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Overview

The Journal of Pediatric Academy is the official publication of the Kayseri Children Health Association. The Journal of Pediatric Academy is an international, peer-reviewed, open-access electronic and conventional published journal in the English language. The Journal of Pediatric Academy is publishing as 3 issues per year. Only for 2020, the Journal of Pediatric Academy will be published in July, September, December. After 2021 the Journal of Pediatric Academy will be published regularly as April, August, and December. The journal 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.

Information About the Journal

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been previously published or be currently under consideration for publication any place else and should report original unpublished research results.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 with membership.

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Manuscript Preparation Guidelines

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been previously published or be currently under consideration for publication any place else and should report original unpublished research results.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 with membership.

Instructions for Authors

Scope

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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A submitted manuscript must be an original contribution not previously published (except as an abstract or a preliminary report), must not be under consideration for publication elsewhere, and, if accepted, must not be published elsewhere in a similar form, in any language. Each person listed as an author is expected to have participated in the study to a significant extent. Although the editors and referees make every effort to ensure the validity of published manuscripts, the final responsibility rests with the authors, not with the Journal, its editors, or the publisher. All manuscripts must be submitted on-line through the journal's Web site at https://wwwjournalpediatricacademy.com/

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JPA is publishing as 3 issues per year. Only for 2020, It will be published in July, September, December after 2021 the JPA will be published regularly as April, August, and December.

Each issue will include at least 4 original research articles, and approximately 4 other types such as editorial comment, invited review, case reports, image corner, and letters to the editor.

Patient Anonymity and Informed Consent

It is the author's responsibility to ensure that a patient's anonymity is carefully protected and to verify that any experimental investigation with human subjects reported in the manuscript was performed with informed consent and following all the guidelines for experimental investigation with human subjects required by the institution(s) with which all the authors are affiliated. The authors should mask patients' eyes and remove patients' names from figures. Photographs with bars placed over the eyes of patients can not be used in publication unless they obtain written consent from the patients and submit written consent with the manuscript.

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Title Page: Include on the title page (a) complete manuscript title; (b) authors' full names, highest academic degrees, affiliations, and ORCID numbers; (c) name and address for correspondence, including fax number, telephone number, and e-mail address; (d) address for reprints if different from that of the corresponding author; and (e) all sources of support, including pharmaceutical and industry support, that require acknowledgment. The title page must also include disclosure of funding received for this work.

Highlights: Highlights are mandatory for original articles, invited review as they help increase the discoverability of your article via search engines. They consist of a short collection of bullet points that capture the novel results of your research as well as new methods that were used during the study (if any). Highlights should be submitted in a separate editable file in the online submission system. Please use 'Highlights' in the file name and include 3 to 5 bullet points (maximum 85 characters, including spaces, per bullet point).

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.

Abbreviations: For a list of standard abbreviations, consult the Council of Biology Editors Style Guide (available from the Council of Science Editors, 9650 Rockville Pike, Bethesda, MD 20814) or other standard sources. Write out the full term for each abbreviation at its first use unless it is a standard unit of measure.

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 in 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.

Units should be prepared by the International System of Units (SI).

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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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Clinical observations may include case histories that demonstrate novel findings or associations, important clinical responses when a larger study is not needed to address a specific issue, or a unique laboratory observation linked to clinical care and/or practice. The text should contain 1500 words or fewer, with a brief abstract of 200 words or fewer. Abstracts outline background, observation(s), and conclusions. Include 5 figures and/or tables or fewer and 15 references or fewer.

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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 manuscripts. 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. 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. Arıcı C, Oğuz V. [Surgical Treatment Options According to Inferior Oblique Hyperfunction in Superior Oblique Palsy]. *Turkiye Klinikleri J Med Sci* 2011;31:1160–1166

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.

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

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Prerequisites Requiring Special Attention

1. Discrimination based on age should be avoided.
2. High lights must be added to the manuscript.
3. Each table and figure must be cited in the text and should be accompanied by a legend on a separate sheet.
4. Each reference cited in the text should be listed in the References section.

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Contents

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Invited Review

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Endocrine Consequences of Childhood Poisoning

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Abstract

Poisoning is reported as a major problem in the childhood period especially under five years. Acute or chronic exposure to toxic material occurs as a different clinical picture. Some cases have different endocrinological findings. Early diagnosis and management are required for careful clinical evaluation. In this article, endocrinological problems of childhood poisoning are reviewed.

Keywords: Poisoning, children, endocrine findings

Introduction

Poisoning is among the important medical problems that occur during the prenatal and postnatal periods.[1-4] 6.2% of the cases admitted to the pediatric emergency department is intoxication.[2] Poisoning occurs in the form of oral, dermal, ocular, intravenous, biting, sting, and inhalation. It is most commonly seen under 5 years of age and in adolescence[2-4] and reported that 88.6% of the cases are occurred at home, 92.1% by accident, 7.9% for suicide.[2] Poisonings can cause a various acute or chronic toxicological problems. Some poisonings result in a variety of endocrinological problems. In this article, the endocrinologic consequences of childhood poisoning are reviewed.

Endocrinological Problems Observed in Poisoning

1. Blood Glucose Changes

Hyperglycaemia: Hyperglycemia can be observed as a laboratory finding in some intoxications such as salicylate, salbutamol, theophylline, carbon monoxide, acetone band acetylene, and organophosphate poisoning (**Table 1**).[5-13] It is observed in 40-48% of cases with organophosphate poisoning[6,7] which may present with a clinical picture of diabetic ketoacidosis and not be diagnosed at the beginning. Therefore, clinicians should carefully evaluate the patient's pupils, halitosis, and conjunctivas

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in terms of miotic pupils, the smell of garlic in the mouth and conjunctival ciliary injection. If the patient has those findings, serum pseudocholinesterase level should be measured.[9]

Hypoglycemia: An important laboratory finding in childhood poisoning is hypoglycemia (**Table 2**).[5-7,14,15] In some poisonings such as iron and organophosphate, hyperglycemia may be observed first, followed by hypoglycemia. The frequency of hypoglycemia in anticholinesterase poisoning was found between 6.4-7.1%.[6,7] Hypoglycemia can cause abstinence, sweating, unconsciousness, and convulsions, and in severe cases, it can lead to irreversible neurological problems.[14]

