kg/day** • Steroid taper for 2 to 4 weeks with gradually reducing the dose.
Low molecular-weight heparin (LMWH) Enoxaparin	• Prophylaxis (low-risk patients) SC, **dose per 12 hours**	

CrCl	<37 week GA	37 wk GA - <3 month	3 month – <1 yr	1 - <6 yr	6 - <18 yr
≥ 30 mL/min	0.7 mg/kg	0.83 mg/kg	0.78 mg/kg	0.6 mg/kg	0.53 mg/kg
< 30 mL/min	0.5 mg/kg	0.58 mg/kg	0.55 mg/kg	0.42 mg/kg	0.37 mg/kg

• Therapeutic (high-risk patients refer to *Box 7* and the note a)
1 mg/kg/dose SC, per 12 hours (consider hematology consultation if thrombosis exists)

Dose adjustment is required in renal insufficiency!!!!	Contraindications	Active major bleeding, heparin-induced thrombocytopenia, or plt <25000 /mm3
	Relative contraindications	Plt <50000 /mm3, fibrinogen <75 mg/dL, ≥2 sec above the upper limit of PT, ≥4 sec above the upper limit of APTT
Aspirin In obese patients, it should be given according to the ideal weight It is contraindicated if Plt ≤ 80000 /mm3 **It should be used with caution in renal failure!!!!**	• Kawasaki Disease like; • Plt ≥ 450000/mm3;	3 – 5 mg/kg/day PO, once per day, max: 325 mg/day
	• If Kawasaki criteria are met and not taking steroids **OR** • If there is coronary artery involvement and fever continues	80 – 100 mg/kg/day PO, 4 doses in a day, Max: 4 gr/day
	In these cases, 48 hours after the afebrile period	Continue with 3 – 5 mg/kg/day PO
	• If Kawasaki Disease criteria are fully met + taking steroids in the treatment	3 – 5 mg/kg/day PO, once per day, max: 81 mg/day
GIS prophylaxis	Pantoprazole 1 mg/kg/day IV	
Anakinra	4 – 10 mg/kg/day, 4 dose per a day, SC or IV Max. **100 mg/dose** (400 mg/day) IV infusion should last at least 1 hour (100 mg/100 ml in 0.9% saline solution) The opened syringe should be used within 24 hours	

Abbreviations: APTT, active partial thromboplastin time; GA, gestational age; GIS, gastrointestinal system; IV, intravenous; Plt, platelet; PO, per oral; PT,Prothrombin time; SC, subcutaneous.

BOX 9 LABORATORY AND RADIOLOGICAL FOLLOW-UP DURING THE HOSPITALIZATION

Lab parameters to be checked daily until the fever is under control	Complete blood count Ferritin D-dimer	CRP Troponin Sodium	Procalcitonin BNP Albumin
ECG	Every 48 hours (every 24 hours if cardiac involvement is present)		
ECHO	Cardiac involvement (+) and clinical findings (+) → Everyday Cardiac involvement (-) and clinical findings (+) → 2 per week Cardiac involvement (-) and clinical findings improve → Decision on case-based Coronary artery involvement (+) → Every 2-3 days until findings are stable, then weekly until discharge		
Radiological studies	If needed in the follow-up		

Abbreviations: BNP, brain natriuretic peptide; CRP, C-reactive protein; ECG, electrocardiogram; ECHO, echocardiogram.

BOX 10 INTENSIVE CARE ADMISSION CRITERIA

Need for vasoactive infusion	Unresponsiveness to fluid resuscitation (shock)
The need for positive pressure ventilation	Clinically manifested cardiac failure
The need for hemodynamic monitoring	Severe electrolyte imbalance
Severe organ failure (kidney, liver, etc.)	Altered mental status (confusion, stupor, etc.)

BOX 11 DISCHARGE CRITERIA (ALL CRITERIA MUST BE MET)

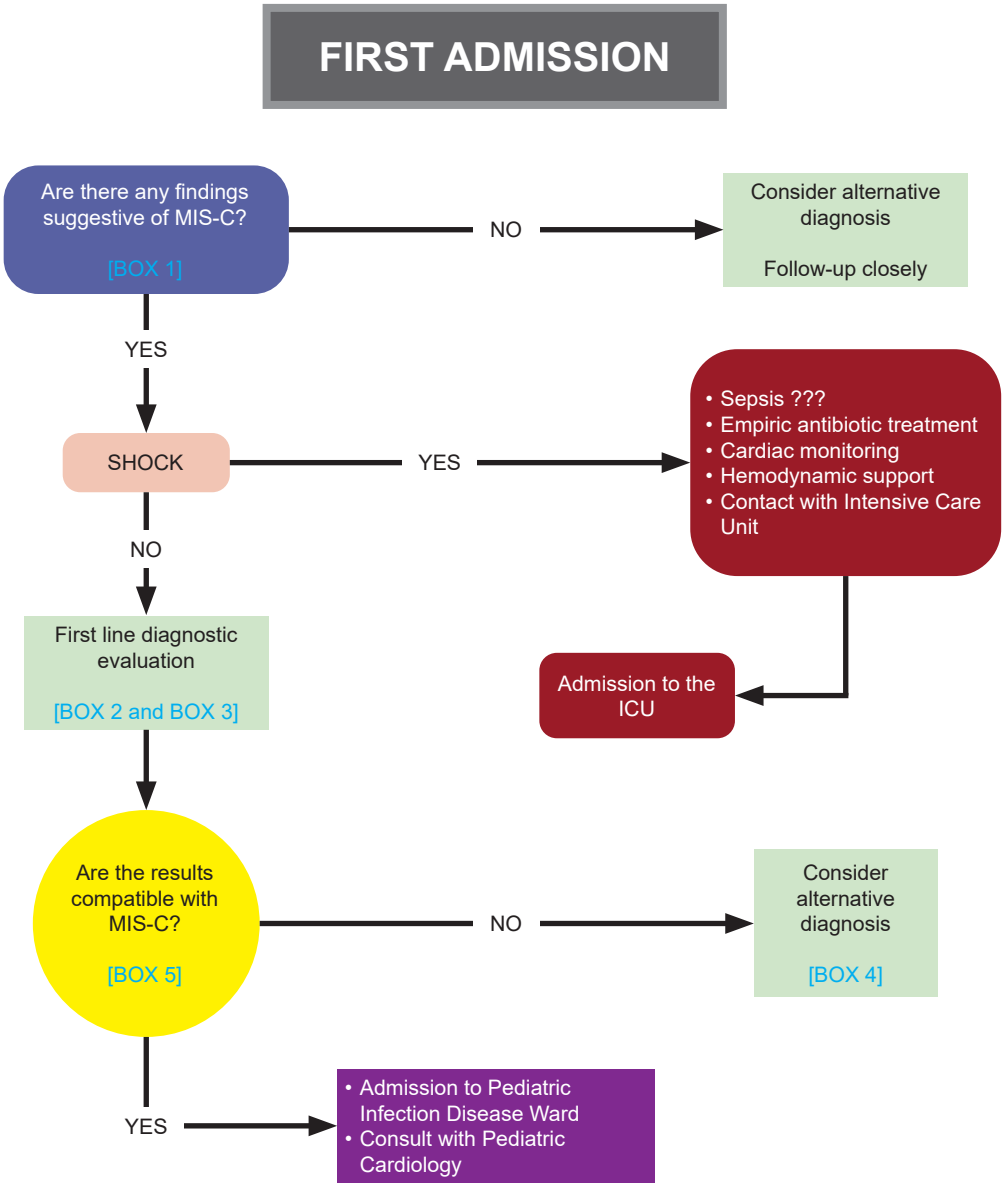
- Good general condition, stable vital signs, fever-free for at least 72 hours
- Acute phase reactants (CRP, procalcitonin, BNP, D-dimer) tend to decrease significantly (3 samples taken at least 24 hours apart in the last 96 hours should show a decreasing trend)
- Good oral intake, enteral feeding, no nausea - vomiting, can take oral medication (steroid and/or aspirin)
- There is no tendency to decrease in platelet values , and platelet value is within normal limits.
- ECG normal in the last 48 hours
- Recent ECHO findings are normal or stable
- Not receiving oxygen support (for at least 48 hours)
- Compatible family with a follow-up plan

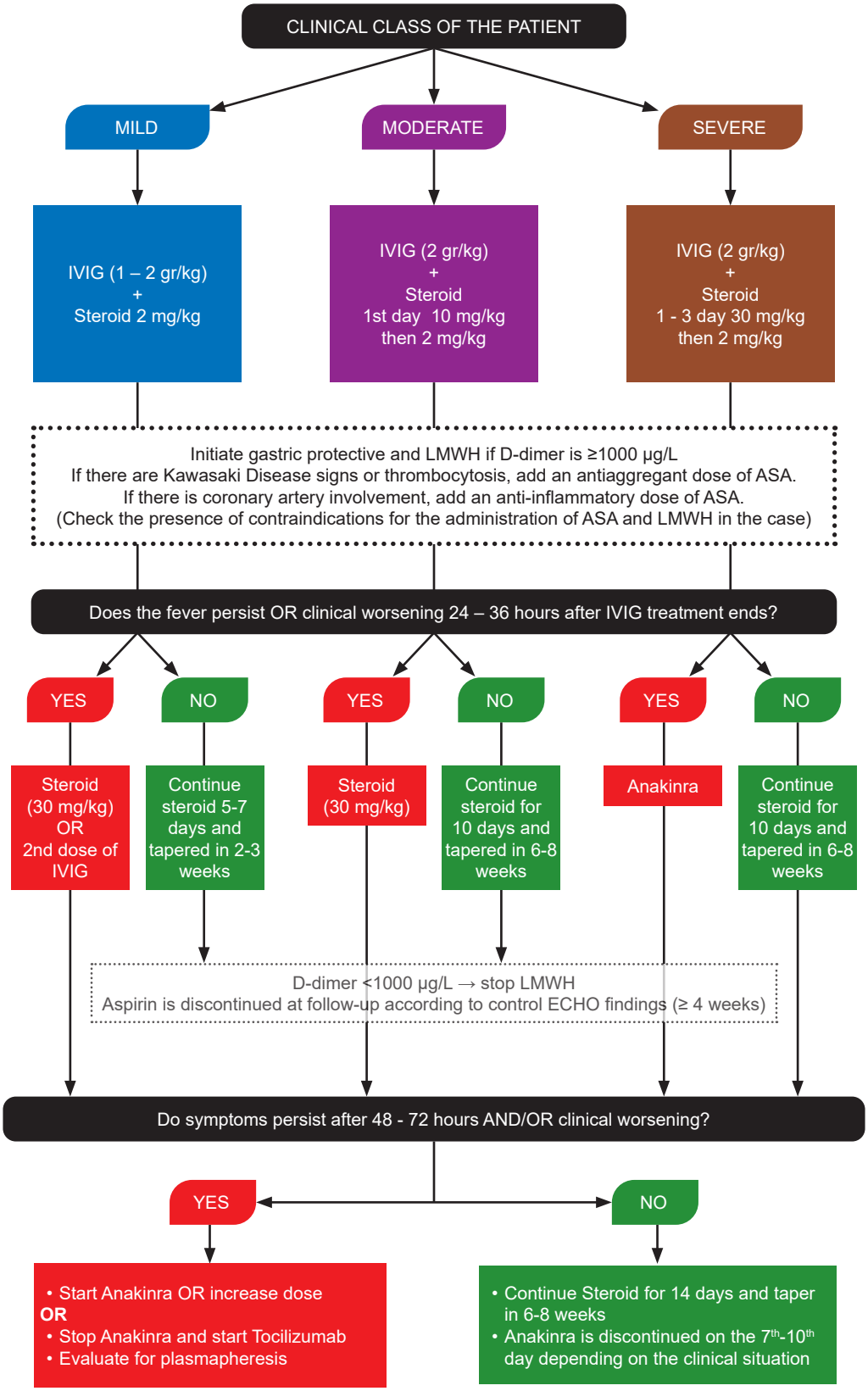
Abbreviations: BNP, brain natriuretic peptide; CRP, C-reactive protein; ECG, electrocardiogram; ECHO, echocardiogram.

BOX 12 POST-DISCHARGE FOLLOW-UP

Low-dose Aspirin (moderate-severe cases) should be completed in a total of at least 4 weeks
The duration of LMWH use should be determined according to thrombosis risk factors, In non-risk groups, LMWH can be discontinued when D-dimer falls below <1000, and acute phase reactants decrease
In cases with EF <35%, LMWH for 2 more weeks after discharge (cardiology and hematology opinion should be obtained)
ECG and ECHO → To be planned by Cardiology Department, depending on cardiac involvement and clinical findings
Steroid treatment should be tapered gradually in 2 weeks in mild cases and in 4-6 weeks in moderate and severe cases, depending on the clinical course

Abbreviations: ECG, electrocardiogram; ECHO, echocardiogram; EF, ejection fraction; LMWH, low molecular weight heparin.




CLINICAL CLASS OF THE PATIENT
MILD
MODERATE
SEVERE
IVIG (1 – 2 gr/kg) + Steroid 2 mg/kg
IVIG (2 gr/kg) + Steroid 1st day 10 mg/kg then 2 mg/kg
IVIG (2 gr/kg) + Steroid 1 - 3 day 30 mg/kg then 2 mg/kg
Initiate gastric protective and LMWH if D-dimer is ≥1000 µg/L
If there are Kawasaki Disease signs or thrombocytosis, add an antiaggregant dose of ASA.
If there is coronary artery involvement, add an anti-inflammatory dose of ASA.
(Check the presence of contraindications for the administration of ASA and LMWH in the case)
Does the fever persist OR clinical worsening 24 – 36 hours after IVIG treatment ends?
YES
NO
YES
NO
YES
NO
Steroid (30 mg/kg) OR 2nd dose of IVIG
Continue steroid 5-7 days and tapered in 2-3 weeks
Steroid (30 mg/kg)
Continue steroid for 10 days and tapered in 6-8 weeks
Anakinra
Continue steroid for 10 days and tapered in 6-8 weeks
D-dimer <1000 µg/L → stop LMWH
Aspirin is discontinued at follow-up according to control ECHO findings (≥ 4 weeks)
Do symptoms persist after 48 - 72 hours AND/OR clinical worsening?
YES
NO
• Start Anakinra OR increase dose
OR
• Stop Anakinra and start Tocilizumab
• Evaluate for plasmapheresis
• Continue Steroid for 14 days and taper in 6-8 weeks
• Anakinra is discontinued on the 7th-10th day depending on the clinical situation

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Assesment of Damage in Juvenile Idiopathic Arthritis: Single Center Experience

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Abstract

After biological treatment options, quality of life and articular functions in patients with Juvenile Idiopathic Arthritis (JIA) have been maintained close to normal. It is essential to evaluate the activation and the articular and extra-articular damage during the disease course. This study aimed to evaluate the damage status and factors affecting JIA patients who were followed up in our clinic. Two hundred four JIA patients who had been followed up for two years or more were included. The data of the patients were collected retrospectively. Demographic data, comorbid diseases, laboratory data (at baseline and during follow-up), disease activity during the follow-up period, and treatments were evaluated. Disease activities, quality of life, and Juvenile Arthritis Damage Index articular(JADI-A) and extra-articular (E) were evaluated at the final examination. Factors affecting JADI-A and E were assessed by univariate and multivariate logistic regression analysis. In this study,127 (62.6%) of the patients were female. The median age was 13 (IQR: 11-16), and the age at diagnosis was 7 (IQR: 4-10) years. The median follow-up time was 5 (IQR: 4-8) years. Ninety-two (45.3%) patients had comorbid diseases. JADI-A scores were median:0(min-max: 0-24), JADI-E scores were median:0(min-max:0-4) in whole study population. In multivariate analysis, the mean annual attacks number [OR: 1,759 (CI: 1,300-2,379], p: <0,001), mean annual eritrocyte sedimantation rate (ESR) [OR: 1,072 (CI: 1,021-1,125), p: 0.005], duration of metotrexate usage [OR: 1.029 (CI: 1.013-1.046, p: 0.001] and biological drug usage [OR: 5.810 (CI: 1.296-26.054), p: 0.022) were effective on JADI-A scores. The CRP value at the first admission [OR: 1.007 (CI: 1,000-1,014), p: 0.037], the mean annual ESR value [OR: 1,051 (CI: 1,008-1,095), p: 0.019] were found to be effective on the JADI-E scores. The ideal cut-off point of the annual attacks number and mean annual ESR affecting JADI-A scores were 1.38 [AUC: 0.734 (0.641-0.828), p: 0.001] and 14.32 [AUC: 0.617 (0.514-0.721), p: 0.027], respectively. The ideal cut-off point of the CRP value at the first admission and mean annual ESR value affecting JADI-E scores were 13,25 [AUC: 0,662 (0,541-0,782), p: 0,009], and 15,10 [AUC: 0.674(0.567-0.780), p: 0.002], respectively. Steroid related complications such as, obesity in 12 (5.9%), hirsutism in 3 (1.5%), transient adrenal suppression in 14 (6.9%), 8 (3.9%), and osteoporosis determined in 7 (3.4%) patients. We have shown that parameters used routinely can be helpful to predict damage. We also think that new criteria should be added to the scoring.

Keywords: Juvenile, arthritis, damage

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Introduction

Juvenile Idiopathic Arthritis (JIA) is the most common cause of chronic arthritis in childhood. There are seven subgroups according to the International leag of Rheumatism (ILAR) classification.[1] The prognosis and morbidity are different in each group. The primary aim of the treatment is to eliminate active disease, normalize joint function, maintain normal growth and prevent long-term joint damage. Treatment protocols were developed over the years. In 2011, the first protocol was published by the American College of Rheumatology (ACR).[2] In 2013, the treatment guideline was updated for the systemic JIA.[3] Finally, in 2019, treatment was revised for groups other than systemic JIA.[4] Biological therapies, which started to be used after 2000, have changed morbidity and mortality. The morbidity is associated with both articular and extra-articular complications. Untreated synovial inflammation causes permanent damage to joint components and may result in joint ankylosis. Cardiovascular complications, amyloidosis, growth retardation, delayed puberty developed due to chronic inflammation. Uveitis can cause eye complications such as vision loss, cataracts, and glaucoma. Depending on the steroids usage, osteoporosis, adrenal suppression, diabetes mellitus (DM) may develop. It is essential to evaluate the disease activation and the articular and extra-articular damage during the disease course.[5] The Juvenile Arthritis Damage Index (JADI) is a comprehensive assessment tool of articular and extra-articular damage in children with JIA. It is calculated by the physician based on the physical examination and clinical history. The index has two parts, JADI-A, which evaluates joint damage, and JADI-E, which evaluates extra-articular damage.[6]

Highlights

- Articular and extra-articular damage secondary to disease or treatment may be seen in JIA.
- The JADI index is the damage assessment tool used in JIA.
- Having persistent high inflammatory markers is a risk factor for a high JADI index.

This study aimed to evaluate the damage status and the affecting factors of the articular and extra-articular damage in JIA patients.

Material and Method

A total of 204 JIA patients under the age of 18, disease duration more than two years, and still in follow-up were included in the study. Diagnostic information, subgroups, anthropometric data, number and location of affected joints, systemic findings, presence of uveitis, comorbid diseases, and family history were recorded. The white blood cells (WBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), ferritin, anti-nuclear antibody (ANA), HLA-B27, rheumatoid factor (RF), Anti- cyclic citrullinated peptide (anti-CCP) were recorded. During the follow-up period, frequency of disease flares, nonsteroid anti-inflammatory (NSAI) drug, and intraarticular steroid (IAS) usage, uveitis attacks, steroid dose (mg/kg/year), mean WBC, ESR, and CRP values were calculated per year. The JIA treatments and durations were recorded. The activity scores, assessment of health quality of life of the patients, and damage scores were evaluated at the last examination. JADAS was calculated for oligo JIA and poly JIA, JSpADAS for enthesitis-related arthritis (ERA), and sJADAS for systemic JIA patients.[7-9] Quality of life score was evaluated with the children's health quality of life (CHAQ) score.[10] Anthropometric data, partial damage, ankylosis, and prosthetic joints were detected in the final examination. JADI-A and E scores were calculated from the collected data.[11] In the JADI-A, 36 joints were evaluated for the presence of damage. Each damaged joint was scored on a 2-point scale (1: partial damage, 2: severe damage, ankylosis, or prosthesis). The maximum total score was 72. In the JADI-E, 13 items were evaluated in five different organs/systems. Ocular (If the patient has had eye surgery, it was scored as 2 for each eye. If the patient developed legal blindness, the score was 3). Cutaneous (subcutaneous atrophy as a result of the intra-articular corticosteroid injection, stria rubrae), endocrine (diabetes mellitus, growth failure, pubertal delay), non-articular musculoskeletal (fractures or vertebral collapses due to osteoporosis, significant abnormality of the vertebral curve as a result of leg-length discrepancy or hip contracture, significant leg length discrepancy or growth abnormality of a bone segment, avascular necrosis of bone, severe muscle atrophy) findings, and secondary amyloidosis were evaluated. Each item was scored as either 0 or 1, according to whether the damage was present, respectively. The maximum total score was 17. Malnutrition, obesity, hirsutism, adrenal suppression, osteoporosis, and development of MAS not included in JADI-E score were recorded.[6]

Statistical Analysis:

Statistics 22.0 (IBM Corp. Armonk, New York, USA) statistical package program was used. Shapiro-Wilk and Kolmogorow-Smirnow Normality test and Q-Q graphs were used to determine whether the data showed normal distribution. Results are given as median (min-max) and quarterly (IQR). In evaluating variables between groups, categorical data were evaluated with the chi-square test; continuous data were evaluated with the normal distribution, one-way analysis of variance ANOVA, and those that did not show the normal distribution were evaluated with the Kruskal Wallis test. Univariate and multivariate logistic regression analysis was performed to assess the factors affecting the JADI-A and JADI-E scores. The risk coefficient and 95% confidence interval were given, and the p-value was accepted as <0.05. The significant cut-off point of the continuous data, the area under the curve, sensitivity, and specificity values were calculated.

Results

Demographic Data of the Patients

Two hundred and four patients with JIAwere included in the study. A hundred and twenty-seven (62.6%) of the patients were female, and 75 (36.9%) were male. The median age was 13 years (IQR: 11-16), and the age at diagnosis was 7 (IQR: 4-10) years. The median follow-up period was 5 (IQR:4-8) years. A total of 92 (45.3%)

patients had comorbid disease. The median age at diagnosis of comorbid disease was 8 (IQR:4-11), and the follow-up period was 5 (IQR:2-9) years. The most common comorbid disease was FMF (n:44). A total of 54 (26.6%) patients had a family history of rheumatologic disease.The demographic data of patients were analyzed separately according to JIA subtypes (**Table 1**).

Clinical Evaluation at Initial Period

The median weight standard deviation score (SDS) was -0.19 (IQR:-0.80-0.50), height SDS was -0.07 (IQR:-1.10-0.40) at the time of diagnosis. The median number of affected joints was 2 (IQR:1-4). Patients who developed uveitis in the first year were detected in oligo, poly, and ERA subgroups. The initial laboratory findings represented in Table 1. The ANA was performed in 96 (47.3%) patients, and it was found to be positive in 90 (44.3%) patients. The HLA-B27 was performed in 92 (45.3%) patients, and positivity was detected in 30 (14.8%) patients. Rheumatoid factor was measured in 83 (40.9%) patients, and positivity was detected in 4 (2%) patients. Anti-CCP was examined in 18 (8.9%) patients, and positivity was detected in 1 (0.5%) (**Table 1**).

Clinical and Laboratory Evaluation in Follow-up Period

The median number of attacks per year was 1 (IQR: 0.50-1.76). It was 2,33 (IQR:1,25-4,37) in poly JIA group. The annual steroid requirement was calculated as 0.92 (IQR:0-5.94) mg/kg/year. Steroid amounts was 22,15 (IQR:5,80-71,81) mg/kg/year in the systemic JIA group. The annual median ESR was 11.81 (IQR:6.46-20.8) mm/h. It was 25 (IQR:18,30-40,15) mm/h in the systemic JIA subgroup. The annual median CRP was 4.72 (IQR: 2.50-8.73) mg/L. It was 11,92 (IQR:8,38-35,09) mg/L in the systemic JIA subgroup. The clinical and laboratory characteristics of the patients during the follow-up are detailed for the subgroups in **Table 2**.

Table 1.
Demographic, clinical and laboratory parameters of the patients at first diagnose

Variables	JIA subgroups						
	Total (n=204)	Systemic (n=17)	Oligoarticular (n=82)	Polyarticular (n=42)	ERA (n=55)	Psoriatic (n=5)	Undifferentiated (n=3)
Age (year)	13 (11-16)	13 (12-14.5)	12 (10-15)	12 (10-15)	15 (13-17)	16 (13-17)	16 (12-16)
Age of diagnosis (year)	7 (4-10)	8 (3.5-10)	6 (3-9)	6 (2-9·5)	9.5 (7.75-11)	12 (6-13)	10 (9-10)
Sex (F/M), n/%	127/75 (62.6/36.9)	12/5 (70.6/29.4)	47/35 (57.3/42.7)	31/10 (75.6/24.4)	30/24 (55.6/44.4)	4/1 (80/20)	3/0 (100)
Disease duration (year)	5 (4-8)	6 (3-8)	6 (4-7)	5 (3-8)	5 (3-7)	4 (4-7.5)	6 (3-6)
Weight SDS	-0.19 (-0.80-0.50)	0.40 (-0.40-1)	-0.30 (-0.80-0.10)	-0.20 (-1.09-0.70)	-0.02 (-0.82-1)	0.70 (-0.43-1.80)	-0.30 (-0.51- (-0.30)
Height SDS	-0.07 (-1.10-0.40)	0 (-0.76-0.64)	-0.40 (-1.20-0.20)	0 (-0.50-0.70)	0 (-0.81-0.82)	-0.60 (-1.17-1.25)	-0.30 (-0.42- (-0.30)
Number of joint	2 (1-4)	2 (0.5-3)	2 (1-2)	6 (4.5-8)	2 (1-3.25)	4 (2-5)	6 (2-6)
Uveitis at first year, n	15	0	8	5	2	0	0
HGB (g/dL)	11.9 (10.8-13)	10.4 (9.7-11.95)[a]	12.3 (11.4-13)[a]	11.4 (10.4-12)	12 (11.2-13.2)	12 (10.5-12)	12.9 (12.9-13.0)
WBC/mm³	9170 (7290-11835)	15712 (9605-19905)[a,b,c]	9320 (7312-11490)[a]	8874 (7022-12135)[b]	8865 (6947-10492)[c]	10625 (8650-10625)	7570 (6840-7570)
PLTx10³/mm³	377 (301-448)	469 (298-750)	340 (293-480)	410 (318-553)	375 (302-420)	395 (275-395)	309 (300-309)
ESR (mm/h)	27 (8.5-55)	65 (33.5-103)[a,b]	19 (5.5-37)[a]	44 (16.2-74.7)	22 (7-45)[b]	35 (4-35)	4 (3-4)
CRP (mg/L)	11.3 (3.3-46.2)	104 (19-148)[a,b,c]	5·4 (3.1-21)[a]	25.9 (5.5-52.6)[b]	7.35 (3.17-31.2)[c]	3 (1-3)	3.4 (2.1-3.4)
Ferritin (mg/dL)	239 (40-2867)	401 (71-3929)	NA	NA	NA	NA	NA
ANA (+/-), %	90/96 (44.3/47.3)	2/12 (11.8/70.6)	45/34 (54.9/41.5)	24/15 (58.5/36.6)	17/30 (31.5/55.6)	1/3 (20/60)	1/2 (33.3/66.7)
HLA-B27(+/-), %	30/92 (14.8/45.3)	1/2 (5.9/11.8)	2/43 (2.4/52.4)	2/15 (4.9/36.6)	23/27 (42.6/50)	2/2 (40/40)	-/0
RF (+/-), %	4/83 (2/40.9)	0/3 (-/17.6)	NA	2/33 (4.9/80.5)	0/17 (0/31.5)	0/1 (0/20)	NA
Anti-CCP(+/-),%	1/18 (0.5/8.9)	0/1 (-/5.9)	NA	1/9 (2.4/24.4)	0/2	NA	NA
CD (n, %)	92 (45.3)	9 (52.9)	37 (45.1)	16 (39)	27 (50)	1 (20)	2 (66.7)
Age of CD diagnose (year)	8 (3.75-11)	8 (7-12)	8 (2-10)	6 (2-12)	9 (5-11)	15 (15-15)	8.5 (8-8.5)
Duration of CD (year)	5 (2-9)	2 (1-6.5)	5 (2-10)	3 (2-7)	5 (3-9)	2 (2-2)	5.5 (3-5.5)
Family history of RD, n (%)	54 (26.6)	2 (11.8)	20 (24.4)	8 (19.5)	19 (35.2)	3 (60)	2 (66.7)

All parameters were given median and Interquartile range. a, b, c: There was a statistically differences between same latters. ANA: Antinuclear antibody, Anti-CCP: Anti-Cyclic Citrullinated peptide antibodies, CD: Comorbid Disease, CRP: C reactive protein, ESH: Erythrocyte sedimentation rate, HGB: Hemoglobin, PLT: Platelets, RD: Rheumatologic disease, RF: Rheumatoid factor, SDS: Standard deviation score, WBC: White blood cells,

Table 2.
Clinical and laboratory parameters during the disease course

Parameters	Total (n=204)	JIA subgroups Systemic (n=17)	Oligoarticular (n=82)	Polyarticular (n=42)	ERA (n=55)	Psoriatic (n=5)	Undifferentiated (n=3)
Number of attacks/year	1 (0.50-1.76)	1 (0.50-0.75)[a]	0.77 (0.50-1.21)[b]	2.33 (1.25-4.37)[a,b,c]	1 (0.40-1.80)[c]	1.40 (0.87-2.12)	0.85 (0.33-0.85)
Number of NSAI usage/year	0.21 (0.14-0.33)	0.09 (0-0.33)	0.25 (0.16-0.28)	0.20 (0.10-0.33)	0.25 (0.19-0.33)	0.25 (0.10-0.25)	0.16 (0-0.16)
Dose of steroid (mg/kg/year)	0.92 (0-5.94)	22.15 (5.80-71.81)[a,b,c,d,e]	0 (0-4.50)[a]	5.58 (0.56-14.83)[b]	0 (0-1.44)[c]	0 (0-6.37)[d]	0[e]
IAS usage/year	0 (0-0.4)	0 (0-0.08)	0.28 (0-0.50)[a]	0 (0-0.30)	0 (0)[a]	0 (0-0.37)	0
Number of Uveitis attacks/year	55	1	34	15	5	0	0
HGB/year, g/dL	12.8 (12.20-13.47)	12.64 (11.98-13.05)	12.8 (12.28-13.61)	12.51 (11.9-13.2)	13 (12.17-13.56)	12.85 (12.65-13.71)	13.5 (12.7-13.5)
WBC/mm³/ year	7845 (7035-8990)	9454 (8543-11073)[a,b,c]	7846 (7067-8938)[a]	7878 (6969-9219)[b]	7447 (6870-8377)[c]	7200 (6481-8350)	7696 (7069-7696)
PLT/ mm³/ year	333 (290-382)	368 (289-403)	318 (278-379)	338 (303-377)	335 (292-377)	330 (267-422)	268 (250-268)
ESR/year, mm/h	11.81 (6.46-20.8)	25 (18.30-40.15)[a,b,c]	9.54 (5.45-17.21)[a]	14.40 (9.57-23.60)[b]	11.98 (6.93-19.70)[c]	11.3 (7.25-32.95)	8.2 (5.6-8.2)
CRP/year, mg/L	4.72 (2.50-8.73)	11.92 (8.38-35.09)[a,b,c,d]	3.70 (1.99-5.42)[a]	6.6 (3.16-9.96)[b]	5 (2.82-8.55)[c]	2.85 (1.11-4.45)[d]	2.13 (1.51-2.13)
Ferritin/year, mg/dl		71.90 (37.82-1392)					

All parameters were given median and Interquartile range. a, b, c, d: There was a statistically differences between same latters. CRP: C reactive protein, ESR: Erythrocyte sedimentation rate, HGB: Hemoglobin, IAS: Intra-articular steroids, PLT: Platelets, WBC: White blood cells

Biological and Non-Biological DMARDs

Non-biological DMARD treatment was applied to 185 (91.1%) of our patients. Methotrexate was the most common non-biologic DMARD (97%). The median duration of methotrexate was 36 (IQR:22-58) months. The number of patients using biological therapy was 98 (48.3%). Psoriatic Arthritis (60%) and poly JIA (63.4%) had the highest rates treated with biological therapy. TNF -α blockers were the most common performing biological drugs were detected 96 (80.6%) times.

Comorbid diseases were detected in 45.3% of the patients. Forty-four patients had familial Mediterranean fever, the most common comorbid disease. Other diseases were Behçet's disease, atopic dermatitis, inflammatory bowel disease, and epilepsy. Colchicine was the most common drug for comorbid diseases.

Evaluation of Disease Activity Scores and JADI Scores

Disease activity scores of the patients at the last examination are shown in **Table 3**. Sixty-five partially damaged joints were detected in JADI-A scores at last visit. Out of the 39 (60%) were in the poly JIA. The ankylosed joint count was 22. Out of the 9 (40.9%) were detected in oligo JIA.

In the JADI-E index, eye involvement was present in a total of 10 (4.9%), partial vision loss in 6 (2.9%), and surgical application in 5 (2.5%) patients. Cataract and visual loss were highest in the systemic JIA subgroup (17.6%, 5.9%). Among the cutaneous findings, 8 (3.9%) patients had stria rubrae, and 2 (1%) patients had scar atrophy secondary to intra-articular injection. Among endocrine disorders, short stature was observed in 20 (9.8%), delayed puberty in 2 (1%), and secondary diabetes mellitus in 1 (0.5%) patients. Among the musculoskeletal system complications, vertebral fractures in 5 (2.5%), limb length differences in 4 (2%), avascular necrosis in 5 (2.5%), amyloidosis in 3 (1.5%) (secondary to FMF) were detected. The JIA subtype in patients with avascular necrosis was oligoarticular JIA in 2, ERA in 2, and polyarticular JIA in 1. localization of necrosis was femoral head in 4 patients and was mandibular condyle in 1 patient. The median cumulative prednisolone dose was 80 mg, maximum cumulative prednisolone dose was 875 mg in these patients. Only one patient did not use steroids.

Malnutrition, obesity, hirsutism, adrenal suppression, osteoporosis, and development of MAS, which were not included in the JADI scoring, were also evaluated. Malnutrition in 20 (9.8%), obesity in 12 (5.9%), hirsutism in 3 (1.5%), transient adrenal suppression in 14 (6.9%), 8 (3.9%), osteoporosis and MAS determined in 7 (3.4%) patients (**Table 3**).

Evaluation of Factors Affecting JADI-A and JADI-E Score

The analysis was performed by univariate and multivariate models. JIA subtype, gender, age at diagnosis, duration of JIA, presence of comorbid disease, duration of comorbid disease, family history of the rheumatological disease, number of affected joints and laboratory parameters, annual number of attacks and NSAI drug usage, median annual steroid amount, mean annual laboratory parameters, DMARD use and duration, biological use and duration were evaluated. In multivariate analysis,

annual number of attacks [OR:1,759 (CI:1,300-2.379]), (p:<0.001), mean annual ESR [OR:1,072 (CI:1,021-1,125),p:0.005] , duration of MTX use [OR: 1.029 (GA: 1.013-1.046, p:0.001]) and the use of biological drugs [OR: 5,810 (GA: 1.296-26.054), (p: 0.022)) were detected independent risk factors affecting on JADI-A score (**Table 4**). On JADI-E score, in multivariate analysis, the CRP value at the first admission [OR: 1.007 (GA:1,000-1.014), p: 0.037], the mean annual ESR value [OR:1.051 (GA:1.008-1.095)), p:0.019] were detected as independent risk factors (**Table 5**).

Determination of Cut-off Points of Factors Affecting JADI-A and JADI-E

The ideal cut-off point for the number of attacks per year, which affects the JADI-A score, was detected at 1.38. There was a significant [AUC:0.734 (0.641-0.828),p:0.001] effect on the JADI-A score (**Table 6, Figure 1**). Sensitivity was calculated as 69% and specificity as 72%.

The median annual ESR ideal cut-off point, which affects the JADI-A score, was detected at 14.32. There was a significant [AUC:0.617 (0.514-0.721), p:0.027] effect on the JADI-A score (**Table 6, Figure 1**). The sensitivity was calculated as 58% and the specificity as 58%.

The ideal cut-off point for CRP at first admission, which affects the JADI-E score, was 13.25. There was a significant [AUC:0.662 (0.541-0.782), p:0.009] effect on the JADI-E score (**Table 6, Figure 1**). Sensitivity was calculated as 57% and specificity as 56%. The annual mean ESR ideal cut-off point was 15.10, which affected the JADI-E score. There was a significant [AUC:0.674 (0.567-0.780), p:0.002] effect on the JADI-E score (**Table 6, Figure 1**). Sensitivity was calculated as 63% and specificity as 63%.

Table 3.
Disease activity scores and JADI-A and JADI-E scores at last visit

Variables	JIA subgroups						
	Total (n=204)	Systemic (n=17)	Oligoarticular (n=82)	Polyarticular (n=42)	ERA (n=55)	Psoriatic (n=5)	Undifferentiated (n=3)
JADAS	NA	NA	0 (0-29)	0 (0-21)	NA	0	0
JSpADAS	NA	NA	NA	NA	0 (0-9)	NA	NA
sJADAS	NA	0 (0-21)	NA	NA	NA	NA	NA
CHAQ	0 (0-1.30)	0 (0-1.25)	0 (0-1.25)	0 (0-1.3)	0 (0-1)	0 (0-0)	0 (0-0)
JADI-A	0 (0-24)	0 (0-14)	0 (0-5)	0 (0-24)	0 (0-4)	0 (0-1)	0 (0-0)
Number of partially damaged joints (n/%)	65 (100)	17 (26.15)	5 (7.69)	39 (60)	7 (10.76)	1 (1.53)	0
Number of ankylosed joints (n/%)	22 (100)	2 (9.09)	9 (40.90)	8 (36.36)	3 (13.63)	0	0
Prosthesis (n/%)	1 (0.5)	0	0	1 (2.4)	0	0	0
JADI-E	0 (0-4)	0 (0-2)	0 (0-3)	0 (0-4)	0 (0-1)	0	0
EYE							
Cataract	10 (4.9)	3 (17.6)	4 (4.9)	1 (2.4)	2 (3.6)	0	0
Vision loss	6 (2.9)	1 (5.9)	4 (4.9)	0	1 (1.8)	0	0
Surgery	5 (2.5)	0	3 (3.7)	1 (2.4)	1 (1.8)	0	0
Blindness	0	0	0	0	0	0	0
CUTANEOUS							
Striae rubrae	8 (3.9)	2 (11.8)	2 (2.4)	3 (7.1)	1 (1.8)	0	0
Atrophy after IAS	2 (1)	0	1 (1.2)	1 (2.4)	0	0	0
ENDOCRINE							
Growth failure	20 (9.8)	3 (17.6)	7 (8.5)	5 (11.9)	5 (9.1)	0	0
Pubertal delay	2 (1)	0	1 (1.2)	0	2 (3.6)	0	0
Diabetes Mellitus	1 (0.5)	0	0	0	1 (1.8)	0	0
MUSCULOSKELETAL							
Muscle atrophy	0	0	0	0	0	0	0
Vertebral fracture	5 (2.5)	0	2 (2.4)	1 (2.4)	2 (3.6)	0	0
Small extremity	4 (2)	0	2 (2.4)	1 (2.4)	1 (1.8)	0	0
Avascular necrosis	5 (2.5)	0	2 (2.4)	1 (2.4)	2 (3.6)	0	0
Amyloidosis	3 (1.5)	0	2 (2.4)	1 (2.4)	0	0	0
OTHERS							
Malnutrition	20 (9.8)	1 (5.9)	7 (8.5)	4 (9.5)	8 (14.5)	0	0
Obesity	12 (5.9)	1 (5.9)	3 (3.7)	3 (7.1)	3 (5.5)	1 (25)	0
Hirsutism	3 (1.5)	1 (5.9)	0	2 (4.8)	0	0	0
Adrenal suppression	14 (6.9)	4 (23.5)	2 (2.4)	6 (14.3)	2 (3.6)	0	0
Cushingoid appearance	12 (5.9)	7 (41.2)	1 (1.2)	3 (7.1)	1 (1.8)	0	0
Osteoporosis	8 (3.9)	3 (17.6)	1 (1.2)	2 (4.8)	2 (3.6)	0	0
MAS	7 (3.4)	7 (41.2)	0	0	0	0	0