2. Serum Calcium Changes

Hypercalcemia: Vitamin A and D intoxication are the most important intoxications that cause hypercalcemia. Vitamin A poisoning occurs as a result of taking high doses of vitamin preparations or consuming foods such as the chicken liver. Acute poisoning develops when taken at a dose of 25000 units/kg, while chronic poisoning occurs after 6-15 months of use at a dose of 4000 units/kg per day. In acute cases, symptoms include vomiting, restlessness, and increased intracranial pressure. Pseudotumor cerebri, bone pain, subfebrile fever, hypertension, polyuria, and polydipsia are observed in chronic poisoning cases.[5] Vitamin D intoxication results from an acute overdose, usually as a result of an overdose of vitamin preparations or fish oil consumption. Clinically, symptoms of pseudotumor cerebri, hypercalciuria, polyuria, and polydipsia are observed. The serum 25-OHD level was higher than 100 ng/ml.[16]

Hypocalcemia: Poisoning causing acute or chronic hypocalcemia is listed in **Table 3**. Clinically, patients present with tremors, jitteriness and convulsion. Besides, hyperphosphatemia may be observed.[5,17,18]

Tablo 1.
Poisoning causing hyperglycemia

• Salicylate	• Difenbahia
• Sodium phosphate enema	• Camel base
• Magnesium hydroxide	• Paramethoxy amphetamine
• Ethylene glycol	• Hydrofluoric acid
• Iskin	• Fluorine
• Colchicine	

Tablo 2.
Poisoning causing hypoglycemia

• Salicylate	
• Iron	• Ethyl Alcohol
• Insulin Metformin	• Venlafaxine
• Sulfonylurea group	• Citalopram
• Diazoxide	• Class 1 antiarrhythmics
• Valproic acid	• Mushroom
• Phenytoin	• Snake bite
• Opioids	• Paramethoxamphetamine
• Cocaine	

Highlight

- Poisoning is an accident occured unintentionally or deliberately at all ages, especially childhood. It can cause a several acute or chronic toxicological problems in human body.
- Acute and chronic endocrinological problems may be appeared in children presenting with poisoning based on the resource of toxic material.
- Therefore, acquiring a clinical history and closely monitorizaiton is required to prevent or decrease endocrinologic abnormalities in poisoned children.

3. Intoxications Affecting the Thyroid Gland

Thyrotoxicosis: Especially thyroxine preparations and iodine-containing drugs and amiodarone may cause thyrotoxicosis.[5,19-21] In the neonates, iodine overload may rarely cause hyperthyroidism.[22] Also, it has been reported that thyrotoxicosis may occur with tetrodotoxin, salicylate, and long term lithium use.[5]

Goiter and Hypothyroidism: Some drugs and chemicals can result in the development of goiter and hypothyroidism.[23-25] Excessive iodine intake during pregnancy, breastfeeding, neonatal period, and childhood can cause goiter and hypothyroidism. Use of antithyroid drugs, cyanide, florurethionamide, phenylbutazone, sulfamides, cobalt, epdantoin, aminoglutethimide, lithium in all ages may cause goiter and hypothyroidism.[25]

4. Drugs Poisoning with Antidiuretic Hormone (ADH) Release or ADH-Like Effect Chlorpropamide, vinblastine, tricyclic antidepressants, vincristine and carbamazepine derivatives may trigger water retention and lead to hyponatremia.[5]

Table 3.
Poisoning causing hypocalcemia

• SalicylateMethadone	• Teofillin
• Calcium channel blockers	• Acetone
• Endosulfan	• Carbon monoxide
• Organophosphates	• Salbutamol
• Phenylbutazone	• Acetylene
• Amitraz Phenytoin	• İsoniazid
• CyanideIron	• Aluminum phosphite

5. Intoxications Affecting Surrenal Gland Functions Some drugs and toxic substances may be a reason for surrenal insufficiency. Especially, the mother's exposure to steroids results in the life-threatening adrenal suppression in the fetus.[26] Oral or dermal application of corticoids in the postnatal period may lead to iatrogenic Cushing.[27] Hydrocortisone and prednisolone can be broken down in the placenta and 10% of prednisolone, 33% of betamethasone and 50% of dexamethasone cross the placenta. If prednisolone is used for a long time, the placental enzyme is saturated and prednisolone passes easily which can cause steroid toxicity.[26] The medications interfering with adrenal steroid synthesis such as Ketoconazole, fluconazole, etomidate, aminoglutethimide, trilostane may lead to adrenal suppression. Epdantoin, phenobarbital, rifampicin, topiramate and thyroxine may result in a marked increase in the rate of catabolism of cortisol. Mifepristone, chlorpromazine and imipramine can cause blockage in the glucocorticoid receptor.[28]

6. Endocrine Problems in Metal Poisoning

Lead poisoning is the most common heavy metal poisoning that causes endocrine disorders. Atabek et al. investigated the effect of cord blood lead level on the serum IGF-1 and neonatal anthropometric measurements.[29] They showed that the cord blood level above 10 micrograms/dl negatively affects birth weight without any effect on the IGF-1 level. Lead poisoning has been observed as a cause of important endocrine problems in person working in lead factories.[30] Lead accumulation in endocrine organs is thought to impair the cell functions. It has been demonstrated that lead poisoning affects the hypothalamus-pituitary axis, blunting the TRH, GNRH and GnRH response of the pituitary, but increasing the prolactin level. Although short-term exposure to lead can cause increased FSH and LH levels, testosterone level remains normal. However, in chronic intoxication, the hypothalamo-pituitary axis is disrupted. Lead accumulates in ovarian granulosa cells and negatively affects pubertal development and fertility. Lead may accumulate in seminiferous tubulus cells in men and negatively affect sperm count and motility. It decreases the level of stress-induced corticosterone by accumulation in the adrenal gland, and affects cytosolic and nucleer corticoid receptor binding. Besides its central effect on the thyroid gland, it may impair the function of binding proteins. It may also affect calcitriol levels and reduce calcium absorption from the intestines.[29,30]

Conclusion

Endocrine functions may be impaired as a result of intoxication in children. Patients presenting with poisoning should be investigated in terms of acute and chronic endocrinological problems and should be followed closely.

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New Diagnostic Methods and Treatment Recommendations in Primary Ciliary Dyskinesia

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Abstract

Primary ciliary dyskinesia (PCD) is a rare and genetically heterogeneous disease and clinically characterized by neonatal respiratory distress, organ laterality defects, persistent rhinosinusitis, chronic bronchitis, and eventually bronchiectasis. Currently, there is no single “gold standard” diagnostic test for PCD. PICADAR (Primary Ciliary Dyskinesia Rule) score is a guide to decide for further evaluation of diagnostic tests in PCD. European Respiratory Society (ERS) and American Thoracic Society (ATS) recommend diagnostic tests, including nasal nitric oxide (nNO), high-speed video analysis (HSVMA), transmission electron microscopy (TEM) and genetic testing. Cryo-electron tomography and immunofluorescence methods are new techniques recently performed by specialized centers and needs to be improved. Age at diagnosis for PCD changes according to awareness of disease and available diagnostic tests in different centers. Regular follow-up and multidisciplinary approach is important in the management of PCD. The main aim of the treatment is to prevent pulmonary exacerbations and slow the progression of the disease since there are no treatment approaches to correct the underlying cilia structure and its functions in PCD. Although, there are not enough randomized controlled trials for the treatment of PCD, recent treatments are usually based on to improve the mucociliary clearance. Early diagnosis with multidisciplinary management and nutritional advice could improve growth and delay disease progression leading to bronchiectasis and lung function impairment in PCD.

Keywords: Primary ciliary dyskinesia, ciliopathy, diagnostic tests, mucociliary clearance

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Introduction

Primary ciliary dyskinesia (PCD) is a rare disease with clinical and genetic heterogeneity and often inherited with autosomal recessive pattern, characterized by chronic lower and upper respiratory tract infections due to impaired ciliary motility.[1,2] It was first described by Kartagener et al in 1936 as a triad of chronic sinusitis, bronchiectasis and situs inversus. After this definition, Afzelius suggested that patients with PCD has impaired cilia structure and mucociliary clearance due to immotile cilia.[3] Recently, the definition of "immotile cilia syndrome" has been replaced by the definition of "primary ciliary dyskinesia", which is also associated with abnormal cilia movements besides immotile cilia.[4,5]

Epidemiology

The prevalence of primary ciliary dyskinesia is estimated to be between 1: 2000-1: 40000 according to last reports.[1] Also the frequency of PCD in Europe is estimated to be 1:10000-1: 20000.[6] The most important reason for this situation is the absence of a standard diagnostic approach between different centers. In addition, it is known that the prevalence is high in populations where consanguineous marriages are high.[7] PCD has mainly autosomal recessive inheritance pattern, however autosomal dominant and X-linked transition have been rarely reported.[2] The mutations identified in 45 genes so far is known to be the cause of the disease.[1] Clinical studies and research in recent years have led to increased awareness of the disease; however, 30% of patients can not be diagnosed despite improvements in diagnostic methods and screening tests.[4]

Highlight

- Primary ciliary dyskinesia should be considered in children with neonatal respiratory distress, organ laterality defects, persistent rhinosinusitis, chronic bronchitis, and eventually bronchiectasis.
- The quality of life in primary ciliary dyskinesia depends on lung involvement therefore treatments focus on to improve the mucociliary clearance

Normal cilia structure and function

Respiratory cilias protect the airways against inhaled pathogens and allergens and cilias have an important role in the host defense. The density of cilias decrease from upper airways to lower airways, and no cilias are seen in the alveoli. The cilia microtubule structure is formed by the combination of α and β tubulin monomers. The axonemal structure consists of nine peripheral microtubule pairs and one central microtubule pair (9+2) or without the microtubule pair (9+0) in the central. Cilia can be categorized into three groups as "9+2" motile cilia (motor cilium) with the dynein arm, "9+0" motile cilia (nodal cilium) with the dynein arm, and "9+0" immotile cilia (sensory cilium) without the dynein arm.[8] (**Figure 1**)

Motor cilias (9+2) are located on the apical surface of the upper and lower airways, central nervous system, ependymal cells in the ventricles, sperm tail and fallopian tubes. The outer dynein arm (ODA) and the inner dynein arm (IDA) contribute to the formation of nine double microtubule structures around the central microtubule. The connection between the central pair and the peripheral microtubule is provided with "radial spoke" protein and the connection between peripheral microtubules is provided by "nexin" proteins. Mucociliary clearance enables to removal of mucus and bacteria.

Nodal cilia has a "9+0" structure and functionally, this cilia has rotational motion and provides organ lateralization during embryogenesis. Mutations in the nodal cilia genes result in laterality defects including situs inversus and situs ambigus.

Sensory cilia has also "9+0" structure with no dynein arm and they are localized in the epithelial cells of the kidneys, bile ducts, pancreas, chondrocytes, fibroblast smooth muscle and neurons. These cilias have roles in the cell signaling pathways.[8]

Mutations in the motile cilias (motor cilia and nodal cilia) are called motile ciliopathies and primary ciliary dyskinesia is the known motile ciliopathy in this group. Mutations in the sensory cilias cause diseases with multiple organ involvement called immotile (sensory) ciliopathies. They are classified as Retinitis pigmentosa, Bardet Biedl syndrome, Polycystic kidney disease, Nephonophtisis, Skeletal dysplasia (Jeune syndrome), Joubert syndrome and Cranioectodermal dysplasia. Recent reports suggested that immotile ciliopathies have also motile cilia dysfunction and similar clinical spectrum like PCD.[9,10]