All parameters were given median (minimum-maximum). CHAQ: Childhood Health Assessment Questionnaire, JADAS: Juvenile Arthritis Disease Activity Score, JADI-A: Juvenile Arthritis Damage Index-artcular JADI-E: Juvenile Arthritis Damage Index-extra-articular, JSpADAS: Juvenile Spondyloarthropahy Disease Activity Score, sJADAS: Systemic Juvenile Arthritis Disease Activity Score, MAS: Macrophage activation Syndrome, NA: Not assessed

Table 4.
Factors affecting JADI-A score

Variables	Univariate logistic regression			Multivariate logistic regression		
	OR	95% CI	P value	OR	95% CI	P value
JIA subgroups	1.322	1.005-1.739	0.046	1.266	0.793-2.020	0.323
Sex	1.035	0.489-2.188	0.929			
Age of diagnosis	0.966	0.877-1.065	0.491			
Disease duration	1.065	0.945-1.200	0.299			
Presence of comorbidity	0.804	0.391-1.655	0.554			
Duration of comorbidity	0.961	0.837-1.103	0.567			
Family history	0.923	0.412-2.066	0.845			
First HGB (gr/dl)	0.802	0.635-1.013	0.064			
First WBC/mm³	1.000	1.000-1.000	0.245			
First PLT/x10³/mm³	1.000	1.000-1.000	0.781			
First ESR (mm/h)	1.012	1.000-1.025	0.047	0.999	0.978-1.020	0.939
First CRP (mg/L)	1.003	0.996-1.010	0.399			
Affected joint number at fist admission	1.219	1.100-1.352	0.000	1.023	0.847-1.236	0.813
Attacks number/ year	1.634	1.292-2.067	0.000	1.759	1.300-2.379	<0.001
NSAI usage/ year	0.345	0.041-2.923	0.329			
IAS/ year	1.853	0.669-5.129	0.235			
Steroid/year (mg/kg)	1.014	0.999-1.029	0.064			
HGB/ year(gr/dl)	0.798	0.546-1.166	0.244			
WBC/year/mm³	1.000	1.000-1.000	0.404			
PLT/year/mm³	1.002	0.997-1.006	0.542			
ESR/year(mm/h)	1.049	1.013-1.085	0.006	1.072	1.021-1.125	0.005
CRP/year/(mg/L)	1.021	0.993-1.050	0.143			
DMARD usage	0.271	0.035-2.116	0.213			
Duration of MTX	1.020	1.008-1.033	0.001	1.029	1.013-1.046	0.001
Biologic drug usage	0.214	0.092-0.498	0.000	5.810	1.296-26.054	0.022

HGB: Hemoglobin, WBC: White blood cells, PLT: Platelets, ESR: Erythrocyte sedimentation rate, CRP: C reactive protein

Table 5.
Factors affecting JADI-E score

Variables	Univariate logistic regression			Multivariate logistic regression		
	OR	95% CI	P value	OR	95% CI	P value
JIA subgroups	1.085	0.797-1.476	0.605			
Sex	1.193	0.526-2.705	0.673			
Age of diagnosis	1.077	0.969-1.197	0.167			
Disease duration	0.996	0.871-1.139	0.955			
Presence of comorbidity	0.749	0.341-1.646	0.471			
Duration of comorbidity	0.865	0.728-1.027	0.097			
Family History	2.621	0.870-7.895	0.087			
First HGB (gr/dl)	0.913	0.727-1.147	0.433			
First WBC/mm³	1.000	1.000-1.000	0.005	1.000	1.000-1.000	0.162
First PLT/mm³	1.000	1.000-1.000	0.788			
First ESR (mm/h)	1.018	1.005-1.031	0.006	0.995	0.974-1.017	0.667
First CRP (mg/L)	1.011	1.004-1.017	0.002	1.007	1.000-1.014	0.037
Affected joint number at fist admission	1.036	0.926-1.160	0.534			
Attacks number/ year	1.061	0.849-1.327	0.601			
NSAI usage/ year	0.237	0.023-3.182	0.300			
IAS/ year	0.712	0.195-2.601	0.608			
Steroid/ year (mg/m²)	1.023	1.007-1.038	0.005	1.008	0.988-1.029	0.421
HGB/ year(gr/dl)	0.880	0.588-1.318	0.537			
WBC/year/mm³	1.000	1.000-1.001	0.003	1.007	0.989-1.026	0.443
PLT/year/mm³	1.000	0.995-1.005	0.977			
ESR/year/(mm/h)	1.068	1.029-1.108	0.000	1.051	1.008-1.095	0.019
CRP/year/(mg/L)	1.035	1.003-1.068	0.031	0.978	0.934-1.024	0.339
DMARD usage	0.757	0.164-3.494	0.721			
Duration of MTX	0.999	0.984-1.013	0.838			
Biologic drug usage	0.817	0.376-1.775	0.609			

HGB: Hemoglobin, CRP: C reactive protein, ESR: Erythrocyte sedimentation rate, PLT: Platelets, WBC: White blood cells

Table 6.
JADI-A and E affecting factors cut point values

Variable	Cut of value	AUC	%95 CI	p	% Sensitivity	% Specificity
JADI-A						
Attacks/year	1.38	0.734	0.641-0.828	0.001	0.694	0.726
Mean ESR/year	14.32	0.617	0.514-0.721	0.027	0.583	0.589
JADI-E						
First CRP	13.25	0.662	0.541-0.782	0.009	0.577	0.566
Mean ESR/year	15.10	0.674	0.567-0.780	0.002	0.633	0.632

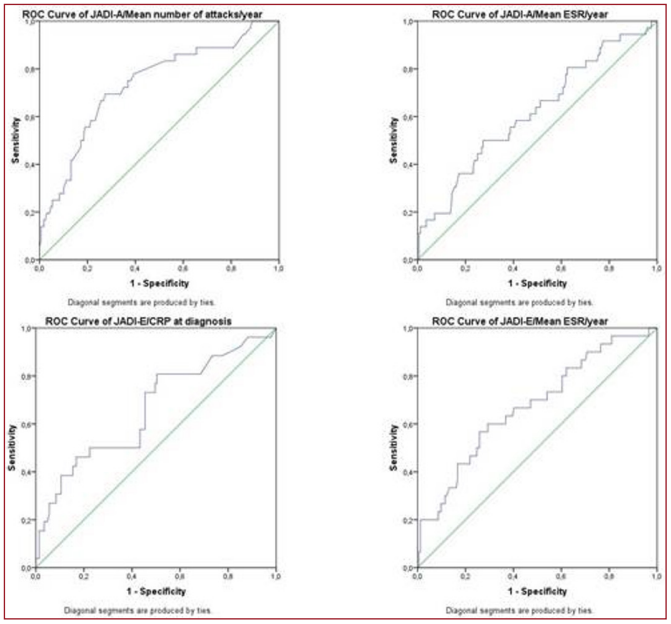

Figure 1. The ideal cut-off points affected JADI-A and E scores

Discussion

This is the first study evaluating the damage status of patients with JIA in Turkey during the biological era. The median JADI-A score was detected 0 (0-24), and the median JADI-E score was 0 (0-4). Viola et al. found JADI-A score median 0 (0-39) and JADI-E median 0 (0-7)) in 2005.[11] Their study involved 158 patients and patients with a mean follow-up period of 7.3 years.[11] Later in 2016, Menon et al.[12] evaluated 1064 patients diagnosed with systemic, oligo and poly JIA with an average of 2 years of follow-up. They determined the JADI-A score as 0 (0-52) and the JADI-E score as 0 (0-6). In our patients, the maximum values were found to be lower than in other studies in the literature. The reasons may be that the study was performed in the biological era and the ease of reach to health care providers.

Comorbid diseases whose had 45.3% of the patients were evaluated in this study. FMF was the most common comorbid disease. Patients with FMF and JIA were reported that they had more destructive arthritis.[13] The ankylosing spondylitis accompanying FMF has been reported as 12.9% in adult studies.[14,15] Our previous study detected that patients with ERA accompanying FMF showed less classical FMF and ERA findings.[16] Therefore, delayed diagnosis and therapy may affect joint destructions in JIA with FMF patients. But our results did not show that comorbid disease was a risk factor for the JADI-A score.

We found that the annual number of attacks and the median annual ESR values were independent risk factors for the JADI-A scores. In addition, it was determined that the duration of MTX usage was longer, and the rate of biological usage was higher in patients with high JADI-A. This result may be an indirect indication that long-term activation increases the articular damage.

Although the sensitivity and specificity were not high, attacks count per year and ESR value may predict articular damage. Menon et al. reported that the articular damage was higher in systemic JIA, and the damage increased with disease duration in systemic JIA and poly JIA.[12] In the study performed in Indian and Italian patients with systemic JIA, articular damage was higher in Indian patients. It was thought due to delays in diagnosis, lack of a multidisciplinary approach, long-term steroid usage, and difficulties in accessing biological drugs.[17] Although the JIA subtype did not appear statistically significant in our patients, the most damaged joints were in the systemic JIA and poly JIA. Giancana et al.[18] evaluated the damage indices of patients who received MTX between 1986 and 1999 and those who received biologics between 2000 and 2017. Joint damage was found to be lower in patients in the biological era.[19]

We found that the CRP value at admission and the median annual ESR were independent risk factors for the JADI-E score. Although its sensitivity and specificity were not high, CRP and ESR values may predict extra-articular damage. Previous studies have shown that the most common extra-articular injuries include growth retardation, muscle atrophy, and short leg length.[17] In our study, short stature (9.8%), cataract (4.9%), and striae (3.9%) were the most common extra-articular damages, respectively—all of these damages related to steroid therapy. Makearlani et al. found that 39% of patients with JIA had growth retardation after three years.[19] Patients with systemic JIA constitute 90% of these patients, and the median duration of glucocorticoid treatment was 46 weeks. Another study published in 2020 reported that patients with poly and systemic JIA who received six months of relatively short-term glucocorticoid treatment were prone to low weight and delayed puberty.[20]

Malnutrition, obesity, hirsutism, adrenal suppression, osteoporosis, which are not included in the JADI-E score, were also evaluated in our study. All of these complications are associated with steroid therapy. But, the annual steroid amount was not detected as an independent risk factor in the multivariate analysis. This may be due to the shorter steroid therapy duration due to DMARDs and biologic agents. A German study reported that high-dose steroid therapy was less performed in systemic JIA after the 2000s than before.[21]

Adrenal suppression was present in 6.9% (14) of our patients, most of which were patients with systemic and poly JIA. In the literature, adrenal suppression has been reported in approximately half of the patients using steroids with rheumatological disease.[22] It was recommended to control adrenal suppression during the steroid reduction phase of treatment.[23]

In our study, osteoporosis was detected at a rate of 3.9%. The causes of osteoporosis in JIA patients are inflammation, glucocorticoid therapy, and immobilization. In other words, JIA itself is a significant risk factor for decreased bone mineral density. Rodd et al. detected 6% vertebral fracture in 6% of pediatric rheumatology patients using steroids, 36.7% of these patients were JIA, and half of them were systemic JIA.[23] Le Blanche et al.[24] showed that 0.5 mg/kg/day steroid dose increased two times the risk of fracture. The control of inflammation, mobilization, and discontinuing GC treatment as soon as possible decrease the risk of osteoporosis. In another study, the factors affecting the progression of patients with systemic

JIA were evaluated. It has been shown that the dose and duration of steroids did not affect the prognosis.[25] An IL-1 receptor antagonist in patients with systemic JIA to reduce the steroid-related JADI-E score was recommended to achieve and maintain the inactive disease.[26]

Osteonecrosis was detected in 2.5% of our patients. Osteonecrosis can be associated with short and long-term steroid use. Steroid-induced osteonecrosis in children has been extensively studied in hematological diseases, and information on rheumatological diseases is limited.[27]

Topical and systemic use of glucocorticoids causes ocular side effects. The use of topical steroids, especially for more than three months, increases the risk of cataracts.[28] Likewise, systemic steroid use increases the risk of cataracts and ocular hypertension. Cataracts occurred in 4.9% of our patients, and half of them underwent surgical intervention. Both steroid side effects and JIA-related uveitis affect the ocular complications. The timely use of DMARDs and biological drugs prevent ocular complications.[29]

India mainly published studies related to the JADI index. In a 2008 study, JADI was detected as a useful index to measure articular and extra-articular damage in ERA. But, it did not adequately reflect lower extremity joint damage, enthesitis, and spinal damage.[29] It has been suggested to include the spine, foot joints, and enthesitis score in JADI to increase usefulness in ERA.[30] Even though they were not included in the JADI-E index, steroid-related side effects such as obesity, adrenal suppression, cushingoid appearance, osteoporosis without fracture were observed in a considerable number of patients in our study.

There are some limitations of our study. Data were obtained retrospectively from the medical records. The activity scores during the follow-up period could not be achieved. The reasons were that the scoring calculations have changed over the years, and especially the incomplete recording of VAS scores. However, all evaluation parameters were obtained at the last examination. In our study, the annual number of attacks, annual median inflammatory markers, drugs, and their doses were calculated in detail. These are the strength of our work.

In our study, we evaluated the damage status of our patients in the biological period. We have shown that parameters used routinely can be helpful to predict disease related damage. We also think that obesity, adrenal suppression, cushingoid appearance, osteoporosis without fracture should be added to the damage scoring as new criteria.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Conflict of Interest: There are no conflicts of interest in connection with this paper, and the material described is not under publication or consideration for publication elsewhere.

Ethics Committee Approval: The study was carried out with the permission of Erciyes University Ethics Committee (Date: 12.02.2020, Decision No: 2020/104).

Financial Disclosure: The authors have no conflicts of interest to declare.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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Evaluation and Neurodevelopmental Outcomes of Infants with Hypoxic Ischemic Encephalopathy Treated with Therapeutic Hypothermia: A Single Center Experience

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Abstract

Hypoxic ischemic encephalopathy (HIE) is an important cause of mortality and morbidity in newborns. The aim of this study is to evaluate the neurodevelopmental outcomes and rehabilition needs of infants followed up with a diagnosis of HIE who were treated with hypothermia in our unit. A total of 23 patients who met the criteria were retrospectively reviewed. Denver Developmental Screening Test II (Denver II DST) was used for the developmental screening. Patients were divided into groups as moderate and severe HIE based on Sarnat encephalopathy staging, as well as normal and abnormal groups based on Denver II DST results. Moderate HIE was detected in 17 (73.9%) patients, and severe HIE was detected in 6 (26.1%) patients. Patients with severe HIE were found to have lower apgar scores, more resistant metabolic acidosis, longer ventilation times, and more abnormal cranial magnetic resonance findings in the neonatal period ($p<0.05$). An abnormal Denver II DST was observed in 29.4% of individuals with moderate HIE and all patients with severe HIE (p:0.005). Speaking and fine motor impairments were more common in patients with severe HIE (p:0.018, p:0.014, respectively). Furthermore, cerebral palsy, epilepsy, and swallowing problems were also detected more frequently in patients with severe HIE (p: 0.035, p: 0.019, p: 0.011, respectively). Despite therapeutic hypothermia treatment, neurodevelopmental impairments were still seen in HIE neonates. Our findings showed that it is important to determine factors that may exacerbate the development of neurological sequelae in HIE patients for better follow-up and treatment approach.

Keywords: Hypoxic ischemic encephalopathy, therapeutic hypothermia, neurodevelopmental outcomes, newborn

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Introduction

Hypoxic-ischemic encephalopathy (HIE) is an acute progressive encephalopathy that manifests as convulsion, apnea, and abnormal muscle tone caused by perinatal hypoxia and ischemia.[1] Its frequency varies between 1-6 per 1000 live births in developed countries and 5-10 per 1000 live births in developing countries.[2] It has been reported to cause death in newborns, acute neurological damage in the early period, and permanent neurodevelopmental problems in motor, cognitive and behavioral areas after years.[3] Apgar score, blood gases, and encephalopathy findings are used for diagnosis. However, the relationship between the diagnostic criteria of asphyxia and the prognosis of patients is not fully known.[4]

Highlights

- Hypoxic ischemic encephalopathy (HIE) is an important cause of mortality and morbidity in newborns.
- In the neonatal period, male gender, low apgar score, severe acidosis, abnormal cranial MRI findings are risk factors that determine the neurodevelopmental prognosis of newborns with HIE.
- Epilepsy, cerebral palsy, and speech disorders are the most common chronic period problems in newborns with HIE.
- Monitoring and supporting the development of HIE cases with risk factors from the first months of life is very important for improving long-term outcomes.

Today, therapeutic hypothermia therapy is used to treat newborns with moderate and severe HIE. Studies have revealed that therapeutic hypothermia reduces mortality and positively affects neurodevelopmental prognoses.[5,6] However, it was reported that severe problems such as cerebral palsy, developmental delay, intellectual disability, epilepsy, blindness, and hearing loss could occur in children who survive despite therapeutic hypothermia.[5,7] HIE is a significant cause of developmental problems in our country, and the number of studies evaluating the developmental outcomes of infants treated with therapeutic hypothermia is a few.[8,9] As the number of data increases, our knowledge regarding the problems encountered in the follow-up of these patients and the frequency of these problems will increase, and timely intervention will be possible. Considering the benefits of early intervention, it is also crucial to know the risk factors to predict neurodevelopmental problems. The aim of this study is to evaluate the neurodevelopmental outcomes and rehabilitation needs of infants followed up with the diagnosis of HIE and treated with hypothermia in our unit.

Material and Method

Infants aged 9-43 months who were followed up with HIE diagnosis in the pediatric neurology outpatient clinic between January 1, 2018, and December 31, 2021, and treated with therapeutic hypothermia in the neonatal period in our unit were included in this study. The study excluded babies with a birth weight of <1800gr, gestational week of <35 weeks, congenital malformation, genetic disease, and congenital metabolic disease.

Whole-body cooling therapy is applied with the Tecotherm Neo (Inspiration Healthcare, UK) device to patients diagnosed with HIE and clinically evaluated as moderate and severe encephalopathy in our unit. Gestational week, birth weight, gender, mode of delivery, Apgar score, Sarnat stage at the first examination, blood gas and other biochemical test results taken in the first hour of life, perinatal risk factors, seizure history, hospitalization time, conventional and diffusion magnetic resonance imaging (MRI) results of patients who were treated with therapeutic hypothermia during the study period were retrospectively recorded from the hospital records. Patients were divided into 2 groups as moderate and severe HIE according to the Sarnat encephalopathy staging. MRI images in the neonatal period were re-evaluated by the same person who had ten years of pediatric radiology experience and was unaware of the patients' clinic.

In our study, the most recent neurological examinations, Denver II developmental screening test (DST) results, Electroencephalography (EEG) results, and hearing-vision evaluation results of the patients who were followed up in the pediatric neurology outpatient clinic were examined. The Denver II DST test was performed by the same person who has a Denver II DST certificate on the patients in our hospital's pediatric neurology outpatient clinic. Denver II DST is a test that evaluates the age-appropriate skills of children aged 0-6. Assessment is made in four sub-areas (personal-social, fine motor, gross motor, and speaking). Scores are determined according to their ability in these four areas.[10] According to Denver II DST results, the cases were classified into normal and abnormal groups.

The diagnosis of cerebral palsy was made considering hypotonia, spasticity, abnormal posture, increased tone, abnormal body movements, continuation of primitive reflexes, increased tendon reflexes, and delayed movement development according to the age of the patient. The patients were evaluated as spastic, dyskinetic, ataxic, hypotonic, and mixed types by cerebral palsy classification.

Ethics committee approval of the study was obtained from Trabzon Kanuni Training and Research Hospital Ethics Committee (Approval no: 2022/30).

Statistics

Statistical analyzes were performed using IBM SPSS (Statistical Package for Social Sciences) statistics software, version 24 (IBM Corp, Armonk, NY, USA). Descriptive statistics were expressed in numbers and percentages. The Chi-Square test and Fisher's Exact test examined relationships between categorical variables. Normally distributed groups were compared through Student's t-test, and non-normally distributed groups were compared through Mann Whitney U test. Results were evaluated at a 95% confidence interval, and a p-value of <0.05 was considered statistically significant.

Results

A total of 23 infants were included in the study. The most common antenatal risk factors were meconium aspiration syndrome (n:6,26%), cord entanglement (n:6,26.1%), placental abruption (n:4, 17.4%), uterine rupture (n:1, 4.3%), and prolonged rupture of membranes (n:1, 4.3%), respectively. The gestational week of the cases was 39.2±1.4 weeks, birth weight was 3194.4±462.0g, 14 (60.9%) were male, and 14 (60.9%) were delivered by cesarean section. Nine cases (39.1%) were born in our hospital, and 14 cases (60.9%) were referred from another hospital. The most common clinical findings were respiratory distress in 21 patients (91.3%), convulsions in 20 patients (87%), hypotension in 12 patients (52.2%), and hepatic dysfunction in 7 patients (30.4%). Inotropic support was administered to 52% of the cases due to hypotension. Resistant metabolic acidosis was detected only in the severe encephalopathy group (50%). According to the Sarnat stage, moderate HIE was found in 17 infants (73.9%) and severe HIE was found in 6 infants (26.1%). Patients with severe HIE were found to have lower apgar scores, more resistant metabolic acidosis, longer ventilation time, and abnormal cranial MRI findings in the neonatal period (p<0.05). A comparison of neonatal parameters of the patients according to the groups is presented in **Table 1**.

The mean age of the patients at the last evaluation was 18.3±9.2 months, and Denver II DST was applied to all patients at the last neurological examination. Denver II DST results were normal in 12 (52.2%) patients and abnormal in 11 (47.8%) patients. 90.9% of infants with abnormal Denver II DST results were male. Denver II DST results were abnormal in 29.4% of patients with moderate encephalopathy and in all patients with severe encephalopathy. Speaking (83.3%) and fine motor (100%) problems were found most frequently in infants with severe HIE.**Table 2** indicates the comparison of the sub-areas of Denver II DST according to the groups.

Tablo 2
Comparison of sub-scales of Denver II DST according to groups

Scale	Denver II DST		p
	Normal (n:12)	Abnormal (n:11)	
Speaking	14 (60.9)	9 (39.1)	0.003
Fine motor	11 (47.8)	12 (52.2)	<0.001
Gross motor	17 (73.9)	6 (26.1)	0.005
Personal social	18 (78.3)	5 (21.7)	0.640

Data are given as n (%), Abbreviation: Denver II developmental screening test, Denver II DST. Chi-Square test was used.

The chronic period results of infants with HIE are shown in **Table 3**. Epilepsy (100%), cerebral palsy (83.3%), and swallowing problems (50%) were found more frequently in infants with severe HIE compared to infants with moderate HIE (p:0.019, p:0.035, p:0.011). All of the infants with severe HIE needed physiotherapy, 66.7% needed speech therapy, 50% needed rehabilitation, and 33.3% needed vision and auditory therapies. Physiotherapy requirement was more frequent in infants with severe HIE compared to infants with moderate HIE (p: 0.014).

Table 1
Comparison of maternal and neonatal parameters of asphyxia infants with moderate and severe HIE

Parameter	Moderate HIE (n: 17)	Severe HIE (n:6)	p
Maternal age (years)	29.4±4.3	31.5±5.2	0.341***
Gravidity	1.7±1.2	3.2±1.7	0.044**
Gestational week (week)	39.4±1.4	38.8±1.3	0.431**
Birth weight (g)	3168.8±522.7	3266.7±238.0	0.666***
Gender (male)	9 (52.9%)	5 (%83.3)	0.340*
Mode of delivery (Cesarean)	9 (52.9%)	5 (%83.3)	0.340*
1st min Apgar scores	3 (0-6)	1 (0-1)	0.002**
5th min Apgar scores	6 (2-9)	2.5 (2-6)	0.002***
Birthplace			0.643*
Our hospital	6 (35.3%)	3 (%50.0)	
Another hospital	11 (64.7%)	3 (%50.0)	
1st hour blood gas			
ph	7.0±0.1	6.9±0.2	0.506***
HCO3	10.9±2.5	13.0±4.7	0.386***
Be	-17.6±3.3	-18.9±8.4	0.714***
Lactate	13.7±4.4	12.3±6.6	0.590***
MRI findings	4 (23.5%)	6 (100%)	0.002*
Diffusion MRI findings	4 (23.5%)	4 (66.7%)	0.131*
Sarnat			
Stage I	2 (11.8%)	0	
Stage II	15 (88.2%)	0	
Stage III	0	6 (100%)	
EEG findings	8 (47.1%)	2 (33.3%)	0.660*
Convulsion	14 (82.4%)	6 (100%)	0.539*
Hypotension	8 (47.1%)	4 (66.7%)	0.640*
Thrombocytopenia	8 (47.1%)	4 (66.7%)	0.640*
Kidney failure	2 (11.8%)	2 (33.3%)	0.270*
Liver dysfunction	5 (29.4%)	2 (33.3%)	1.000*
Pulmonary hypertension	1 (5.9%)	1 (16.7%)	0.462*
Inappropriate ADH	2 (11.8%)	1 (16.7%)	1.000*
Infection	4 (23.5%)	1 (16.7%)	1.000*
Mechanical ventilator duration (days)	3.5±5.2	8.3±6.8	0.016**
Total oxygen time (days)	9.8±8.9	17.5±12.5	0.101**
Neurological finding at discharge	1 (5.9%)	2 (33.3%)	0.155*
Length of stay (days)	22.6±13.8	24.5±11.3	0.392**

Data are given as mean±standard deviation or n (%). Abbreviations: HIE, Hypoxic-ischemic encephalopathy; EEG, Electroencephalography; ADH; Antidiuretic hormone. Chi-Square test*, Mann Whitney U test** and The Student's t-test*** were used.

Tablo 3
Chronic period outcomes of infants with HIE

Outcomes	n (%)
Epilepsy	13 (56.5)
Cerebral palsy	10 (43.5)
Language speaking	8 (34.8)
Swallowing problem	3 (13)
Deafness	2 (8.7)
Vision loss	2 (8.7)
Microcephaly	1 (4.3)
Hyperactivity/ anxiety disorder	1 (4.3)
Physiotherapy	12 (52.2)
Special education	6 (26.1)

Data are given as n (%). Abbreviation: HIE, Hypoxic-ischemic encephalopathy

The time of EEG for infants with HIE was 6.2±1.4 months, and the time of MRI scan was 12.4±9.5 days. 87% (n: 20) of the patients had convulsions in the neonatal period, but 50% (n: 10) of these patients had abnormal findings in MRI and EEG, and 55% (n:11) of them had abnormal Denver II DST results. There was no difference in pH, HCO3, and bE values between the infants with and without MRI findings (p>0.05). One of the patients with abnormal EEG had infantile spasm, while the others had focal epilepsy. It was determined that 65% (n:13) of the patients who had convulsions in the neonatal period were receiving drug treatment for epilepsy. All patients had monotherapy or adjunctive drug therapy. The most commonly used antiepileptic drugs were phenobarbital, levetiracetam, and clonazepam, respectively. EEG findings of all patients with abnormal EEG findings in the follow-up were improved as of the ninth month.

Discussion

In this study, neurodevelopmental delay was detected in approximately half of the cases that we followed up with the diagnosis of HIE for three years.

Detection of risk factors in neonatal asphyxia is of great importance in reducing the incidence and mortality rate of asphyxia.[11] The study of Majeed et al.[11] reported that lack of prenatal care, poor nutritional status, prenatal bleeding, and maternal toxemia increase the incidence of asphyxia. In our study, it was found that meconium aspiration syndrome and cord entanglement were more common in infants with HIE.

Our study detected a significant gender difference between asphyxia infants with normal and neurodevelopmental delay. 90% of infants with neurodevelopmental delay were male. Hussein et al.[12] investigated the levels of interleukin 8 and antioxidants in the cerebrospinal fluid of asphyxiated infants and reported that these were lower in male infants than in females. This result shows that male infants are more prone to brain damage and have a higher risk in terms of prognosis. The result of our study is compatible with the literature.

The relationship between mode of delivery and perinatal asphyxia is not clear. Utomo et al.[13] reported that cesarean delivery is a risk factor for asphyxia. Boskabadi et al.[4] reported that they could not find a relationship between the mode of delivery and birth asphyxia. In our study, 60% of asphyxia infants were delivered by cesarean section. However, considering the possible relationships between cesarean section indication and antepartum period, we think that it is not possible to establish a direct relationship between asphyxia and delivery method.

There are conflicting results in the literature regarding the effectiveness of the Apgar score in predicting mortality and neurodevelopmental outcomes.[4,14-18] Boskobadi et al.[4] reported that the 5th minute Apgar score helps predict neurodevelopmental problems in asphyxiated children. In the study of Nataraji et al.[15], in which 174 patients treated for hypothermia were investigated, it was reported that 75% of those with a 10-minute Apgar score of 0-3 died or became neurodevelopmentall disabled at the age of 6-7, and one-fifth of them lived unhindered at school age. Publications have reported that the neurodevelopment of infants with an Apgar score of zero at the 10th minute is not unfavorable.[17,18] In our study, 1st and 5th minute Apgar scores were lower in babies with severe HIE, and all of them had impaired neurological development. This result supports the idea that the Apgar score effectively predicts neurodevelopmental issues.

It has been previously reported that both pH and partial pressure of carbon dioxide in blood gas in newborns with HIE are potent modulators of cerebral blood flow and may contribute to brain damage.[1] Wayock et al.[19] reported a relationship between the initial low pH values and severe brain damage in MRI in newborns with HIE treated with therapeutic hypothermia. In our study, there was no difference in blood gas values between cases with moderate and severe encephalopathy and cases with and without MRI findings.

HIE is responsible for 60% of early-onset neonatal seizures.[20] The prognostic significance of seizures in infants with HIE is still controversial.[1] Despite hypothermia treatment, infants with HIE have been reported to have a higher risk of epilepsy in the first 2 years of life compared to the general population.[21] Seo et al.[22] reported that 82.4% of 83 infants diagnosed with asphyxia developed epilepsy during follow-up. In addition, it was reported in this study that epilepsy developed in only 41.2% of those who had convulsions in the neonatal period, and abnormal MRI scans were more common. In our study, it was found that 56.5% of infants with HIE were followed up with the diagnosis of epilepsy, and 65% of those who had convulsions in the neonatal period were diagnosed with epilepsy. MRI and EEG were abnormal in 50% of those who had convulsions in the neonatal period, and Denver II DST results were abnormal in 55%. These results show that convulsions alone are not sufficient to predict neurodevelopmental problems in asphyxia infants, and MRI and EEG findings are more determinative in evaluating the resulting brain damage and predicting prognosis.

The stage of clinical encephalopathy in infants with HIE treated therapeutic hypothermia may be helpful in predicting the neurodevelopmental prognosis of infants.[1] Wyatt et al.[23] reported that Sarnat's encephalopathy in the first 6 hours of life is strongly associated with neurodevelopmental outcomes in infants. However, Lally et al.[24] reported that the presence of moderate and severe encephalopathy in infants with HIE was insufficient to determine the poor prognosis. In our study, 26.1% of the cases had severe encephalopathy and all of these patients had neurological developmental delay. This result supports the idea that the Sarnat encephalopathy score can predict poor prognosis in patients.

Hemodynamic instability has been reported in 33-77% of newborns with HIE treated with therapeutic hypothermia.[1] In our study, inotropic support was administered to 52% of the cases due to hypotension. In a study evaluating 190 asphyxia newborns treated with hypothermia, it was reported that infants with hypotension had a higher

risk of developing brain damage on MRI.[25] More et al.[26] determined a relationship between the development of pulmonary hypertension and the development of brain damage. It was also reported that both hypoglycemia and hyperglycemia in early life are associated with poor neurodevelopmental outcomes.[1,26] However, in our study, no significant difference was found between patients with moderate and severe HIE in terms of clinical findings, except for resistant metabolic acidosis and prolonged ventilation. These results suggest that clinical findings alone are insufficient to determine neurodevelopmental outcomes in neonates with HIE.

Therapeutic hypothermia is the only known and effective treatment method in HIE today. A systematic review of a randomized controlled trial evaluating 1500 term and late preterm infants with moderate/severe encephalopathy reported that therapeutic hypothermia reduced mortality and improved neurodevelopmental outcomes in infants surviving 18 months of age.[6] In another systematic review of 1214 neonates with HIE who treated therapeutic hypothermia, death or severe neurodevelopmental disorders were observed in approximately half of them, whereas neurodevelopmental outcomes were normal in only 40%.[27] As far as we know, there are only two studies in the literature on the neurodevelopmental outcomes of patients treated with therapeutic hypothermia in our country.[8,9] It was reported that 92.4% of the patients in one of these studies and 44.6% of the patients in the other showed normal neurodevelopment.[8,9] In our study, similar to the study of Çelik et al.[9], normal neurodevelopment was found in 52% of the cases.

HIE is a critical cause of cerebral palsy. Studies have shown that the rate of cerebral palsy in newborns treated with therapeutic hypothermia is between 13-28% at 18 months.[5,7,27] In our study, the rate of cerebral palsy was 43.5%. The high rate of cerebral palsy in our study may be related to the fact that most of the cases were in the severe encephalopathy group and the number of cases was small. Sensory problems are common in children with HIE. In studies in the literature, the rate of vision loss was reported as %1.3-7 and the rate of hearing loss as 2.5-4% in children treated with therapeutic hypothermia.[5,7,29] In the study of Çelik et al.[9], in which 47 asphyxic infants were evaluated, it was indicated that 3 (%6.4) of the patients had hearing and 1 (%2.1) had vision disorders. In our study, vision loss was detected in 2 cases (%8.7), and hearing loss in 2 cases (%8.7). Similar to the study of Çelik et al.9, our study also showed that the need for physiotherapy is higher in patients with severe HIE. It was reported that social problems such as anxiety/depressive states, attention, memory, time perception, and orientation problems are more common in children with mild and moderate encephalopathy.[30,31] In our study, anxiety disorder and hyperactivity were found in a child with moderate encephalopathy findings in the neonatal period. In a study in which 239 children followed up with the diagnosis of moderate HIE were evaluated, it was reported that 12 of the cases were diagnosed with autism spectrum disorder at the age of 5 years.[32] No case diagnosed with autism was found in our study. However, studies evaluating the results of the longer-term follow-up of these patients are needed.

Our study has some limitations. The small number of cases, the experience of a single center, and the retrospective nature of our study are among the limitations of our study.

Conclusion

The incidence of neurodevelopmental problems in neonates with HIE is high and is associated with the severity of asphyxia. Our study is important in terms of revealing the effect of therapeutic hypothermia on morbidity in infants living in our country. The presence of severe encephalopathy findings, resistant metabolic acidosis, prolonged ventilation time and abnormal cranial Mrg findings in the neonatal period should be a warning for the risk of neurodevelopmental delay. In order to improve long-term outcomes of patients with HIE, it is essential to support their development by assessing the rates of neurological sequelae development throughout follow-up.

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Original Article

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Predictive Parameters of Steroid Dependency in Minimal Change Disease

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Abstract

The most common type of nephrotic syndrome in children is minimal change disease (MCD), which is usually responsive to steroid therapy. Steroid dependency is one of the handicaps in the management of these children. Thus, the early prediction of the disease course may improve treatment strategy. Demographic characteristics and laboratory parameters of 35 patients at the time of MCD diagnosis were retrospectively obtained from the hospital records. There were 23 (65%) patients with steroid sensitive (SSNS) and 12 (35%) with steroid dependent nephrotic syndrome (SDNS). There was a significant difference between the patients with SSNS and SDNS in terms of age at diagnosis, remission time, and mean values of platelet volume, low density lipoprotein cholesterol, uric acid, urine protein-to-creatinine ratio, total cholesterol and creatinine ($p=0.003$, $p<0.001$, $p=0.013$, $p=0.006$, $p=0.036$, $p=0.02$, $p=0.003$, and $p=0.034$, respectively). The prediction of early markers of steroid dependency can reduce the side effects of steroids and facilitate the use of appropriate drugs.

Keywords: Children, minimal change disease, nephrotic syndrome, steroid dependency

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Introduction

Nephrotic syndrome (NS) is the most frequent pediatric glomerulopathy characterized by proteinuria, hypoalbuminemia, and edema.[1] The most common type of childhood NS is minimal change disease (MCD)accounting for up to 90% of cases.[2] As the main treatment of MCD is immunosuppression with corticosteroids, immune system dysregulation strongly indicates a pathogenic role in disease development.[3,4] MCD generally responds well to corticosteroids, although 50-75% of patients, especially those aged <5 years, experience frequent disease relapses and half of the frequent relapsers eventually become steroid-dependent during steroid tapering or after discontinuation.[3-6] Patients with frequently relapsing NS (FRNS) or steroid-dependent NS (SDNS) are at a major risk of developing complications related to the prolonged use of steroids.[6,7] Thus, this study aimed to verify the predictive factors for NS attacks in pediatric patients with MCD.

Highlights

- It is important to predict the risk factors for steroid dependency in nephrotic syndrome.
- Age at diagnosis, remission time, mean platelet volume, total and low density cholesterol, uric acid, creatinine, and proteinuria levels can be used as the predictive markers of steroid dependency in nephrotic syndrome.

Material and Method

The study included 35 patients (23 male, 12 female) diagnosed with steroid-responsive MCD and 35 healthy children (16 male, 19 female) as the control group. After the ethical approval was obtained from Manisa Celal Bayar University ethic committee) (29.12.2021, Decision No:20.478.486/1119), the demographic characteristics and laboratory parameters of the patients at the time of MCD diagnosis were retrospectively conducted from the patients' files and hospital records. The children were separated into two groups based on their steroid response as steroid-sensitive NS (SSNS) and SDNS. SSNS was defined as on response to 60 mg/m2 corticosteroid per day within four to six weeks, SDNS as two consecutive attacks during corticosteroid treatment or within 14 days of its cessation, and FRNS as ≥2 relapses per six months or ≥4 relapses per year.[2,8] Hemoglobin levels, leukocyte, lymphocyte, neutrophil, monocyte and platelet counts, platelet indices [mean platelet volume (MPV), platelet distribution width (PDW), and plateletcrit (PCT)], red cell distribution width (RDW), C-reactive protein (CRP), lipid profile [LDL (low-density lipoproteins) cholesterol, HDL (high-density lipoproteins) cholesterol, triglycerides (TG), total cholesterol], albumin, creatinine, urea, and uric acid levels were recorded at the time of the patients' first diagnosis. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), which is considered to be parameters for predicting severity and prognosis of many inflammatory diseases, including kidney disease [9-12], were calculated using the complete blood counts. Nephrotic range proteinuria was determined as urine protein/creatinine ratio of >2 mg/mg. Patients with any inflammatory, immunologic or other chronic illness (hyperthyroidism, hypertension, obesity, vitamin D deficiency, obesity) those taking medication other than steroids, and those resistant to steroids were excluded. There were no patients with kidney disease.

Statistical analysis

Statistical analysis was achieved using the SPSS version 22.0. Continuous parameters were detected as mean±standard deviation and qualitative data as frequencies and percentages. The normality of the distribution of data was evaluated with graphical methods, and the Kolmogorov-Smirnov or Shapiro-Wilk test. The chi-square test was performed to compare qualitative parameters while Student's t-test or the Mann-Whitney U test was utilized to analyze the differences in continuous variables. A p value of <0.05 was determined as significant.

Results

The demographic characteristics and laboratory data of the children with MCD and the control group are presented in **Table 1**. The mean age of the patients with MCD was 5.2±1.8 years, and 66% were male. The platelet counts were significantly higher and MPV level were lower in patients with MCD than the controls (p=0.002 and p=0.02, respectively. No significant difference was detected among the two groups in terms of age, gender, hemoglobin level, leukocyte count and uric acid levels (p=0.27, p=0.09, p=0.77, p=0.69, and p=0.17, respectively).