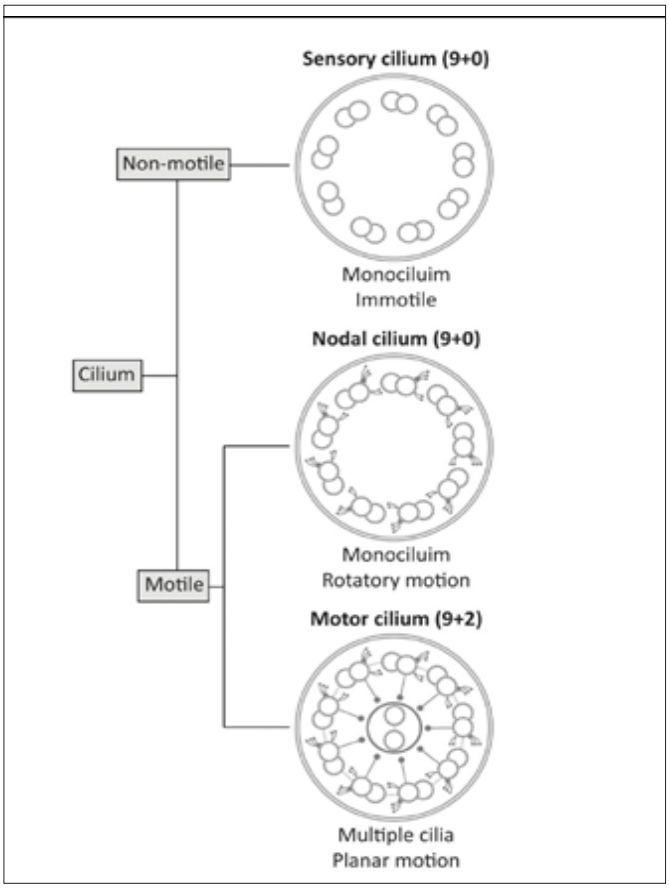

Figure 1. Motile and non-motile cilia types

Diagnosis

The median age of diagnosis has been reported as 5.3 years in Europe and 2.6 years in UK, although it is younger in patients with situs inversus.[5,11] The diagnostic age changes according to awareness of disease and available diagnostic tests in different centers. Therefore, clinicians should suspect PCD in patients with typical clinical signs.

Clinical findings

Clinical findings are characteristic for patients with PCD. Abnormal structure and functions of motile cilia in the nasopharynx, middle ear, paranasal sinuses, lower airways and reproductive system cells are the cause of clinical findings in PCD. Symptoms can start at birth or develop in the first few months of life. Respiratory distress is observed over 80% of neonates despite term birth including history of mechanical ventilation or neonatal unit admission.[12] Respiratory distress occurs mostly 12-24 hour after the birth, with no known cause. Chest X-ray shows atelectasis on different lobes. PCD should be suspected when the baby born on term and admits to hospital with unexplained respiratory distress, hypoxia and radiographic abnormalities such as atelectasis.[9,13]

Cilia ultrastructural defect and impaired cilia functions cause to decrease in the mucociliary clearance; therefore chronic productive cough is the most common reason to refer these patients. Persistant rhinorrhea or nasal congestion starting at first month of age is also a characteristic feature in almost 80% of the patients with PCD.[9] Chronic rhinosinusitis, nasal polyp, recurrent acute otitis media, otitis media with effusion, chronic otitis media and conductive hearing loss are other common clinical findings in these patients.[14,15]

Recurrent bacterial infections in the lower airways eventually cause to bronchiectasis. Despite intensive medical treatments, PCD is generally a slow progressive disease, although some patients develop respiratory failure and lung transplantation is required.[1]

Situs inversus occurs in 40-50% and situs ambigus including heterotaxy occurs in 12% of patients with PCD.[1] Complex congenital heart disease (6.2%), esophageal atresia, biliary atresia are more common in patients with PCD compared with the normal population.[16,17] Also hydrocephalus may be a sign in patients with PCD due to impaired cilia functions in the ependymal cells of ventricles. Respiratory symptoms are common in patients with heterotaxy (polysplenia-aspleni) and complex heart defects.[17] Other phenotypic features include pectus excavatum seen in 10% of cases and scoliosis seen in 5-10%.[4]

Since there are cilia in the sperm flagella nearly 100% of adult PCD male patients come with infertility. In women, the transition time of the ovum in the fallopian tubes is prolonged due to cilial dysfunction in the fimbria of fallopian tubes. Thus, males with PCD have diminished fertility due to reduced sperm motility, however females with PCD have increased risk of ectopic pregnancy because of abnormal fallopian tube transit of oocytes.[9]

In 2016, American Thoracis Society (ATS) defined four main most sensitive features to diagnose PCD. These are: Presence of laterality defect (OR 7.7); Unexplained respiratory distress lasting more than 24 hours in term newborn (OR 6.6); Early-onset (below 6 months) continuous nasal congestion (OR 3.4); Early-onset productive cough (OR 3.1). If there are at least three of these clinical characteristics, the specificity is over 96%, and four of these clinical findings the specificity is over 98%.[18] In another study, Behan et al developed a scoring tool called “PICADAR (Primary Ciliary Dyskinesia Rule)” to predict the diagnosis of PCD. In this scoring, there are seven features, in addition to persistant productive cough including term born, neonatal chest symptoms, history of neonatal intensive care unit admission, chronic rhinitis, ear symptoms, situs inversus and congenital heart defect. The PICADAR score is a guide to decide for further evaluation of diagnostic tests in PCD. If the PICADAR score is 10 or more, probability of PCD is over 90%, and if the score is 5 or more, patients should be evaluated for PCD.[19] **Table 1** shows which patients should refer for diagnostic tests of PCD according to ERS taskforce in 2017.[15]

Table 1.
Which patients should undergo to diagnostic tests for Primary Ciliary Dyskinesia according to ERS Taskforce in 2017[15]

Persistent wet cough, situs anomalies, congenital heart defect, persistent rhinitis, chronic otitis, hearing loss, unknown bronchiectasis, upper airway and lower airway symptoms in term newborn, patients who need intensive care unit in the neonatal period
Patients without a situs anomaly but having the above findings
Patients with a sibling with PCD and who have symptoms
Patients with PCD symptoms and high PICADAR scores

Airway microbiology:

Different microorganisms colonize the airways or infect the lungs. Therefore, respiratory tract cultures are obtained in 3-6 months intervals in patients with PCD in many centers. In childhood, *Haemophilus influenza, Staphylococcus aureus, Moraxella catarrhalis* and *Streptococcus pneumonia* colonization are common in the airways; *Pseudomonas aeruginosa* is common in young adults and is defined as the dominant microorganism in adult PCD patients. Non-tuberculosis mycobacteria are also seen in 15% of adults.[12]

Pulmonary Function Tests

In primary ciliary dyskinesia patients, as with non-CF bronchiectasis, progressive pulmonary obstruction develops with the progression of the disease. Unlike cystic fibrosis, the progression rate of the disease is slow in PCD. FEV1 shows an average decline of 0.8% per year. However, monitoring pulmonary functions is important in determining the treatment approach and prognosis.[20] Goutaki et al reported that both growth and nutrition are affected adversely in PCD patients from early life and are both strongly associated with lung functions.[21]