Table 1.
Demographic and laboratory parameters of the patient with MCD and control groups

	Patient	Control	p value
Age at diagnosis	5.2±1.8	5.6±2.8	0.27
Gender (male/female)	23/12	16/19	0.09
Hemoglobin (g/dL)	12.8±1.6	12.7±1.5	0.77
Platelet (103/µL)	418 ±150	328±69	0.002
MPV (fL)	7.9±1.2	8.5±1	0.02
WBC (103/µL)	9.8±2.5	10±2.5	0.69
Uric acid (mg/dL)	4.5±1.1	4.3±1	0.17

Abbreviations: MCD: minimal change disease, MPV: mean platelet volume, WBC: white blood cell

There were 23 (65%) children with SSNS and 12 (35%) children with SDNS (**Table 2**). All the patients with SDNS had frequent relapses. Five patients of the SSNS group were frequent relapsers. Sixteen patients with SSNS (70%) and 11 with SDNS (92%) had relapses associated with concomitant upper respiratory tract (URT) infections although the difference between these groups was not significant (p=0.27). There was a significant difference among these two groups in terms of age at diagnosis, remission time, and MPV, LDL, uric acid, urine protein-to-creatinine ratio, cholesterol and creatinine levels (p=0.003, p < 0.001, p=0.013, p=0.006, p=0.036, p=0.02, p=0.003, and p=0.034, respectively) (Table II). There was no significant difference in gender, hemoglobin, leukocyte, platelet, PCT, PDW, RDW, neutrophil, lymphocyte, NLR, PLR, monocyte, albumin, TG, HDL, CRP, and urea between the SSNS and SDNS groups (p=0.5, p=0.8, p=0.8, p=0.7, p=0.7, p=0.6, p=0.9,

p=0.8, p=0.65, p=0.38, p=0.5, p=0.2, p=0.6, p=0.4, p=0.2, and p=0.3, respectively) (**Table 2**). MPV counts at the time of initiation of steroid therapy remained low, while they normalized after steroid response and during remission.

Table 2.
Comparison of demographic and laboratory parameters of the patients according to steroid response

	SSNS (n=23)	SDNS (n=12)	p value
Age at diagnosis	5.8±2	4±0.7	0.003
Gender (M/F)	16/7	7/5	0.5
Remission time (day)	5.4±1.4	12±1.7	<0.001
Attack number	2.5±1.6	8.5±3.7	0.006
Hemoglobin (g/dL)	12.7±1.6	12.9±1.7	0.8
WBC (103/µL)	9.8±2.6	10±2.3	0.8
PLT (103/µL)	425±161	404±133	0.7
PCT (%)	0.34±0.1	0.32±0.1	0.7
PDW (fL)	16±0.6	16±0.7	0.8
MPV (fL)	8.4±1.2	7.5±0.8	0.013
RDW (%)	14.4±1.9	13.8±1	0.6
Neutrophil (103/µL)	4.8±1.8	5±2.4	0.9
Lymphocyte (103/µL)	3.9±2	4±1.3	0.8
NLR	1.7±1.2	1.5±1.1	0.65
PLR	131±60	111±59	0.38
Monocyte (103/µL)	615±212	691±407	0.5
Albumin (g/dL)	1.7±0.3	2±1	0.2
TG (mg/dL)	215±76	206±66	0.6
Total cholesterol (mg/dL)	412±88	311±103	0.003
LDL (mg/dL)	300±78	209±104	0.006
HDL (mg/dL)	77.7±20	72±19	0.4
Uric acid (mg/dL)	4.2±1	5±1	0.036
CRP (mg/dL)	0.7±1.4	0.3±0.3	0.2
Urea (mg/dL)	27±13.5	27±26	0.3
Creatinine (mg/dL)	0.3±0.2	0.4±0.1	0.034
Urine Pr/Cr (mg/mg)	6.5±1	11±1.5	0.02

Abbreviations: SSNS: steroid-sensitive nephrotic syndrome, SDNS: steroid-dependent nephrotic syndrome, F: female, M: male, WBC: white blood cell, CRP: C-reactive protein, MPV: mean platelet volume, PCT: plateletcrit, PDW: platelet distribution width, PLR: platelet-to-lymphocyte ratio, NLR: neutrophil-to-lymphocyte ratio, RDW: red cell width distribution, Pr/Cr: protein-to-creatinine ratio)

Discussion

Nephrotic syndrome is the most common childhood chronic glomerular disease.[1,2] Steroid dependency is one of the major difficulties in the treatment of patients with NS. The long-term steroid administration in patients with SDNS can cause complications such as diabetes, hypertension, obesity, osteoporosis, short stature, susceptibility to infections, gastritis, and posterior subcapsular cataracts, and therefore the use of alternative immunosuppressant agents is necessary in these patients.[6,7] Although, the pathogenesis of nephrotic syndrome remains uncertain, the role of the immune system and inflammation is reported in many studies.[3,4,13] Inflammatory mediators, such as neutrophils, lymphocytes, platelet, and platelet indices have been shown to be activated in NS.[14-17] The early prediction of patients with SDNS using these inflammatory parameters or other biochemical markers will therefore be useful to closely monitor these patients. This report aimed to find out the demographic characteristics and laboratory markers to predict steroid dependency in patients with NS.

In the current research, the mean age of the patients at the onset of MCD was 5.2±1.8 years, consistent with previous reports.[18,19] There was 2:1 male dominancy in the MCD group, which is also in agreement with the literature.[2,5] The patients in the SDNS group were found to be younger at the onset of the disease, similar to the research of Andersen et al.[20] Conversely, Kabuki et al. have reported an increase of steroid dependency with age.[21] It was reported that males were more at risk of developing steroid dependency than females.[20] This may be a result of the predominance of male patients with NS. However, we found no significant difference in steroid dependency between males and females in the current study.

Most SDNS cases in the current study had relapses after URT infections. Similarly, Yap et al.[6] and Abdel-Hafez et al.[22] reported that patients who did not have any attack during URT infection might be less likely to be steroid-dependent, although this was not statistically significant.

Platelets and platelet indices were found to be related to the inflammatory process of NS in previous studies.[15-17,23] Previous studies detected thrombocytosis at the diagnosis of MCD[23], similar to the current study. It is assumed that hypoalbuminemia and hypercholesterolemia that occur in NS lead to platelet aggregation and are responsible for thrombocytosis as it is presented a negative correlation between albumin and PLT in the current study. However, Mittal et al. reported normal PLTcounts in children with NS.[24] Although, Kocyiğit et al.[17] and Gulleroglu et al.[15] reported higher MPV in patients with MCD, in the current study, MPV was determined to be lower in the MCD group than in the control group, supporting the results presented by Wasilewska et al.[16] Gulleroglu et al.[15] detected lower MPV levels in steroid-resistant NS. In the current study, steroid dependency was observed to be correlated with decreased MPV levels but did not have any correlation with platelet levels.

NLR and PLR are used as inflammatory indices for the prognostic prediction of autoinflammatory diseases.[9-12] However, in the recent search, we found no association between these parameters and steroid dependency in MCD. Jamee et al. reported NLR and PLR not suitable for predicting steroid response in their patients with childhood NS.[25] However, they included steroid sensitive and resistance patients with NS, not only MCD patients to their study.

This study showed that uric acid levels were associated with steroid dependency in MCD. Song et al.[26] revealed hyperuricemia as an independent risk factor for progression to end stage kidney disease in children with MCD. Asakawa et al.[27] reported that hyperuricemia was related to podocyte injury and proteinuria. MCD is also known as a podocytopathy, and there may be an association between podocyte damage in SDNS and hyperuricemia. The rate of proteinuria was also detected to be statistically higher in the SDNS group in our study. Proteinuria and hyperuricemia may cause steroid dependency through podocyte injury.

The limitations of the recent research are that the retrospective nature and the small sample size, which may limit the generalization of results.

Conclusion

It is important to predict the risk factors for steroid dependency in NS in order to plan long-term management and avoid complications related to steroid use. Age at diagnosis, remission time, MPV, total and LDL cholesterol, uric acid, creatinine, and proteinuria can be used as the predictive markers of steroid dependency in NS. Future large-scale and multicenter studies are needed to corroborate our findings.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Conflict of Interest: There are no conflicts of interest in connection with this paper, and the material described is not under publication or consideration for publication elsewhere.

Ethics Committee Approval: The study was carried out with the permission of Manisa Celal Bayar University Clinical Researches Ethics Committee (Date: 29.12.2021, Decision No:20.478.486/1119).

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Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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Off-label Use of ADO II® in the Closure of Various Congenital Heart Defects

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Abstract

Devices may be used for special purposes different than their production purpose. For instance, Amplatzer Ductal Occluder is actually designed for duct closure and its usage for closing defects other than ductus is named as off-label. The aim of this study is to emphasize off-label use of device: not only for VSD but also for other various defects. This study is designed retrospectively, performed by the evaluation catheterization records of patients in whom ADO II and ADO II-AS devices were used in Erciyes University Medical Faculty Children Hospital, Pediatric Cardiology Department between 2011 and 2018. Patients' demographic criteria: age, weight at the time of procedure was gathered. The diagnosis, size of device, follow-up period and complications were also noted. From April 2011 to March 2018, a total of 122 patients underwent transcatheter closure by ADO II and 66 patients by ADO II AS. The number of PDA closure with ADO II was 48; with ADO II AS were 62. Rest of the procedures were all off-label. Types of off-label procedures performed were: VSD closure, residual mitral cleft closure, Aorta-Right atrium tunnel closure, pulmonary arteriovenous fistula occlusion, aorta-pulmonary window closure, and occlusion of the artery feeding accessory lobe in scimitar syndrome, Gerbode defect occlusion. Up to our knowledge; this study includes the largest pediatric case series with various different congenital heart defects which were closed with ADO II. Also our ADO-II occluded VSD case series is one of the largest series in the literature with almost 6 years' follow-up. We believe in that ADO-II device may be an alternative in percutaneous closure of various rare heart defects. It is used successfully for non-ductal defects with low complication and high compliance rates.

Keywords: ADO II, congenital heart defect, Gerbode defect, pulmonary arteriovenous malformation, mitral valve cleft

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Introduction

Off-label use is a term used for the treatment modalities or drugs for an unapproved indication or in an unapproved age group, route of administration or dosage. This is a legal issue unless breaks ethical guidelines or safety regulations. The ability to use a treatment modality beyond the officially approved indications is commonly used to good effect by healthcare professionals. Usage Amplatzer Ductal Occluder for the occlusion of defects other than PDA is off label. Safety and efficiency of ADO II and ADO II AS in PDA closure have been discussed before in literature.[1-4] However, the number of reports concerning off-label use of ADO II and ADO II AS is very limited especially in pediatric age group. According to our knowledge, this study is the largest one that discuss the off-label use of ADO II and ADO II AS in children. The aim of this study is to emphasize the usage of off-Label devices in congenital heart defects by giving different case examples.

Highlights

- ADO II device has been used safely in PDA occlusion for many years.
- This device can also be used for occlusion of rare different congenital heart defects.
- However, since these defects are very rare and the procedure is likely to be risky, it is best to perform the procedure in experienced centers and by experienced pediatric interventional cardiology teams.

Material and Method

It is a retrospective study. During the time interval beginning from 2011 to 2018 we have used ADO II and ADO II-AS devices (St. Jude Medical, St. Paul, MN) for off-label uses in our department. We have collected the demographic data (age, weight etc), the diagnosis, device type, size, time of follow-up period and the complications of the patients.

Erciyes University Ethic Committee approved our study (Decision No: 2019-730). A written informed consent was taken from all parents before each procedure.

Before the catheterization; detailed work-up was done. We had to use computed tomography only in the patient with Scimitar syndrome in order to determine the artery supplying accessory lobe before the procedure.

The devices used in the study were ADO II and ADO II AS (St Jude Medical, Inc.; Plymouth, MN, USA).

Physical examinations, electrocardiogram, and trans-thoracic echocardiography were performed before and after the procedure and repeated in 3 months' interval till 1 year and then yearly thereafter.

Results

During the time interval between April 2011 to March 2018: total defect closure by ADO II device was 122 and ADO II AS device was 66. The 48 of total 122 cases with ADO II Device was PDA and 62 of 66 cases with ADO II AS was PDA. The main procedures that ADO II device used for off label were the closure of VSD, Gerbode defect, residual mitral cleft, aorta-pulmonary window, Aorta-Right atrium tunnel, pulmonary arteriovenous fistula, closure, artery feeding accessory lobe in Scimitar syndrome, occlusion.

VSD Closure

Till April 2011 ventricular septal defects have been closed percutaneously with ADO-II device in our hospital. Procedures were performed according to the indications and techniques we used, which were mentioned in our previous studies.[5,6]

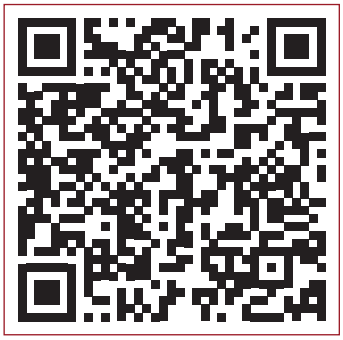
The number of VSD closure with ADO II was 68, with ADO II-AS was 3 till now. The age and weight of patients was 83 months (48-120), 23 kg (13-27) respectively. Twelve of these patients were less than 1 year of age (10 were closed with ADO II, 2 with ADO II AS).

Aorta-RA tunnel Closure

A newborn baby was admitted to emergency with tachypnea, respiratory insufficiency. Aorta-right atrium tunnel was diagnosed by TTE. The orifice of aorta right atrium tunnel was occluded with 5 × 6 ADO II AS from retrograde side.[7]

Mitral Cleft Closure

18-month-old infant operated for incomplete AVSD when he was 6-month-old. After surgery he had residual mitral cleft and second degree regurgitation through cleft, first degree insufficiency through mitral valve. Left chambers of the heart were enlarged. Family did not want their boy to have a second operation. Therefore; we have decided to close mitral cleft percutaneously. From femoral arterial route, delivery system was placed to pulmonary vein passing through mitral cleft. 3 mm × 4 mm ADO-II was used to occlude mitral cleft by transthoracic echocardiography guidance (**Video 1**). Up to our knowledge it is the first case whose mitral cleft was closed percutaneously.



Video 1: The mitral cleft was occluded using a 3×4 ADO-II device with transthoracic Echocardiography guidance.

Pulmonary Arteriovenous Malformation Closure

6-month-old infant was recognized that she was cyanotic during her vaccination. Transcutaneous oxygen saturation was 60%. All secondary causes of cyanosis were discarded. Transthoracic echocardiography and chest X ray revealed normal. Pulmonary Arteriovenous malformation was found by CT. The angiographic imaging revealed four major arteriovenous connections in the-left-lower-lobe. The largest two were closed with two separate devices: 6 mm × 6 mm ADO II and 5 mm × 6 mm ADO II (**Video 2**). Oxygen saturation of patient was increased to 98% and discharged from hospital.

Video 2: Two large pulmonary arteriovenous malformation were closed with two separate devices, one 6×6 ADO-II and one 5×6ADO-II

Aorta-pulmonary window Occlusion

Five years old boy was admitted to the clinic with heart murmur, tachycardia and tachypnea. It was learnt from parents that he had undergone surgical repair of aortopulmonary window at 2 years of age. He was found to have a residual defect by transthoracic echocardiography, left chambers were enlarged and second degree mitral insufficiency was present. Treatment options were discussed with family and transcatheter closure was planned. Aorta-pulmonary window was closed through arterial side with 6 mm × 4 mm ADO II device successfully.

Occlusion of the artery feeding accessory lobe in scimitar syndrome

13 years old girl admitted to our clinic for dyspnea. Dextrocardia and hypoplasia of right lung was seen in chest X ray. Transthoracic echocardiography revealed that right pulmonary veins abnormally connected to the IVC. Therefore; in suspicion of Scimitar syndrome CT was performed and confirmed the diagnosis. Treatment options were discussed with family. Family did not want to have cardiac surgery; therefore, we decide perform percutaneous closure. Artery supplying accessory lobe was occluded with 6 mm × 4 mm ADO II device (**Figure 1**). After closure her symptoms were relieved. 2 months' later control CT demonstrated that sequestrated lung lobe was decreased significantly.

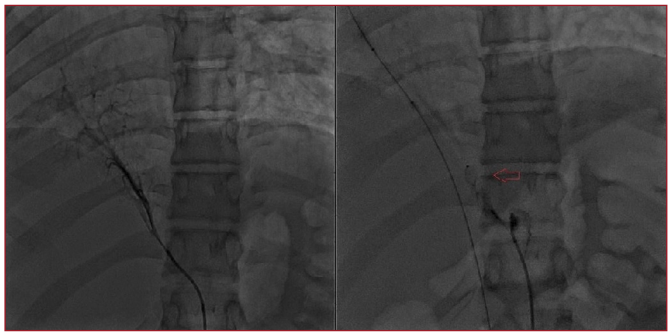


Figure 1: The artery-supplying accessory lobe was occluded with a 6×4 ADO-II device in Scimitar Syndrome.

Gerbode defect occlusion

Ten years old boy, operated for VSD 3 years ago. He admitted to the hospital for respiratory difficulty and grade 3 holosystolic murmur. Left side of the heart was enlarged therefore we have decided to occlude the defect. We have discussed the parents about treatment method (surgery and transcatheter method). Family did not want to have surgery. Qp/Qs ratio of the patient was calculated as 1.9. Narrowest diameter of Gerbode defect (LV to RA shunt) was measured as 2 mm. The distance of the defect to aortic valve was 6 mm. The defect was occluded with 4 mm × 4 mm ADO II (AGA Medical) device.

Discussion

Amplatzer Duct Occluder-II is originally designed for PDA closure however; recently its off-label uses increase in number. The main reasons that improves its popularity are: it is flexible, is easy to proceed through angulations, requires 4F or 5F Amplatzer® TorqVue® LP Delivery Sheath (St. Jude Medical, Plymouth, MN, USA). Therefore, using ADO II makes the procedure easier, delivery is more comfortable, and smaller sheath size decrease vascular complications.[7] Also it is suitable for either vascular delivery.

Its improved form, the ADO II additional sizes (ADO II-AS) (St. Jude Medical, Inc.; St.Paul, Minnesota, USA) have discs that has low risk to protrude into surrounding vessels (peripheral pulmonary arteries or aorta).[8]

Most popular off-label use of ADO II is VSD occlusion. It is preferred mainly for treating aneursymatic VSDs even when they are adjacent to aortic valve. Vijayalakshmi et al.[9] reported VSD closure using ADO-II. They have occluded perimembranous, apical/mid muscular and Gerbode defects. The major challenge in percutaneous perimembraous VSD closure is heart block. They told that unlike the other occluder devices ADO II device because of its soft structure it does not apply pressure on the conducting system. Kanaan et al.[10] have used ADO II device for 31 patients in 8-year time interval. Baspinar et al.[11] used ADO II for only 3 patients, 2 of them were muscular VSD and the other one was aneurysmatic perimembranous VSD. Mahmoud et al.[12] reported percutaneous closure of one muscular ventricular septal defect with ADO II AS.

We have both published our center early and midterm results of transcatheter VSD closure with ADO II.[5,13] Between April 2011 and October 2016 VSD closure of 49 patients with ADO-II device was performed and 7 of them were <1-year-old.[13] This number is now increased to 71. Amplatzer Ductal Occluder II was used for 68 of these patients and ADO II-AS was used for 3 patients. Twelve of these 71 patients were less than 1 year of age. The procedure and follow-up results of this age group were recently published.[6]

Gerbode defect is a connection between right atrium and left ventricle. It is accepted as different type of VSD. It is usually acquired secondary to cardiovascular surgery, endocarditis rarely to the trauma. Congenital forms are very rare. The gold standard treatment is surgery but the risk of complications is high. In recent years' percutaneous closure of these defects have been performed in adults but not so common in children. Vijayalakshmi et al reported percutaneous closure of 4 patients with Gerborde defect. Only one patient of Gerbode defect developed transient complete heart block.

Our case is the first pediatric example reported in Turkey that percutaneous acquired Gerbode defect occlusion was performed. Percutaneous closure of Gerbode defects is another option for off-label use of ADO II.

Aorta–right atrial tunnel is a rare congenital defect and etiology is unknown. Surgery is the gold standard treatment. Previously the first percutaneous aorta–right atrial tunnel closure with a coil was reported.[14] The youngest child was 4-day old newborn whose tunnel closed with transcatheter method by Mahesh et al.[15] In our institution the first transcatheter aorta–right atrial tunnel closure was done with the Amplatzer Vascular Plug 4 device.[16] The case in our study was the first one in our center that we have used ADO II for closure.

Vijayalakshmi et al also reported one case with aorta-RV tunnel that they closed with ADO II device.

Pulmonary arteriovenous malformations (PAVM) are the abnormal vascular connections between the pulmonary artery and pulmonary vein that may cause right-to-left shunts and rarely seen in children. Percutaneous closure is preferred treatment modality for these children because success rate is high and complication rate is low.[17] Various different devices were used for closure like coils, vascular plugs and ductal occluders I and II.[18-20] Beck et al.[20] closed a total of 14 PAVMs (11 ADO I and 3 vascular plugs) in five adult patients. They defined that Amplatzer Ductal Occluder and vascular plugs are safe and effective in the closure of PAVMs in the acute setting and at intermediate follow-up. Giordano et al reported a 5-month-old infant with PAVM. They used ADO II AS and Amplatzer vascular plug for closure.[21] We have used 6 mm × 6 mm ADO II and 5 mm × 6 mm ADO II for closure of 2 PAVM in a 6-month-old infant.

Aorto-pulmonary window (APW) is a rare congenital heart defect which results left-to-right shunt and typically present within the first weeks or months of life because of congestive heart failure. Transcatheter closure of APW has been done for a while. Various devices, coils, vascular plug, symmetrical membranous ventricular septal occluder have been used to occlude APW.[22] Firstly, transcatheter closure of postsurgical residual defects was reported.[23] Later on; Nayak et al.[24] shared their experience of transcatheter native congenital APW closure via antegrade and retrograde routes using ADO II. They reported that ADO II was a suitable device because retention discs of each side are in equal size that is advantageous for retrograde closure of APW in young children. There are only case reports about APW closure in pediatric age group in the literature.

The other various defects that we used ADO II off-label were: occlusion of the artery feeding accessory lobe in scimitar syndrome and residual mitral cleft closure. These two procedures are unique that we cannot find any similar case in the literature.

Conclusion

Our study has summarized different off-label usages of ADO II device. It is important to give an idea to the clinicians in the occlusion of various non-ductal defects especially in the centers where the opportunities are restricted.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Conflict of Interest: There are no conflicts of interest in connection with this paper, and the material described is not under publication or consideration for publication elsewhere.

Ethics Committee Approval: The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation (Turkey) and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the institutional committees (Erciyes University clinical research ethics committee, 2019/730).

Financial Disclosure: The authors have no conflicts of interest to declare.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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Evaluation of Thiol/Disulfide Homeostasis and Neurogenin 3 Levels as a Marker of Oxidative Stress in Children and Adolescents Newly Diagnosed with Type 1 Diabetes

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Abstract

The objective of the study was to examine thiol/disulfide homeostasis, neurogenin 3 (ngn 3) status in the newly diagnosed with type 1 diabetes mellitus (T1DM), and to investigate the changes in these parameters due to treatment. Totally 60 children aged 1-18 years old, 30 of them newly diagnosed with T1DM (patients), and 30 of them healthy children in the same age group (control) were included in the study. Insulin and C-peptide levels of newly diagnosed T1DM patients were lower than the control group, however HbA1c, glucose, creatinine, cholesterol, triglyceride and LDL levels were found higher in patients. Total thiol level and glutamic acid decarboxylase (GAD) antibody positive rate were found higher in children newly diagnosed with T1DM. In addition, it was observed that the rate of anti-insulin antibody positivity rate increased in the 6th month control of patients. However, it was determined that the HbA1c and glucose levels of the patient group decreased at the 6th month control. Insulin and C-peptide levels were found lower in patients admitted with diabetic ketoacidosis (DKA). A negative correlation was observed between native thiol and anti-insulin antibody parameters and a positive correlation between ngn 3 and total cholesterol, and LDL. In conclusion, thiol levels can be used as an oxidative stress marker in children newly diagnosed with T1DM and there was a significant difference between groups with or without DKA for insulin and C-peptide levels.

Keywords: Children, type 1 diabetes mellitus, thiol/disulfide, neurogenin 3, oxidative stress

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Introduction

Type 1 diabetes mellitus (T1DM) is a chronic metabolic disease most common in childhood and adolescents, characterized by insulin deficiency and hyperglycemia, resulting from damage to beta (β) cells of the pancreas due to autoimmune reasons. One of the mechanisms that are frequently emphasized in the etiopathogenesis of T1DM is oxidative stress.[1]

Highlights

- Abnormal thiol/disulfide balance is involved in the pathogenesis of diabetes mellitus.
- Few studies were available on the relationship between autoimmunity and dynamic thiol/disulfide, neurogenin 3 states in newly diagnosed with type 1 diabetes mellitus.
- Thiol/disulfide homeostasis and neurogenin 3 parameters can be used as oxidative stress markers in children and adolescents newly diagnosed with type 1 diabetes mellitus.

Thiols are organic compounds containing a sulfhydryl group consisting of a sulfur atom and a hydrogen atom attached to a carbon atom and have a critical role in preventing the formation of oxidative stress.[2] Thiols can be oxidized via oxidants and form disulfide bonds. The disulfide bonds formed can be reduced to thiol groups again, thus providing a dynamic thiol/disulfide homeostasis.[1] It has been reported that thiol/disulfide homeostasis has an important role in many physiological processes, such as detoxification, antioxidant defense, apoptosis, signal transduction, and stabilization of the chemical structures of proteins.[3] Abnormal thiol/disulfide homeostasis plays a role in the pathogenesis of many diseases such as diabetes, cancer, cardiovascular diseases, and rheumatoid arthritis.[1] Neurogenin 3 (ngn 3) is a pro-endocrine factor that plays a role in the determination of neural precursor cells in the neuroectoderm of the pancreas and is temporarily released by exocrine cells that are reprogrammed when the endocrine cell is damaged.[4]

The aim of this study was to determine the relationship between autoimmunity and dynamic thiol/disulfide, ngn 3 status in children with newly diagnosed T1DM, to examine thiol/disulfide homeostasis and ngn 3 level after insulin therapy and blood sugar regulation, and to evaluate the change in ngn 3 level due to beta-cell damage.

Material and Method

This study is a single-center, a prospective analytical study conducted with the permission of Aydın Adnan Menderes University Faculty of Medicine Ethics Committee, numbered 2019/21. Thirty patients aged 1-18 years who applied to Aydın Adnan Menderes University Faculty of Medicine Pediatric Endocrinology Clinic between 01 February 2019 and 01 February 2020 who newly diagnosed with T1DM and 30 healthy children of the same age group were included in the study. Detailed information was given to the subjects included in the study and their families, and a voluntary consent form was obtained. The study was conducted in accordance with the Declaration of Helsinki.

Serum insulin levels were measured by electrochemiluminescence immunoassay (ECLIA) technique (Abbott i2000). The C-peptide levels were measured on a Roche Modular Analytics Cobas 8000 Immunoassay analyzer with the ECLIA technique. The chromatographic/photometric method was used for HbA1c. Serum lipid profile, total cholesterol, HDL, and LDL levels were determined by enzyme colorimetric method, serum triglyceride level was measured by GPO/PAP (glycerine phosphate oxidase peroxidase) method using a commercial kit, and serum glucose level was determined by hexokinase method using a commercial kit (Abbott Architect c800). Anti-insulin antibodies were measured by the radioimmunoassay (RIA) method and glutamic acid decarboxylase (GAD) antibodies were measured by the immunoradiometric assay (IRMA) method. Plasma ngn 3 level and thiol/disulfide parameters were determined by ELISA (Enzyme-Linked Immunosorbent Assay) method using a commercial kit.

Anti-insulin and GAD antibody analysis of the patient group was repeated at the 6th month control to determine time-dependent changes.

Inclusion/exclusion criteria

Children aged 1-18 years old, newly diagnosed with type 1 diabetes (patients), and healthy children in the same age group (control) were included in the study. Patients with concomitant acute or chronic diseases, patients with a genetic syndrome, diabetes mellitus patients with the previous diagnosis, and children and adolescents under the age of 1 and above 18 years of age were excluded from the study.

Statistical analysis

SPSS (Statistical Package for Social Sciences) 22.0 program was used to analyze the data. Variables are presented as mean±standard deviation (SD), number (n), and percent (%). Kolmogorov-Smirnov test was applied to find the normality of the distribution of the numerical variables. For non-normally-distributed parameters Mann Whitney U-test or Kruskal Wallis test was performed, for normally distributed parameters Student t-test, or one-way ANOVA (analysis of variance). If there was a significant difference, the one-way ANOVA was applied to determine the arithmetic mean of a dependent variable between more than two independent groups. The relationship between a dependent variable and one or more independent variables was examined with logistic regression analysis.

Pearson's correlation coefficient has been preferred to determine whether there is a linear relationship between two numerical measurements when the data are normally distributed, and if so, in what direction and how strong that relationship is. If the data are not normally distributed, Spearman's correlation coefficient was preferred. Numerical variables with "mean±SD" and "median, 25-75% percentile" and categorical variables

with numbers and percentages were grouped together. The suitability of continuous variables for normal distribution was examined with visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). A Chi-square test was performed to show whether there was a difference between categorical variables in the study.

In independent groups, "Student t-test" for comparison of data with parametric properties and "Mann-Whitney U test" for comparison data without parametric properties were performed. In dependent groups, "T-Test for Dependent Groups" for comparison of data with parametric properties and "Wilcoxon Test" for the comparison of data without parametric properties were used. The P-values less than 0.05 were assumed significant.

Results

A total of 60 cases were included in the study. While 30 of them were newly diagnosed with T1DM, 30 were healthy (control). There was no statistical difference between the groups in terms of age and gender (p=0.975, p=0.999, respectively). Sixth-month examinations of 5 patients who did not come to their controls during the follow-up period could not be obtained. The characteristics and laboratory findings of the groups were shown in **Table 1**. The median insulin and C-peptide values of the newly diagnosed T1DM patients were lower than the control group (p<0.001). Furthermore, an increase was observed in HbA1c, glucose, creatinine, cholesterol, triglyceride, and LDL levels (p<0.001, 0.009, and 0.033, respectively) in the patient group. GAD antibody positivity was found to be higher in newly diagnosed with T1DM patients compared to the control group (p=0.001).

Plasma total thiol concentrations of newly diagnosed with T1DM and the control group were found 212.289±58.767 µmol/l and 186.058±32.862 µmol/l, respectively (p=0.038). Similarly, it was determined that native thiol levels tended to be higher in the patient group (p=0.052). However, no statistical difference was determined between the groups for other thiol/disulfide and ngn 3 parameters (**Table 2**).

Table 2.
The thiol/disulfide value of the groups

Item	Patient (n=30)	Control (n=30)	p
Total thiol (µmol/l) (mean±SD)	212.289±58.767	186.058±32.862	0.038
Native thiol (µmol/l) (mean±SD)	164.694±33.262	149.310±26.291	0.052
Disulfide (µmol/l) (mean±SD)	48.232±37.439	36.748±28.960	0.189
Disulfide/native thiol (%) (median) 25-75%	57.496 19.981-87.311	40.596 16.658-57.863	0.231
Disulfide/total thiol (mean±SD)	0.207±0.119	0.188±0.129	0.556
Native/total thiol (%) (mean±SD)	0.798±0.129	0.812±0.129	0.685
Neurogenin 3 (pg/ml) (median) 25-75%	32.431 (24.920-47.388)	33.896 (19.366-85.162)	0.941

Table 1.
The characteristics and laboratory findings of the groups

Item	Newly diagnosed with T1DM (n=30)	Control (n=30)	p
Age (year) (mean±SD)	9±4	9±4	0.975
Gender (male), n (%)	18 (60)	18 (60)	0.999
Height (cm) (mean±SD)	136±23	136±27	0.963
Height SDS (mean±SD)	-0.04±0.91	-0.26±1.07	0.385
Weight (kg) (mean±SD)	33±15	36±19	0.469
Weight SDS (mean±SD)	-0.34±1.13	-0.07±1.14	0.358
BMI (kg/m²) (mean±SD)	17.10±3.52	18.45±3.37	0.136
BMI SDS (mean±SD)	-0.50±1.43	0.08±1.01	0.075
Insulin (uU/ml) (median) 25-75%	2.15 1.40-2.70	7.65 4.10-11.90	<0.001
C-peptide (ng/ml) (median) 25-75%	0.22 0.16-0.34	1.39 0.82-1.80	<0.001
HbA1c (%) (median) 25-75%	12.5 11.5-13.2	5.2 5.1-5.5	<0.001
Glucose (mg/dl)(mean±SD)	422.17±169.34	83.33±12.29	<0.001
Urea (mg/dl)(mean±SD)	26±13	23±5	0.205
Creatinine (mg/dl) (median) 25-75%	0.84 0.76-1.03	0.61 0.52-0.65	<0.001
Total cholesterol (mg/dl) (mean±SD)	159±36	139±26	0.020
Triglyceride (mg/dl) (median) 25-75%	102 73-124	71 58-101	0.009
LDL (mg/dl) (median) 25-75%	94 69-117	76 61-97	0.033
HDL (mg/dl) (mean±SD)	40±12	46±10	0.074
Anti-insulin antibody, n			0.500
Negative	29 (96.7%)	30 (100.0%)	
Pozitive	1 (3.3%)	0 (0.0%)	
GAD antibody, n			0.001
Negative	15 (50.0%)	27 (90.0%)	
Pozitive	15 (50.0%)	3 (10.0%)	

GAD,glutamic acid decarboxylase

Laboratory findings of newly diagnosed with T1DM at diagnosis and at the sixth month control was shown in **Table 3**. HbA1c and glucose levels at diagnosis were found higher than at the sixth month control (p<0.001). There was no significant difference in thiol/disulfide parameters and ngn 3 between groups. It was determined that the anti-insulin antibody positivity of newly diagnosed T1DM patients increased at the 6th-month control compared to that at diagnosis (p=0.004).

It was determined that 63.3% of newly diagnosed with T1DM applied to clinics with diabetic ketoacidosis (DKA). There was a significant difference between groups with or without DKA for insulin and C-peptide levels (p=0.031 and p=0.011, respectively). For the thiol/disulfide parameters and ngn 3 levels no significant difference was determined between groups (**Table 4**).

The correlations of thiol/disulfide parameters with anthropometric data and laboratory tests are presented in **Table 5**. A negative correlation was found between native thiol and anti-insulin antibody parameters (r=-0.375, p<0.05), however, a positive correlation was found between ngn 3 and total cholesterol, and LDL (r=0.377, p<0.04; r=0.521, p<0.003, respectively).

Discussion

One of the most common chronic diseases of childhood is T1DM. In regions with a high incidence, it is more common in males.[5] Similarly, in the current study, it was determined that 60% of the newly diagnosed patients were male. In addition, similar to studies conducted in Turkiye,[6] the peak age of the disease was found to be

Table 4.
Laboratory findings of the patients who admitted with or without diabetic ketoacidosis (DKA)

Item	Group 1 without DKA (n=11)	Group 2 with DKA (n=19)	p
Insulin (uU/ml) (mean±SD)	4.19±3.09	1.83±0.71	0.031
C-peptide (ng/ml) (median) 25-75%	0.34 0.21-0.93	0.18 0.12-0.27	0.011
HbA1c (%) (mean±SD)	11.5±2.6	12.3±1.5	0.303
Glucose (mg/dl) (mean±SD)	392.82±236.85	439.16±119.18	0.555
Urea (mg/dl) (median) 25-75%	28 19-31	22 17-33	0.590
Creatinine (mg/dl) (mean±SD)	0.80±0.16	0.94±0.22	0.066
Total cholesterol (mg/dl) (mean±SD)	161±44	158±31	0.847
Triglyceride (mg/dl) (median) 25-75%	74 66-114	105 87-131	0.162
LDL (mg/dl) (median) 25-75%	97±37	97±28	0.983
HDL (mg/dl) (mean±SD)	44±13	39±10	0.271
Total thiol (µmol/l) (median) 25-75%	221.362 198.276-261.275	200.276 173.529-235.971	0.312
Native thiol (µmol/l) (mean±SD)	169.121±24.669	162.131±37.755	0.588
Disulfide (µmol/l) (median) 25-75%	47.787 41.075-56.196	22.586 10.614-72.330	0.292
Disulfide/native thiol (%) (median) 25-75%	61.882 51.090-82.333	25.966 11.561-98.113	0.292
Disulfide/total thiol (%) (median) 25-75%	0.216 0.195-0.250	0.130 0.077-0.305	0.333
Native/total thiol (%) (mean±SD)	0.767±0.058	0.816±0.154	0.232
Neurogenin 3 (pg/ml) (median) 25-75%	33.047 20.941-40.980	31.814 25.722-64.648	0.355

Table 3.
Laboratory findings of newly diagnosed with T1DM at admission and at the sixth month

Item	At diagnosis (n=25)	6th-month control (n=25)	p
C-peptide (ng/ml) (median) 25-75%	0.22 0.16-0.34	0.17 0.10-0.43	0.808
HbA1c (%) (median) 25-75%	12.5 11.6-13.6	7.0 6.4-7.6	<0.001
Glucose (mg/dl) (median) 25-75%	403 319-498	137 94-189	<0.001
Urea (mg/dl) (mean±SD)	25±14	27±7	0.257
Creatinine (mg/dl) (mean±SD)	0.89±0.23	0.62±0.08	0.307
Total cholesterol (mg/dl) (median) 25-75%	159 124-174	145 137-161	0.572
Triglyceride (mg/dl) (median) 25-75%	103 74-131	83 56-108	0.085
LDL (mg/dl) (median) 25-75%	94 69-117	72 66-87	0.067
HDL (mg/dl) (mean±SD)	39±12	54±12	0.076
Total thiol (µmol/l) (median) 25-75%	212.389 180.000-261.275	186.992 163.307-198.020	0.183
Native thiol (µmol/l) (mean±SD)	168.617±32.058	157.833±25.774	0.075
Disulfide (µmol/l) (mean±SD)	49.678±40.392	38.669±28.884	0.350
Disulfide/native thiol (%) (median) 25-75%	60.943 19.555-95.645	32.650 19.477-58.094	0.300
Disulfide/total thiol (%) (mean±SD)	0.204±0.126	0.197±0.126	0.994
Native/total thiol (%) (mean±SD)	0.802±0.136	0.865±0.193	0.371
Neurogenin 3 (pg/ml) (median) 25-75%	34.286 24.120-51.731	32.224 20.153-49.552	0.288
Anti-insulin antibody, n			0.004
Negative	24 (96.0%)	15 (60.0%)	
Pozitive	1 (4.0%)	10 (40.0%)	
GAD antibody, n			0.625
Negative	12 (48.0%)	10 (40.0%)	
Pozitive	13 (52.0%)	15 (60.0%)	

GAD,glutamic acid decarboxylase

Tablo 5.
The correlation of thiol/disulfide parameters with anthropometric data and laboratory tests in newly diagnosed with T1DM patients

Item	Total thiol		Native thiol		Disulfide		Disulfide/ native thiol		Disulfide/total thiol		Native/total thiol		Ngn 3	
	p	r	p	r	p	r	p	r	p	r	p	r	p	r
Age	0.734	0.065	0.345	-0.179	0.215	0.233	0.219	0.231	0.104	0.302	0.064	-0.342	0.074	-0.331
Height	0.845	0.037	0.332	-0.184	0.303	0.194	0.340	0.180	0.162	0.262	0.100	-0.306	0.142	-0.275
Height SDS	0.783	-0.052	0.905	0.023	0.602	-0.099	0.641	-0.089	0.594	-0.101	0.598	0.100	0.918	-0.020
Weight	0.931	0.016	0.423	-0.152	0.458	0.141	0.360	0.173	0.229	0.226	0.173	-0.256	0.259	-0.213
Weight SDS	0.866	0.032	0.480	0.134	0.775	-0.054	0.761	-0.058	0.836	-0.039	0.719	0.068	0.278	0.205
BMI	0.725	0.067	0.914	0.021	0.559	0.111	0.578	0.106	0.404	0.158	0.381	-0.166	0.657	0.085
BMI SDS	0.683	0.078	0.506	0.126	0.899	0.024	0.871	0.031	0.829	0.041	0.978	-0.005	0.090	0.315
Insulin	0.774	-0.055	0.148	-0.271	0.303	0.194	0.282	0.203	0.171	0.256	0.143	-0.274	0.200	-0.241
C-peptide	0.847	0.037	0.858	-0.034	0.599	0.100	0.551	0.113	0.466	0.138	0.381	-0.166	0.458	-0.141
HbA1c	0.592	0.102	0.892	0.026	0.504	0.127	0.426	0.151	0.557	0.112	0.505	-0.127	0.911	-0.021
Glucose	0.071	0.334	0.200	0.241	0.092	0.313	0.298	0.196	0.305	0.194	0.356	-0.175	0.235	0.223
Urea	0.061	0.346	0.079	0.326	0.195	0.243	0.177	0.253	0.361	0.173	0.328	-0.185	0.357	-0.174
Creatinine	0.546	0.115	0.757	-0.09	0.117	0.292	0.102	0.304	0.113	0.296	0.099	-0.307	0.646	0.087
Total cholesterol	0.497	0.129	0.454	0.142	0.691	0.076	0.232	0.225	0.576	0.106	0.592	-0.102	0.040	0.377
LDL	0.412	0.155	0.342	0.180	0.637	0.090	0.473	0.136	0.740	0.063	0.803	-0.047	0.003	0.521
Triglyceride	0.290	0.200	0.142	0.275	0.661	0.083	0.598	0.100	0.943	0.014	0.949	-0.012	0.392	0.162
HDL	0.098	-0.308	0.189	-0.247	0.134	-0.280	0.578	-0.106	0.518	-0.123	0.687	0.077	0.964	-0.009
Anti-insulin antibody	0.211	-0.235	0.041	-0.375	0.706	0.072	0.742	0.063	0.363	0.172	0.387	-0.164	0.134	0.280
GAD antibody	0.781	-0.053	0.226	-0.228	0.961	0.009	0.987	-0.003	0.939	0.015	0.882	-0.028	0.057	-0.351

BMI, body mass index, GAD,glutamic acid decarboxylase

10-14 years. In this study, the rate of admission with DKA to the clinic was 63.3%; HbA1c level was 12.5% (11.5-13.2), and glucose level was 422.17±169.34 mg/dl at admission. According to similar studies,[7,8] this increase in HbA1c might be related to the fact that the patients were diagnosed with DKA and longer insulinopenia.