Radiological findings

High resolution chest tomography (HRCT) is the most sensitive imaging method in the detection of bronchiectasis. However, it can not distinguish different

causes of bronchiectasis, because the distribution of radiological findings change in different diseases. In primary ciliary dyskinesia, middle, lower lobe and lingula of the lungs are more involved and upper lobe involvement is seen later in the disease. Subsegmental atelectasis, peribronchial thickening, mucous plugging, air trapping, mosaic perfusion pattern, tree in bud pattern and ground glass appearance are shown in high resolution chest tomography, where structural changes in the pulmonary parenchyma begin in the infancy and childhood.[22] (**Figure 2**)

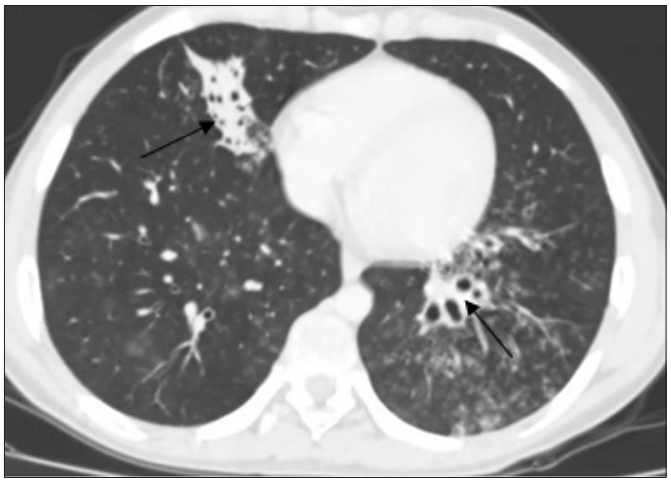

Figure 2a. Chest Computer Tomography Finding of Primary Ciliary Dyskinesia Patient- Bronchiectasis in the middle lobe of the right lung and ground glass appearance-consolidation - subsegmental atelectasis-bronchiectasis (arrow) in the lower lobe and lingula of the left lung

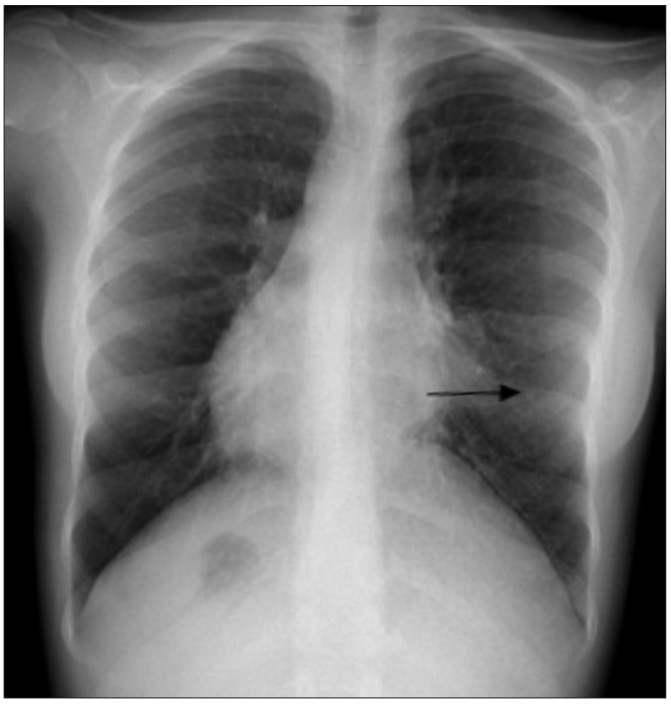

Figure 2b. Dextrocardia and atelectasis (arrow) on the chest radiograph of the patient with the diagnosis of Kartagener syndrome

Diagnostic Tests in Primary Ciliary Dyskinesia

European Respiratory Society (ERS) and American Thoracic Society (ATS) have published two evidence based guidelines in PCD diagnosis. However there is still no gold standard diagnostic test for PCD. Both of these guidelines recommend to use the combination of tests including nasal nitric oxide measurement, high speed video microscopy, immunofluorescence, transmission eletron microscopy and genotype analysis.[15,23]

Screening Tests

Nasal saccharin test, which was previously used as a screening test is not standardized and a subjective method, so it is not recommended for use as a screening test in PCD. Nasal saccharin tests and mucociliary clearance tests are not recommended since the false positivity rate is high in these methods.[4,9]

Nasal nitric oxide measurement

Nasal nitric oxide (nNO) levels are usually low in patients with PCD, therefore nNO is used as a screening test according to ERS and ATS guidelines.[15,23] Nasal NO measurement can be performed with tidal breathing or breath holding maneuver. However, lower values are usually obtained during the tidal breathing. NO measurement by chemiluminescence method and velum closure technique is recommended in patients over 6 years of age and nasal NO cutoff value of 77 nL/min has 98% sensitivity, 99% specificity.[15, 24-26] Measurement during tidal breathing is recommended in patients under 6 years of age with suspected PCD. It is used as a first-line test in patients with the diagnosis of PCD in most countries.[15] Low nNO can also be detected in cystic fibrosis, nasal polyposis, upper respiratory tract infections and smokers.[25] Nasal NO is usually normal in patients with mutations in few PCD-associated genes (*RSPH1, GAS8, RPGR, CCNO, CDC103, CFAP221, DNAH9, FOXJ1, GAS2L2, LRRC56, NEK10, SPEF2, STK36, TTC12*). Thus, nNO concentrations >77 nL/min do not exclude the diagnosis of PCD.[27]

Diagnostic Tests

Diagnostic tests are used to evaluate the ultrastructure and motility of motile cilias. Nasal samples obtained from the inferior nasal turbinate are preferred in the cilia evaluation, but samples can also be taken from the lower airways if bronchoscopy is performed. Epithelial cells can be obtained by curette, forceps or brushing methods. Nasal brushing method should be the first choice due to easy approach and samples should be obtained at least 2-4 weeks after the infection period.[2]

High speed videomicroscopy analysis (HSVMA)

In patients with suspected PCD, ERS recommends to use high speed videomicroscopy (HSVMA) including ciliary beat frequency and beat pattern examination for the diagnosis.[15] The number of cilias, cilia beat frequency, beat pattern and efficiency of mucociliary clearance are evaluated with this method.[1] Ciliary beat frequency was found 7-12 hz in the distal airways, 13-27 hz in the trachea, main bronchus and nose. Biopsy samples are usually evaluated under a 37°C and inverted microscope. Specific beat patterns are classified as completely immotile, immotile with occasional residual movement, reduced bend and reduced beat amplitude, hyperfrequent with reduced amplitude or with circular motion. Mixed patterns may be observed in some situations.[1] Exposure to air pollution, respiratory viral

infections can cause non-specific ultrastructural changes and cilia dysfunction in the cilia. Secondary causes can be excluded by evaluating the samples of cilia at different times and culturing the cells in a sequential single layer / suspension system after biopsy. For definite diagnosis, high-speed videomicroscopy should be repeated after the cell culture.[28,29] The sensitivity of HSVM in the diagnosis of PCD is 100%, and its specificity is reported as 96%. It is suggested that HSVMA is a reliable diagnostic test in experienced centers.[30] However, in *RSPH1, CCDC103, DNAH9, GAS8* mutations, HSVM may be normal.[1]

Transmission electron microscopy

Transmission electron microscopy should be used for the diagnosis of patients with suspected PCD according to ERS guidelines.[15] Electron microscopy provides the cilia ultrastructural evaluation to confirm the diagnosis. Although it was previously known as the gold standard method in the diagnosis of PCD, normal electron microscopy findings are observed in 30% of patients.[31] In patients with a compatible history of PCD, further investigations should be carried out even electron microscopy is normal. However; there is no need for further diagnostic tests in patients with characteristic cilia ultrastructural defect suggesting PCD in electron microscopy. "Outer dynein arm defect, outer and inner dynein arm defect, microtubular disorganisation with inner dynein arm defect" are defined as hallmark diagnostic electron microscopy findings according to last ERS guideline.[32] Electron microscopy findings including "central complex defect, mislocalization of basal bodies with few or no cilia, microtubular disorganisation defect with inner dynein arm, absent outer dynein arm from 25%-50% cross sections, combined inner and outer dynein arm absence from 25%-50% cross sections", indicate PCD diagnosis with other supporting evidence. However isolated inner dynein arm defect, compound cilia, naked cilia, membrane blebs, disorganized microtubuler structure are all secondary ciliary dyskinesia defects and usually disappear after the cell culture.[32] Electron microscopy is frequently normal in "nexin link defects, central microtubule pair defects (*RSPH*), cilia biogenesis defects (*CCNO* and *MCIDAS), DNAH11, HYDIN* mutations".[1,2]

Cryo-electron tomography

This method is a computed tomography adapted to electron microscopy. This method provides three dimensional evaluation of the cilia ultrastructureand demonstrates ultrastructural defects in patients with normal electron microscopy, such as *DNAH11* and *HYDIN* mutations.[33]

Immunofluorescence method

Immunofluorescence method is based on the analysis of antibodies against axonemal proteins in the evaluation of abnormalities of the cilia ultrastructure. ERS recommends this method because it is cheaper and easier than the other tests. Immunofluorescence staining can detect PCD patients with normal ultrastructural evaluation. In addition to the outer dynein arm defects and microtubule disorganisation with the inner dynein arm defects that can be diagnosed by electron microscopy, it is also a useful method in abnormalities in the "nexin" connection and "radial spoke" defects.[15] There are different antibody stainings (*DNAH5, DNALI1, RSPH4A, RSPH9, RSPH1, GAS8*) for many proteins developed for this purpose.[1,2]

Genetic analysis

ERS and ATS recommend genetic testing in patients with suspected PCD.[15,23] It can be used to diagnose patients who can not be diagnosed by high-speed videomicroscopy, electron microscopy and immunofluorescence method. Genetic tests should be evaluated with clinical findings and other results. Bi-allelic pathogenic mutation or hemizygous X-linked mutation in a known gene will confirm the diagnosis. Allele segregation analysis to the family is important to confirm the genetic diagnosis. In a study from different clinical centers in the USA and Canada, 65% of 200 PCD patients have been reported to have a bi-allelic mutation.[34] Almost 65-70% of PCD patients can be diagnosed with the next generation sequencing technology, so that the method will contribute to early diagnosis and treatment.[4,35] Genetic testing can not diagnose approximately 30% of patients and negative genetic testing does not exclude PCD. Genetic analysis is also important in giving the family genetic consultation.[1] Genes related with ultrastructural defects in PCD are summarised in **Table 2**.[36]

Table 2.
Classification of subgroups according to genetic mutations in PCD[36]

Cilia Ultrastructural Defect	Genes
Normal ultrastructure	*DNAH11, CCDC164, CCDC65, RPGR, OFD1*
Outer dynein arm	*DNAH5, DNAI1, DNAI2, CCDC114, CCDC151, ARMC4, DNAH1, TTC25, TXNDC3, DNAL1, CCDC103*
Outer and inner dynein arm	*DNAAF1, DNAAF2, DNAAF3, HEATR2, LRRC6, SPAG1, ZMYND10, DYX1C1, C21orf59, CCDC103, PIH1D3*
Inner dynein arm and axonemal organization	*CCDC39, CCDC40, GAS8*
Central apparatus and radial spoke	*RSPH1, RSPH3, RSPH4A, RSPH9, HYDIN, DNAJB13*
Absent or reduced cilia	*CCNO, MCIDAS*

Different genetic mutations affect the cilia ultrastructure, high speed videomicroscopic features and also clinical findings of patients in different ways. Situs abnormalities are seen in the ultrastructural defects affecting the dynein arm. Disorders in the cilia biogenesis (*MCIDAS, CCNO*), central pair (*HYDIN*), and radial spoke (*RSPH1, RSPH4A, RSPH9*) do not cause situs abnormalities. Despite *RSPH1* and *DNAH9* mutations leading to mild clinical findings; *CCNO, MCIDAS, CCDC39* and *CCDC40* mutations are associated with serious disease. Respiratory system findings appear early and are serious in mutations those with reduced cilia. Hydrocephalus is more common in *CCNO* and *MCIDAS* mutations. Nasal NO levels were found to be low in mutations causing loss of function in the motile cilia.[1,37,38]

In summary, diagnosis of PCD should be confirmed by at least two of the following methods in addition to the clinical features suggesting PCD: Abnormal high-speed videomicroscopy at least three times, abnormal electron microscopy findings, abnormal immunofluorescence examination findings, low nasal NO, the biallelic mutations causing disease.[2] According to ERS taskforce; in addition to clinical findings, suggestive electron microscopy findings for PCD or pathogenic biallelic mutations on genetic testing is necessary to define definitive PCD positive patients. However; in addition to clinical findings and low nasal NO, HSVM findings suggestive for PCD on three seperate occassions or HSVM findings suggestive for PCD following cell culture with normal electron microscopy is necessary to define highly likely PCD patients.