Demiral et al. and Aras et al.[9,10] found the C-peptide level at diagnosis 0.57 and 0.82 ng/ml, respectively, and it was determined 0.22 ng/ml in the current study. Additionally, the C-peptide level of the group without DKA at admission was higher than the group with DKA. It can be thought that children with DKA at the time of admission have fewer residual beta cells and avoidance of DKA at admission is important for better residual beta cells.

In this study, thiol parameters (total and native) were found to be higher in children newly diagnosed with T1DM, and thiol/disulfide parameters were found to be statistically similar between the groups. Contrary to our findings, in previous studies, it was reported that thiol values were lower and disulfide/thiol ratios were higher in patients, and all of these studies were conducted in patients with has been diagnosed already.[11-13] In other words, it can be said while the patients in our study were exposed to acute stress, the patients in previous studies were exposed to chronic stress. It is known that humans and animals can adapt to chronic stress, and accordingly, their physiological responses and antioxidative defense mechanisms (such as thiol levels) can be changed against acute or chronic stress. However, the response of antioxidative defense can be affected by the severity and amount of stress too. The inconsistency between the data may be due to these physiological changes. Meanwhile, it can be thought that balance was in favor of thiol in the early stages of the disease and turned in favor of disulfide with time.

Although previous studies[11,12] showed that the increase in glucose and HbA1c changed the thiol/disulfide balance towards disulfide, no correlation was found between glucose and HbA1c and thiol/disulfide parameters in the current study. This may be according to the small number of patients in the study.

Çakıcı[14] stated that there is a positive correlation between disulfide parameters and total cholesterol. In the present study, no correlation was found between lipid parameters and thiol/disulfide parameters. Although it is known that hyperlipidemia increases oxidative stress, the lipid parameters of the patients in the current study were within the normal range.

In the present study, when the thiol/disulfide change was monitored prospectively, it was observed that there was a decrease in thiol/disulfide parameters over time but this was not statistically significant. This may be indicative of an acute inflammatory response due to the metabolic disturbance at the time of diagnosis. In addition, the decrease in native and total thiol levels compared to the admission may indicate that thiol/disulfide homeostasis shifted in favor of disulfide with the disease process. However, further studies with more patients are needed for definitive assumptions about the relationship between disease duration and oxidative stress.

Durmus et al.[11] reported that there was no relationship between the positivity of diabetes autoantibodies and thiol/disulfide parameters. But, a negative correlation was found between native thiol and anti-insulin antibody in the present study. According to these results, although it was thought that autoimmunity could increase oxidative stress, on the contrary, it was thought that oxidative stress could also increase autoimmunity. In order to distinguish between these two conditions, possible antioxidant treatment and evaluation of antibody titer may be required.

Ngn 3 is a pro-endocrine factor that is involved in the identification of neural precursor cells in the pancreatic neuroectoderm and is released by reprogrammed exocrine cells when the endocrine cell is damaged. Based on this, while the ngn 3 level was expected to be higher in patients, in the current study no statistical significant difference was determined between the patient and control groups. However, it was found that there was a positive correlation between ngn 3 and total cholesterol (p=0.040), and LDL (p=0.003), and also, total cholesterol (p=0.020) and LDL (p=0.033) levels were higher in patient group. This is the first study about ngn 3 levels in children newly diagnosed with T1DM and we believe that further studies are needed to clarified ngn 3 and other pathways in the differentiation stage from exocrine cell to endocrine cell.

Limitations of the study

The limitations of our study are the small sample size of the patient and control group, the dropout of five patients, the early counting of the sixth month in children newly diagnosed with T1DM for metabolic control, and the inability to compare thiol/disulfide homeostasis parameters with other oxidant and antioxidant markers.

Advantages of the study

This is the first study to evaluate the relationship between autoimmunity and thiol/disulfide homeostasis, ngn 3 status in newly diagnosed with T1DM and to investigate thiol/disulfide homeostasis and ngn 3 levels after insulin therapy and blood sugar regulation.

Conclusion

In conclusion, total thiol level and GAD antibody positive rate was found higher in children newly diagnosed with T1DM. The positive rate of the anti-insulin antibody of newly diagnosed T1DM patients increased at the 6th-month control compared to that at diagnosis. The HbA1c and glucose levels at diagnosis were found higher than at the sixth-month control in newly diagnosed T1DM patients. Insulin and C-peptide levels were determined lower in patients who were admitted with DKA. A negative correlation was found between native thiol and anti-insulin antibody parameters, however, a positive correlation was found between ngn 3 and total cholesterol, and LDL. According to these results, thiol levels can be used as oxidative stress markers in children newly diagnosed with T1DM, more studies should be conducted on thiol/disulfide homeostasis and ngn 3 levels, especially in these children.

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Assessment of Factor Affecting the Quality of Life in Children with Juvenile Idiopathic Arthritis

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Abstract

Juvenile idiopathic arthritis (JIA) is a frequently seen chronic rheumatoid disease in childhood, which may cause disability and severely affect quality of life (QoL). The aim of present study was to assess relationships between disease activation and socio-cultural status of family, QoL, anxiety level, and depression level in patients with JIA and their parents. The study included 100 patients with JIA. The socio-demographic data were obtained from all patients. Child- and parent-reported PedsQL, Beck depression inventory (BDI), Kovacs' Child Depression Inventory (CDI), SCARED child version, CHAQ discomfort and disability scales were applied and JADAS-27 score was calculated in a cross-sectional manner. Then, we compared the characteristics of patients with the scales' results. JADAS-27, BDI, and CHAQ discomfort scores were higher and child- and parent-reported PedsQL scores were lower in patients with active disease than patients on remission ($p<0.05$). The SCARED score was higher in girls than boys. The CHAQ disability score was high in children aged 8-12 years ($p<0.05$). JADAS-27 and CHAQ disability scores were significantly low in patients with better compliance to treatment. Parental statements about changes in mental health after diagnosis were consistent with results of depression and anxiety scales of children. Quality of life is adversely affected in children with JIA, which may result in depression and anxiety. In management of JIA, one of our goals should be maintaining QoL. Further comprehensive studies in relationships between QoL and depression, anxiety, socio-demographic parameters, disease activation and social circle of patient are needed.

Keywords: Anxiety, chronic disease, depression, juvenile idiopathic arthritis, quality of life

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Introduction

Juvenile idiopathic arthritis is the most common chronic rheumatoid disease of childhood in the world. It is a heterogeneous group of disorder characterized by articular inflammation that begins before 16 years of age and persists at least 6 weeks within the same joint.[1] It is a significant cause of loss of ability and functionality overtimes. Medical therapies are not curative although they may alter the severity of inflammatory joint disorders. These therapies only provide occasional remission.[2]

Highlights

- Juvenile idiopathic arthritis, heterogeneous group of disorder characterized by articular inflammation, is the most common chronic rheumatoid disease of childhood in the World.
- Children and adolescents with chronic illness have lower self-esteem and are more problematic regarding mental health, behavior and social adjustment when compared to those without chronic disease.
- Similar to children having other chronic diseases, QoL is negatively affected in children with JIA likely due to pain, frequent hospital visits, hospital admission and chronic drug use which make them more depressed and anxious. Therefore, physicians should focus on maintaining QoL in the management of JIA.

Quality of life is the perception of self-status in own culture and value system by an individual. It includes physical function, psychological state, social interactions within the family and with others, environmental influences and beliefs. The concept of QoL has multiple aspects and can change over time as it is associated with expectations and experiences of individuals. Thus, it is difficult to measure the QoL objectively. Health-related quality of life (HRQoL) defines physical, mental and social domains and functionality that the individual perceived. In the modern era where rapid advances are experienced in medicine, it is not only aimed to eliminate disease but also to improve QoL. Thus, it should be increasing efforts to measure well-being and QoL.[3,4] It is known that children and adolescents with chronic illness have lower self-esteem, poorer body image and are more problematic regarding mental health, behavior and social adjustment when compared to those without chronic disease. For this reason, it is thought that children and adolescents with chronic illness are at risk for psychosocial problems.[5]

In this study, we aim to measure the QoL of children with JIA, the level of depression and anxiety of them and their family. We also investigate whether the activity of disease and socio-cultural status of parents have any effect on QoL, the level of depression and anxiety of children and their family

Material and Method

The study included 100 patients (55 girls and 45 boys; aged 8-18 years) who admitted to Pediatric Rheumatology Department of Erciyes University, Medical School and were diagnosed as JIA according to International League of Associations for Rheumatology (ILAR) criteria between April 2016 and January 2017. The patients who are illiterate, those with mental retardation, psychotic disorder, schizophrenia, bipolar disorder and anxiety disorder, and those separated from parents were excluded. The study was designed cross-sectional. The study protocol was approved by the local ethics committee of Erciyes University. Patients and their parents gave written informed consent before participation.

The patients were classified according to ILAR criteria as follows: systemic JIA, oligoarticular JIA, RF-positive polyarticular JIA, RF-negative polyarticular JIA, enthesitis-related arthritis, psoriatic arthritis and undifferentiated JIA. Disease activity was assessed according to the activity criteria defined by Wallace et al.[6] Based on these criteria, patients were divided into 3 groups: active disease, remission on medication and remission without medication. The patients were classified according to age in order to assess children and adolescents separately: children aged 8-12 years and those aged 13-18 years. In all patients and parents socio-demographic data questionnaire, PedsQL 3.0 Turkish arthritis module, The screen for child anxiety related emotional disorders (SCARED), Kovacs' child depression inventory (CDI), Beck depression inventory (BDI) and Childhood health assessment questionnaire (CHAQ) were obtained. In addition, disease activity was estimated by using the Juvenile Arthritis Disease Activity Score (JADAS27). Turkish validation and reliability study was performed for all scales.[7-12]

The socio-demographic data questionnaire included questions about age, gender, educational status, interaction with parents, siblings and peers, structure and socioeconomic status of the family. Also, there were some questions about parents (age, educational status, occupation). This tool also questioned presence of relatives with similar rheumatoid disease, compliance to medications and other advice (exercise, sports activity), frequency of presentation to healthcare services, and mood alteration after diagnosis (fear, anxiety, frustration, anger, perversion, attention deficit, averseness, intrusion, nonrestorative sleep, eating disorders, unwillingness, and forgetfulness).

The PedsQL 3.0 Turkish arthritis module is a scale developed to measure HRQoL in children and adolescents; validated by Tarakcı et al. at 2013.7 It is a questionnaire including 22 items which questions physical health, emotional functionality and social functionality of wellbeing as described by World Health Organization. Each item is rated on 0-100 points scale. The higher total score indicates better HRQoL.

The SCARED was developed by Birmaher et al in 1997. The scale includes 41 items which assess anxiety in children. Each item is rated by 0-2 points. The scale produces 5 factors scores and a total score. The cut-off value is recommended as 25 for the total score, which indicates the presence of anxiety disorder.[13]

The CDI is a self-reported scale which is applicable to children aged 6-17 years. The scale includes 27-items. For each item, the child is asked to most appropriate phrase for prior 2 weeks: 1) "I sometimes feel sad"; (0 point); 2) "I often feel sad" (1 point), and 3) "I always feel sad" (2 points). The higher scores indicate more severe depression.[14]

The BDI was developed to measure behavioral symptoms of depression in adolescents and adults.15 It is a self-reported scale which is designed to measure the severity of depression, to monitor treatment response and to define disease itself. The scale score increases with the severity of depression.[16]

The CHAQ was adapted from Stanford health assessment questionnaire. It modified by adding additional items, resulting in more valid and sensitive tool for assessment of functional outcomes in children with chronic arthritis.[17] It is the most commonly used tool for survival assessment children with JIA. It is a self-reported QoL questionnaire including disability and discomfort indices.[18] Disability index measures functional ability in 8 daily living activities including dressing and grooming, arising, eating, walking, hygiene, reach, grip and other. The discomfort index assesses pain and wellbeing on 0-100 mm visual analog scale (VAS).[19] High scores indicate high disease activity.[20]

The Juvenile Arthritis Disease Activity Score (JADAS) is a measurement of absolute disease activity in juvenile idiopathic arthritis and includes clinician's global assessment for disease activity on 0-100 mm VAS; parent's/patient's assessment for wellbeing on 0-10 cm VAS; number of joints with active arthritis and erythrocyte sedimentation rate (ESR).[21] In our study, JADAS27 was used for assessment.

Data were analyzed by using SPSS version 21.0. Data distribution was assessed by the histogram, q-q plots, and Shapiro-Wilk test. For quantitative variables, the Mann-Whitney U test was used in binary comparisons while Kruskal-Wallis was used for comparisons between >2 groups. Pearson $\chi 2$ test was used to compare categorical variables while Bonferroni test was used for multiple comparisons. Data were analyzed by R 3.2.2 software (www.r-project.org). A p value<0.05 was considered as statistically significant.

Results

The study included 55 girls (55%) and 45 boys (45%). The median age of the study group was 12 years (8-18 years). There were 51 patients aged 8-12 years and 49 patients aged 13-18 years. When education was assessed, it was found that the number of patients attending primary, secondary and high school were 18 (18%), 45 (45%) and 37 (37%), respectively. **Table 1** shows age and gender distributions of patients according to JIA subgroups.

Table 1
Age and gender distributions according to disease subgroups

Disease subgroups	Gender (F/M)	Age (median min-max) years
Oligoarticular (n:53)	37/16	12 (8-18)
Polyarticular* (n:17)	8/9	11.5 (8-17)
Systemic (n:9)	3/6	14 (8-17)
Enthesitis-related arthritis (n:19)	6/13	14 (9-17)
Psoriatic arthritis (n:1)	0/1	14
Undifferentiated (n:1)	1/0	12

* One girl with positive RF (+).

Of patients included, while 51 patients had active disease, 49 patients were in remission. Of 49 patients with remission, 34 had remission on medication. The patients in remission on medication and those having remission without medication (n=15) were assessed together as remission group in all comparisons.

While BDI and child- and parent-reported PedsQL scores were significantly lower, JADAS27 and CHAQ-discomfort scores were significantly higher in patients with active disease compared to those in remission. However, no significant difference was detected in CDI, SCARED-anxiety and CHAQ-disability scores (**Table 2**). The SCARED-anxiety score was markedly higher in girls (21.0 [16.0-29.0]) than in boys (16.0 [8.0-23.0]; p=0.005). When scores were separately assessed in active disease and remission groups, it was found that JADAS27 and CHAQ-discomfort scores were significantly higher in girls than boys in active disease group and that parent-reported PedsQL score was significantly lower and SCARED-anxiety score was significantly higher in girls than in boys on remission group (**Table 3**). It was found that CHAQ-disability score was higher in children aged 8-12 years (0.125 [0.000-0.375]) compared to those aged 13-18 years (0.000 [0.000-0.187]; p=0.022).

Table 2
Assessment of scores according to disease activity

Scales	Active disease (n:51) [Median (25-75)]	Remission (n:49) [Median (25-75)]	P	All group (n:100) [Mean ± SD/ Median (min-max)]
JADAS 27	6.0 (3.0-11.0)	1.0 (0.0-2.6)	<0.001	4.5 ± 5.3 / 3 (0-24)
PedsQL-child	83.3 (71.4-90.5)	90.4 (81.3-96.4)	0.004	83.7 ± 13.5 / 86.9 (38-100)
PedsQL-parent	75.0 (60.0-89.7)	84.0 (75.5-92.6)	0.014	78.8 ± 15.4 / 80.6 (38.6-100)
BECK	7.0 (3.0-14.0)	14.0 (4.0-20.0)	0.045	10.8 ± 8.5 / 9 (0-37)
KOVACS	9.0 (4.0-12.0)	7.0 (4.0-13.0)	0.901	8.9 ± 6.3 / 8 (0-29)
SCARED	18.0 (12.0-24.0)	19.0 (12.0-25.0)	0.497	20 ± 12.4 / 19 (0-68)
CHAQ disability	0.125 (0.000-0.375)	0.000 (0.000-0.250)	0.256	0.220 ± 0.359 / 0 (0-2)
CHAQ discomfort	0.800 (0.700-1.600)	0.500 (0.300-0.900)	0.001	0.795 ± 0.569 / 0.7 (0-2.5)

Table 3
Assessment of scores according to gender

Scales	Active disease			Remission		
	Girls (n:24)	Boys (n:27)	p	Girls (n:31)	Boys (n:18)	p
JADAS 27 [Median (25-75)]	7.5 (5.0-15.0)	4.7 (2.0-8.0)	0.009	1.0 (0.0-3.0)	1.0 (0.0-2.2)	0.410
PedsQL-child [Median (25-75)]	81.45 (72.0-86.3)	85.7 (61.6-91.6)	0.364	88.0 (80.9-95.2)	93.4 (90.1-96.7)	0.067
PedsQL-parent [Median (25-75)]	72.7 (54.7-86.3)	80.6 (62.5-94.3)	0.143	79.5 (71.5-89.7)	88.4 (82.6-100)	0.035
BECK [Median (25-75)]	7.0 (1.5-14.0)	8.0 (4.0-14.0)	0.762	14.0 (5.0-22.0)	8.5 (3.7-17.0)	0.324
KOVACS [Median (25-75)]	8.0 (4.0-11.7)	10.0 (4.0-14.0)	0.630	8.0 (5.0-13.0)	7.0 (3.0-13.2)	0.486
SCARED [Median (25-75)]	20.5 (14.5-22.25)	15.0 (7.0-23.0)	0.106	21.0 (17.0-29.0)	16.5 (8.0-21.7)	0.023
CHAQ disability [Median (25-75)]	0.125 (0.000-0.812)	0.125 (0.000-0.250)	0.314	0.000 (0.000-0.250)	0.000 (0.000-0.250)	0.899
CHAQ discomfort [Median (25-75)]	1.150 (0.800-1.750)	0.700 (0.500-1.200)	0.013	0.700 (0.300-0.900)	0.450 (0.075-0.750)	0.181

When looking at the educational status of parents, 5% of mothers were unschooled. While the percent of mothers graduated from primary, secondary, high and university were 57, 13, 18 and 6, the percent of fathers graduated from primary, secondary, high and university were 43, 20, 26 and 11, respectively. No significant difference was detected in terms of educational status of parents (p>0.05). The mean age of mothers and fathers were 39.47±6.14 and 43.38±6.46 years, respectively. Of patients, 84% had the nuclear family (two parents and children) and 16% had extended family (parents, children, and other family members). Household income was <280$ per month in 12%, 280-560$ per month in 58%, 560-850per month in 16% and >850$ per month in 14% of families. It was seen that BDI score was negatively correlated with monthly income in the active disease group.

Number of patients using medication as recommended were 88%. JADAS27 and CHAQ-disability scores were significantly low in compliant patients (p=0.005 and p=0.037, respectively). It was found that number of JIA patients with active disease was significantly higher than number of patients with remission when there was a sibling with chronic disease (n=11 and n=2, respectively; p=0.013). The frequency of hospital visits for follow-up was admitted monthly, bimonthly, by 3 months, by 6 months interval, respectively in 5 %, 9%,70%, 5% in of patients.