The limitations of the diagnostic tests are summarised in **Table 3**.[2,23]

Table 3.
Limitations of Diagnostic Tests in PCD

Diagnostic Test	
Nasal NO	It may also be low in other diseases such as sinusitis, cystic fibrosis. Sensitivity and specificity is higher in patients older then 5 years old. Nasal NO can be found normal in few mutations *(RSPH1, GAS8, RPGR, CCNO, CDC103, CFAP221, DNAH9, FOXJ1, GAS2L2, LRRC56, NEK10, SPEF2, STK36, TTC12)*
High speed videomicroscopy	Mild disorders can be considered as normal. Ciliary dyskinesia secondary to infection and inflammation is common. In these cases, discrimination between PCD and secondary ciliary dyskinesia can be difficult.
Electron microscopy	Normal ultrastructural findings are detected in 30% of cases. It may cause a false positive diagnosis in inner dynein arm defects.
Immunofluorescence method	It may be normal in 20% of cases. When there is too much mucus in the material, it becomes difficult to stain technically.
Genetic tests	It is expensive due to the large number of PCD genes (45 genes). Genetic tests can identify about 75% of cases. New mutations in known genes should be investigated in patients with suspected PCD.

Management of Primary Ciliary Dyskinesia

General management

The main aim of the treatment is to prevent pulmonary exacerbations and slow the progression of the disease since there are no treatment approaches to correct the underlying cilia ultrastructural defect and ciliary dysfunction in PCD. ERS taskforce recommend to manage patients with definitive diagnosis of PCD and highly likely diagnosis of PCD to treat like PCD.[15] There are not enough randomized controlled trials for the treatment of PCD, treatments are usually based on the treatment of cystic fibrosis and non-cystic fibrosis bronchiectasis leading to improve mucociliary clearance. Patient education and airway cleaning techniques form the basis of the treatment. Prevention of smoking, protection from the air pollution, minimizing the exposure to respiratory pathogens, annual flu vaccines, pneumococcal polysaccharide vaccines and childhood routine vaccines are recommended. Body weight, height and body mass index (BMI) should be evaluated at each follow-up visit. Early diagnosis with multidisciplinary management and nutritional advice could improve growth and delay disease progression and lung function impairment in PCD.[1,39]

Pulmonary management

Patients should be monitored in every 3-6 months. Chest x-ray is recommended at the time of diagnosis; however it is not recommended in every follow-up visit. Since chest x-ray is not sensitive enough, it is not recommended other than the pulmonary exacerbation period.[1,2] Chest CT is important in the early diagnosis of bronchiectasis.[4] Chest CT and MRI have high compatibility in defining the bronchiectasis. Lung MRI can be used in the follow-up of PCD, middle and lower lobe involvement is common in these patients.[40] In addition, other radiological findings are peribronchial wall thickening, mucus plugging, bronchiectasis, atelectasis and bud tree appearance.[2]

Pulmonary function tests should be done in every 3-6 months. Lung clearance index (LCI) can detect the lung pathology before the pulmonary function tests. Especially in microtubule defects, LCI is higher and FEV1 is lower.[1,2]

Sputum culture, cough swab or nasal swab should be taken 2-4 times in a year. For non-tuberculosis mycobacteria, a sputum sample should be taken every two years. Fungal culture should be obtained from cases unresponsive to treatment and patients should be evaluated in terms of Allergic Bronchopulmonary Aspergillosis.[1,2]

Different airway clearance techniques are recommended in PCD at least twice daily. Daily cardiovascular exercises, percussion techniques, manual chest physiotherapy techniques, positive pressure expiration methods increase clearance of secretions, regulate ventilation, increase exercise tolerance and reduce shortness of breath.[1,2,4] Nebulized treatments may help patients to clear secretions, although evidence is not strong in PCD. In PCD, there was no difference on the pulmonary function tests, lower respiratory tract symptoms, sputum cytokines, inflammatory markers, quality of life scores at 3 months of treatment with 7% hypertonic saline compared to isotonic SF.[41] Dornase α is used in CF that cleavages DNA released from neutrophils, reducing mucus viscosity and increasing airway clearance. However, in a study conducted in adults, inhaled dornase α treatment in non-CF bronchiectasis has been shown to increase the rate of pulmonary exacerbation and cause a decrease in the respiratory functions.[42] There is no recommendation to use inhaled hypertonic saline, dornase α and also inhaled corticosteroids are not recommended if they have not asthma diagnosis in patients with PCD.

Antibiotic treatments are recommended for symptomatic infections, prophylaxis, in *P. aeruginosa* eradication and chronic *P. aeruginosa* colonization. Pulmonary exacerbation is defined by the presence of three or more of the following seven items: 1) increased cough, 2) change in sputum volume and/or colour, 3) increased shortness of breath perceived by the patient or parent, 4) decision to start or change antibiotic treatment because of perceived pulmonary symptoms, 5) malaise, tiredness, fatigue or lethargy, 6) new or increased haemoptysis, and 7) temperature >38°C.[43] Antibiotic treatments are decided based on the most common microorganisms *H. influenzea, S. pneumonia, M. catarrhalis, S. aureus* in children and *P. aeruginosa* in older people. Treatment of asymptomatic infection is commonly changes according to clinican attitude. Although there is not strong evidence, it is recommended to treat the first isolates of pathogens with at least two weeks of antibiotic treatment. For *P. aeruginosa*, inhaled antibiotics are usually preferred and in some conditions oral antibiotics may be added. In chronic *P. aeruginosa* colonization inhaled antibiotics (colimycin, tobramycin, gentamycin) are usually recommended based on the CF literature.[44,45]

In patients with frequent pulmonary exacerbations, chronic or periodic oral or inhaled antibiotics reduce the pulmonary exacerbations and improve the quality of life of patients, also stabilizing their pulmonary functions. First multinational randomised controlled trial (BEST CILIA) in PCD showed that azithromycin maintenance therapy for 6 months was well tolerated and halved the rate of respiratory exacerbations. The authors concluded that azithromycin maintenance therapy is an option for patients with PCD with frequent exacerbations potentially leading to reduced need for additional antibiotic treatments and preventing irreversible lung damage.[46]