We asked to parents whether their children had changes in mental health after diagnosis, 52% of parents responded as yes. It was found that CDI, SCARED-anxiety, and BDI-parent scores were significantly higher and parent-reported PedsQL score was significantly lower in patients with having changes in mental health than those without (p≤0.01, p=0.018, p=0.05, and p=0.028, respectively; **Table 4**). Also, we asked parents whether their children had any problem to join social activities such as playing games with peers, sport activity or exercises, we found that JIA affected severely in 9%, moderately in 22%, mildly in 37% of them. The PedsQL child and parent score were significantly high and CDI, CHAQ-discomfort, and CHAQ-disability scores were significantly low in individuals who reported the disease has no any effect on social activities (respectively, p=0.001, <0.001, 0.002, 0.005, and 0.006) (**Table 5**). It was found that there were 6 patients having poor relationship with peers in active disease group, there was no such patient in remission group (p=0.027). There was no significant difference in terms of relationships between patients and their family members (parents and siblings) during the active disease period. However, CDI score was found to be higher in children having poor relationship with father (7.0 [4.0-12.0]; p=0.016).

Table 4
Comparison of scores according to changes in mental health after diagnosis

Scales	Change in Mental Health		p
	No (n:48)	Yes (n:52)	
JADAS 27 [Median (25-75)]	3.0 (0.0-6.8)	3.0 (0.0-7.2)	0.886
PedsQL-child [Median (25-75)]	88.0 (80.0-96.4)	85.1 (67.2-92.5)	0.065
PedsQL-parent [Median (25-75)]	85.1 (73.2-95.5)	78.7 (62.5-88.3)	0.028
BECK [Median (25-75)]	7.0 (2.0-15.7)	11.0 (5.0-17.0)	0.050
KOVACS [Median (25-75)]	6.0 (3.0-9.7)	11.0 (7.0-15.0)	<0.001
SCARED [Median (25-75)]	17.0 (9.0-23.7)	21.0 (16.0-30.5)	0.018
CHAQ disability [Median (25-75)]	0.000 (0.000-0.250)	0.125 (0.000-0.343)	0.223
CHAQ discomfort [Median (25-75)]	0.700 (0.150-0.900)	0.800 (0.500-1.200)	0.105

Table 5
Comparison of scores according to effects on social life

Scales	Effects on Social Life				P
	High (n:9)	Moderate (n:22)	Mild (n:37)	No Effect (n:32)	
JADAS 27 [Median (25-75)]	5.0 (0.0-8.5)	4.3 (2.1-11.2)	3.0 (1.0-6.7)	2.0 (0.0-4.0)	0.066
PedsQL-child [Median (25-75)]	83.3 (63.0-88.7)	74.4 (66.3-90.7)	88.0 (81.5-92.2)	92.8 (82.0-99.7)	0.001
PedsQL-parent [Median (25-75)]	84.0 (57.9-89.5)	72.1 (55.6-83.4)	76.1 (65.8-84.0)	92.0 (84.5-97.4)	<0.001
BECK [Median (25-75)]	16.0 (5.0-22.0)	14.0 (5.0-20.2)	9.0 (3.0-15.0)	6.0 (1.25-15.5)	0.100
KOVACS [Median (25-75)]	9.0 (6.0-14.5)	11.5 (6.7-16.5)	10.0 (4.5-12.5)	5.0 (2.0-8.5)	0.002
SCARED [Median (25-75)]	16.0 (11.5-28.5)	20.5 (16.7-28.2)	18.0 (14.0-23.5)	20.0 (8.2-27.0)	0.481
CHAQ disability [Median (25-75)]	0.375 (0.062-0.812)	0.125 (0.000-0.500)	0.000 (0.000-0.187)	0.000 (0.000-0.218)	0.005
CHAQ discomfort [Median (25-75)]	1.200 (0.500-1.550)	0.900 (0.700-1.500)	0.800 (0.450-1.150)	0.500 (0.025-0.800)	0.006

Discussion

In this study, we used QoL, depression and anxiety questionnaires in order to assess disease activity measures and QoL in children with JIA and their parents. JADAS27 and CHAQ-discomfort scores were found to be higher while child- and parent-reported PedsQ scores were found to be lower in patients with active disease. In addition, it was found that observations of parents regarding mental health of children were in accordance with results obtained by depression, anxiety and QoL measures. Best of our knowledge, there is no study evaluating multiple QoL scales in children with JIA.

Many studies have been conducted to assess QoL in JIA. It is seen that, in general, JADAS, CHAQ, and PedsQL scales have been used in these studies. For instance, in the international study on 3324 pediatric patients and 3315 healthy children by PRINTO, CHAQ was used to evaluate differences in QoL between patients and healthy children. Authors found that CHAQ score was significantly higher in the patient group when compared to healthy children.22 In addition to these scales, we used BDI to assess parental depression level as well as CDI to assess depression level and SCARED-anxiety test to assess anxiety level in the children. All tests were applied in a cross-sectional manner with calculation of mean scores and patients with active disease and those in remission were compared regarding results obtained. BDI and child- and parent-reported PedsQL scores were found to be significantly lower while JADAS27 and CHAQ-discomfort scores were found be significantly higher in patients with active disease when compared to those in remission. These results showed that patients with active disease experienced more difficulty in daily living activities due to severe pain when compared to those in remission. Thus, results were interpreted as there will be marked decrease in QoL indices.

When effects of gender on QoL scales were assessed, it was seen that SCARED-anxiety scores were markedly higher in girls than boys. This finding is attributed to previous findings indicating that girls are more predisposed to anxiety than boys. Similarly, in a study by Offord et al, it was reported that depression, anxiety, and physical symptoms were more common among girls than boys with tendency to increase by advancing age.23 The effects of age on results were assessed in the all study population and remission group, it was found that CHAQ-disability scores were higher in patients aged 8-12 years than those aged 13-18 years. In traditional or renewed Turkish families, it is seen that parents don't allow children to perform daily living activities alone due to protective approach adapted, providing excessive support to child. We think that above-mentioned approach resulted in higher CHAQ-disability scores aiming to assess ability to perform daily living activities in children aged 8-12 years, even in those at remission, in our study.

Present study reveal inequality of opportunity for education between genders in our country and the education of girls is still problematic in our country. According to data from Turkish Statistical Institute, the rate of illiterate population was 5.4% among individual's aged ≥25 years. Most of them were women.24 We hope this inequality should be eliminated using contemporary education policy throughout the country.

Parents of children with chronic disease may inevitably face high depression because of social and economic problems during children's treatment. Interestingly, BDI scores were found to be significantly lower in the parents of patients with active disease than on remission group in our study. We could not find any argument to explain this result. Toros et al25 found that BDI scores were significantly higher in parents of children with chronic disease when compared to controls. In a study on 67 pediatric patients by Stevanovic et al26, a negative correlation was found between QoL and depression/anxiety.

Low-income families may struggle to bring their children with chronic disease to medical center regularly and it may make them more stressful and cause decreased quality of life score. In our study, BDI score was significantly high in low-income level. This finding is interpreted that families experience difficulties in coping economic burden caused by high costs related to transportation, nutrition due to frequent hospital visits

and admission. In the literature, studies have focused on economic burden on healthcare system rather than on families. For instance, Angelis et al27 used EQ-5D test in order to assess QoL and economic burden related to patients with JIA. The authors reported that QoL is significantly lower in patients with JIA than normal populations and that economic burden associated with JIA patients on healthcare system has been increasing due to diagnostic and therapeutic costs, poorer QoL, need for assistance in daily living activities and decreased productivity. In a study on 162 patients from six European countries, Kuhlman et al28 reported similar findings.

Adherence to treatment, associated with an improved HRQOL, is still a very important problem in the setting of the chronic disease both in adult and children, especially adolescents.29 JADAS27 and CHAQ-disability scores were significantly lower in patients with better adherence to treatment than non-compliant patients in our study as expected.

Chronic illness in young children may be a risk for vulnerability to mental and developmental disorders.30 We found that half of parents thought their children had change in mental health status after diagnosis. This observation was supported by scores obtained in questionnaire used. Given the fact that children may have mental health problems in the setting of JIA, physicians should give pay attention changes in mental health in children with JIA. The statements of parent regarding the effects of disease on social activities such as playing games with peers, sport activities and exercises were evaluated and compared with quality of life scores we obtained. It was seen that child- and parent-reported PedsQL scores were significantly low and CDI, CHAQ-discomfort, and CHAQ-disability scores were high in who affected. This result suggests that as the disease activity increases, patients are compulsory or preferably isolating themselves in social environment, resulting in significant increase in depression level. It is known that, particularly at childhood, individuals experiencing functional loss or disability due to chronic disease or any other cause are marginalized by peers. In our study, it was found that patients with active disease had poorer relationship with peers than on remission group. In a review including nine studies on relationship with parents and peers in patients with JIA, Foregon et al31 found that children or adolescents with chronic disease had fewer friends, that they were exposed more bullying by peers; and that they were more isolated when compared to healthy peers. In our study, all patients reported good relationship with mother while 5% of patients reported poor relationship with father and depression scores were significantly higher in these patients. This result showed that father have an important influence on child although children have stronger emotional attachment with mother.

Conclusion

Similar to children having other chronic diseases, QoL is negatively affected in children with JIA likely due to pain, frequent hospital visits, hospital admission and chronic drug use which make them more depressed and anxious. Therefore, physicians should focus on maintaining QoL in the management of JIA. Although there are similar studies in the literature, our study is the first study comparing QoL, depression level (parents and patients), and anxiety level with sociodemographic characteristics, disease activity, and social relationships. Further studies are needed to assess QoL using different scales in children with JIA.

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Conflict of Interest: There are no conflicts of interest in connection with this paper, and the material described is not under publication or consideration for publication elsewhere.

Ethics Committee Approval: The study was carried out with the permission of Erciyes University Faculty of Medicine Ethics Committee (Date: 01.04.2016, Decision No: 216/242).

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Nephrotic syndrome in a patient with Glycogen Storage Disease Type IXb

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Abstract

Glycogen storage disorder (GSD) IXb is characterized by liver and muscle involvement. We present a GSD IXb patient with an incidental union of nephrotic syndrome. A 4 year-old-patient was diagnosed with GSD IXb at 13 months of age with mildly elevated transaminases and hepatomegaly. During the follow-up period, there was no hypoglycemia. Development and growth were normal. In the last month, the onset of generalized edema was reported. Urinalysis showed a high protein level. He had low serum albumin, high serum triglycerides cholesterol. Complement levels were normal. The patient was diagnosed as minimal change disease with a renal biopsy. He was treated with oral prednisone. Minimal Change Disease is the most common cause of idiopathic nephrotic syndrome cases in children, and the first step for therapy is the usage of corticosteroids. This is the first report of nephrotic syndrome associated with GSD IXb disease.

Keywords: Glycogen Storage Disease, Nephrotic syndrome, proteinuria

Introduction

Phosphorylase kinase is a vital regulator enzyme regarding glycogen metabolism. Glycogen storage disease (GSD) type IX occurs due to an inherited deficiency in phosphorylase kinase. Two types of phosphorylase kinase deficiency are defined. The liver-specific form is characterized by early childhood onset hepatomegaly, growth restriction, fasting ketosis, and hypoglycemia. Symptoms of the muscle-specific form are exercise intolerance, myalgia, muscle cramps, myoglobinuria, and progressive muscle weakness. This variation is because of mutations affecting different various phosphorylase kinase subunits. Many isoforms of phosphorylase kinase subunit function fine-tune in different cell types. The multiple subtypes of GSD IX are classified: GSD IXa, GSD IXb (gene PKHB), GSD IXc, and GSD IXd. The gene encoding the autosomal recessive β subunit, PHKB (OMIM *172490), is expressed in all tissues. PHKB mutations could be responsible for conditions of phosphorylase kinase deficiency where multiple tissues, especially muscle and liver, are affected.[1] The diagnosis should be considered in children with unexplained hepatomegaly accompanied by ketotic hypoglycemia. Diagnosis is best provided by mutation analysis using a DNA panel. Asymptomatic patients may not need treatment. Growth failure and symptomatic hypoglycemia could avoid with uncooked cornstarch and frequent meals.

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Nephrotic syndrome is a significant chronic disease in childhood and the common primary etiology in steroid-sensitive nephrotic syndrome (SSNS). Rare genetic disorders, drugs, and infections are among the secondary causes of isolated nephrotic syndrome.[2]

Case Report

A 4-year-old male patient was diagnosed with GSD IXb with mild transaminase elevation and hepatomegaly at 13 months. Parents were first-degree cousins. A GSD gene panel detected homozygosity for c.305+1 G>A mutation in the PHKB gene. In the segregation analysis, both parents were carriers for the heterozygous of the c.305+1 G>A variant. During the follow-up period, there was no hypoglycemia. Lipid levels and uric acid were normal. Development and growth were normal (body height at the 15th and weight at the 50th percentile). The patient had treated with uncooked cornstarch. He was admitted to the emergency with generalized edema. His symptoms had started two days before. It was not accompanied by fever or a history of recent illnesses. His blood pressure and vital signs were normal. Renal function tests were normal; urea 29 mg/dL (normal range:10-50), creatinine <0.27 mg/dL (normal range:0.3-1.0). Blood testing showed; AST:149 U/L (N<35), ALT:107 U/L (N<45), low serum albumin of 10 g/L (normal range 3.5-5.2), high serum triglycerides of 199 mg/ dL (normal range <100) and high serum cholesterol of 304 mg/dL(reference 200). Complement levels resulted in C3:144 mg/ dL (normal range 90-180) C4:22 mg/ dL (normal range 10-40), were normal. Electrolytes were normal. The laboratory tests were suggestive of hypothyroidism (thyroid-stimulating hormone (TSH): 24 mU/L(normal range 0.7-5.97 24 mU/L, serum-free thyroxine (FT4): 0.7 ng/dL (normal range 0.96-1.77 ng/dL). Urinalysis showed a nephrotic proteinuria level (88 mg/m²/h and 1610 mg/24 hours) with no signs of hematuria. Renal ultrasonography was normal. Abdomen ultrasonography showed enlarged liver (140 mm) with grade 1 hepatic steatosis. Echocardiography was normal. Testing for active infections: Rhinovirus detected in the respiratory viral panel.

The patient nephrotic proteinuria, hypoalbuminemia, and edema were evaluated as nephrotic syndrome. Although the primary nephrotic syndrome was suspected in the patient without macroscopic hematuria and average complement level, the biopsy was performed due to the accompanying disease. Pathological findings included four global cases of sclerosis of approximately 50 glomeruli (**Figure 1**). Oral prednisolone treatment was initiated at 2 mg/kg daily. However, the patient experienced two attacks while on the steroid reduction scheme. The patient was evaluated as steroid-dependent nephrotic syndrome. Cyclosporine treatment was started in the patient (parents did not accept the recommended cyclophosphamide treatment according to our protocol). The patient followed in remission. The patient did not have hypoglycemia or hyperglycemia with steroid treatment. Levothyroxine was started due to hypothyroidism.

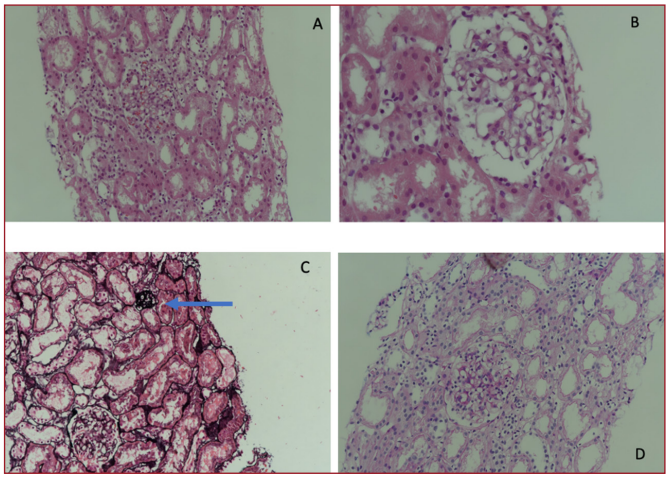

Figure 1: A, **B.** In light microscopic examination, the glomerulus is closely related to Bowman's capsule and distance narrowed. **C,** Global sclerotic glomeruli in Jones methenamine silver stain. **D,** Closely related appearance of tuft and capsule in PAS stain

Discussion

Although renal tubular dysfunction, glomerulopathy, FSGS, proteinuria, renal failure, and nephrocalcinosis have been reported in other GSDs, they were not reported in GSD IXb.[3] There are no cases in the literature with nephrotic syndrome associated with GSD IXb disease. GSD IXb is a metabolic disease with liver and muscle involvement. Renal involvement has not been reported. PHKB gene results in GSD type IXb, and mutations affect muscle and liver. However, PHKB is expressed in all tissues.[1] Less than 20 patients reported clinical symptoms, with less severe to severe hepatic involvement.[4] Patients typically present with hepatomegaly. Hypoglycemia can be mild. In the literature, adenoma-like mass was described in one patient[5], liver fibrosis was reported in another patient[6], and one patient had interventricular septal hypertrophy.[5] In our patient, renal involvement presenting with steroid-sensitive nephrotic syndrome was observed. Due to sclerosis of glomeruli in renal biopsy, FSGS can be evaluated as early-stage findings in the patient. However, this disease was assessed as an independent accompanying condition rather than an involvement.

The (c.305+1 G>A) variant has not been reported in the literature or ClinVar database and is classified as likely pathogenic in ACMG guidelines[7]; it has an adverse change due to its location in the intronic region. The association with GSD type IXb and nephrotic syndrome may be a coincidental association or an involvement of the disease. Other forms of GSD associated with renal manifestations are Fanconi-Bickel syndrome (GSD XI) and GSD I, which present renal tubular dysfunction (proteinuria, phosphaturia, glucosuria, generalized aminoaciduria).[8]

The association between viral infections and glomerulopathy is known. Rhinoviruses belong to the Enterovirus genus in the Picornaviridae family. The literature stated that enteroviruses could cause nephrotic syndrome, but no cases caused by rhinovirus were reported on a case-by-case basis.[9] Although the increased prevalence of hypothyroidism in GSD Ib is known, hypothyroidism has not been reported in GSD type IX or other forms of GSD.[10] It is thought our patient developed hypothyroidism due to urinary loss of thyroid hormones.

Conclusion

We reported the association between GSD IXb and nephrotic syndrome for the first time in the literature. However, this coexistence was evaluated as a comorbid condition rather than a disease involvement. Future studies will guide the clinical course of the GSD XIb with new cases to be reported.

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Image Corner

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Wrist Radiography for Hand Bone Age Tells A Lot; A Girl with SHOX Deficiency

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Madelung's deformity (MD) occurs as a result of premature closure of the medial and volar aspects of the distal radial physis.[1] It is more frequent and severe in girls, and usually develops in middle/late childhood.[2] MD is one of the most characteristic features of the short-stature homeobox gene (SHOX) deficiency, which causes short stature.[3] Radial bowing is one of the well-known radiological futures. On the other hand, there are three typical radiological sign of the hand radiograph for SHOX deficiency; triangularization, pyramidalization of the os lunatum, and radiolucency at the distal radius.[4]

In the evaluation of a 9-year-old girl who was investigated for precocious puberty, her height measurement was 18th percentile. On the wrist X-ray taken for the determination of the bone age of the patient, there was an appearance compatible with MD (**Figure 1**). In the genetic studies of the patient with MD, normal female karyotyping (46, XX) was demonstrated by Trypsin G banding Technique. Heterozygous SHOX deletion was detected by Fluorescence In Situ Hybridization technique using a probe specific to the SHOX gene region (Xp22.33).

Interpreting the direct X-ray is important in recognizing the MD. Thus, it will be easier to detect SHOX gene deletion in the etiology of short stature patients with this deformity.

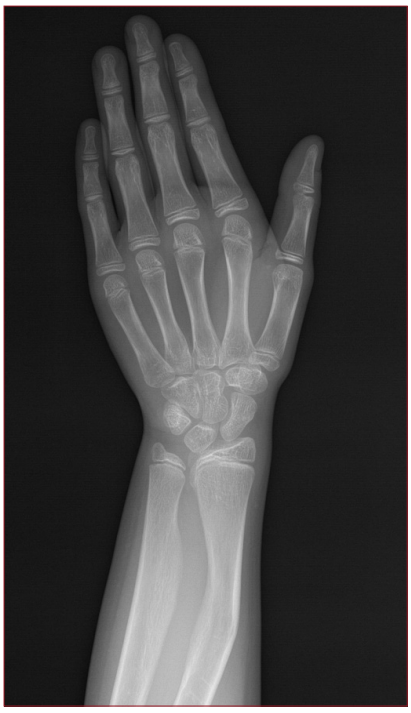

Figure 1: Madelung deformity detected on left wrist radiograph: radial bowing, premature fusion of the distal radial epiphysis

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