The role of thoracic surgery in patients with PCD is unclear and it is rarely indicated in PCD. Surgical resection therapy should be considered in localized lung disease, which causes serious symptoms, patients with frequent exacerbations, progressive with life-threatening hemoptysis despite medical treatment.[47] Long-term results of patients with thoracic surgery are unknown. Thoracic surgery is not generally recommended in PCD as diffuse lung involvement decreases the success of localized surgical resection. In a multicentric study from different countries in Europe showed that patients who are lobectomized have lower FEV1, FVC z scores, and FEV1, FVC levels continue to decrease more than the non-lobectomy group after the surgery period.[48] Lung transplantation is also an option in the end stage of lung disease.[1]

Upper airway management

Because of many patients suffer from chronic rhinosinusitis, recurrent otitis media; ear, nose and throat examination 1-2 times a year and hearing test is recommended at least once a year.[1,49]

Nasal steroids, sinonasal rinsing with saline, nasal lavage with intermittent antibiotics and systemic antibiotics are used in the treatment. Surgical and nasal polypectomy can be applied to provide sinus drainage in patients resistant to medical treatment. Nasal surgery is not the first treatment option due to the risk of recurrence of nasal polyps.[2,49]

In chronic upper respiratory diseases, conductive hearing loss and speech delay are observed in the long term period. Standard medical treatment is recommended in acute otitis media attacks. Adequate data are not available on surgical tympanostomy and ventilation tube management.[1,2] ERS also recommends hearing aids in these patients rather than ventilation tubes.[39]

Other system management

Echocardiogram and abdominal ultrasound should be obtained in patients with PCD after the diagnosis.[1]

Compared to healthy controls in PCD patients; obstructive sleep apnea (60%), attention deficit and hyperactivity are more common.[1] This should be evaluated in the clinical history of PCD patients.

Infertility is common in men due to sperm immotility, assisted reproductive techniques with intracytoplasmic sperm injection are promising. In women, the transition time of the ovum to the fallopian tube is prolonged, but patients can have children with the invitro fertilization method. According to this; fertility tests should be obtained in adult PCD patients.

Conclusion

In primary ciliary dyskinesia, the awareness of the disease is low due to the symptoms and signs that are not specific to disease, and the difficulty in diagnostic tests cause delay in diagnosis. In the long-term evaluation, regular follow-up and multidisciplinary approach is important. Early diagnosis and treatment will slow chronic lung disease with bronchiectasis and positively affect the patients' quality of life.

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The Factors Affecting the Occurrence of Renal Involvement in Children with IgA Vasculitis

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Abstract

Henoch-Schönlein purpura or IgA vasculitis that involves small vessels is the most common vasculitis in childhood and the long term prognosis is contingent on the severity of renal involvement.In this study, we aimed to determine the frequency of organ involvements and to identify potential risk factors for renal involvement in children with IgA vasculitis.This study included 416 patients with IgA vasculitis who had been followed in our department between 1990 and 2016. The patients were retrospectively reviewed in terms of type of treatment, organ involvement and clinical outcome, and potential risk factors for renal involvement were determined. Overall, 416 patients with IgA vasculitis were identified, including 174 girls (41.7%) and 242 boys (58.3%). The mean age at presentation was 8.3±3.1 years. The distribution of organ involvement was: skin involvement, 100%; joint involvement, 77.1%; gastrointestinal system (GIS) involvement, 58.6%; renal involvement, 38.3%; scalp edema, 10.1%; scrotal involvement, 5.3% (9.0% in boys), central nervous system (CNS) involvement, 1.6% and pulmonary involvement, 0.25%. When risk factors for renal involvement were assessed, it was found that GIS involvement was more frequently seen in patients with nephritis (p=0.01). Age, diastolic blood pressure and GIS involvement at the onset were found to be correlated with renal involvement. GIS involvement and diastolic blood pressure were found as risk factors for renal involvement. Age, elevation in diastolic blood pressure and GIS involvement were important findings in prediction of nephritis. In particular, patients with GIS involvement should be cautiously monitored for renal involvement.

Keywords: IgA vasculitis, Children, Kidney involvement

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Introduction

Immunoglobulin A (IgA) vasculitis, formerly known as Henoch-Schönlein purpura, is the most commonly encountered vasculitis in children, which is characterized by deposition of IgA within small vessels of skin, gastrointestinal system and kidneys. Common findings include palpable purpura without thrombocytopenia and accompanying arthritis-arthralgia, gastrointestinal involvement and renal involvement ranging from asymptomatic hematuria to rapidly progressive glomerulonephritis.[1] Although its etiology remains unclear, it has been reported that IgA vasculitis is more common following allergen exposure and upper respiratory tract infection caused by streptococci and other microorganisms. In addition, vaccines, drugs and insect bite may have facilitating role in the disease. Although life-threatening pulmonary and CNS involvements can occur, renal involvement is primary organ involvement determining clinical outcomes. It can be seen in 17-58.1% of cases.[1-7] It generally develops within first 4-6 weeks after onset of IgA vasculitis. Microscopic hematuria, proteinuria, hypertension, nephrotic syndrome, or acute or chronic renal failure may develop but end-stage renal disease is rare.[1]

Highlight

- Immunoglobulin A vasculitis is a multisystemic disorder that mainly affects skin, joints, gastrointestinal system (GIS) and kidneys.
- Kidney involvement ranges from asymptomatic hematuria to rapidly progressive glomerulonephritis
- In this study, pulmonary involvement was rare but had fatal course
- Renal involvement was more frequently seen in patients with GIS involvement
- Renal involvement was positively correlated with age, diastolic blood pressure and GIS involvement

The aim of this study was to review clinical and laboratory findings of patients who had been managed with a diagnosis of IgA vasculitis in our hospital, to identify other organ involvements predisposing renal disease, and to assess long-term outcomes in patients with nephritis.

Materials and Methods

We retrospectively reviewed files of patients who had been followed with a diagnosis of IgA vasculitis at Pediatric Nephrology and Rheumatology Department of Erciyes University, Medicine School between 1990 and 2016. This study was approved by The Ethics Committee of Erciyes University, Faculty of Medicine (approval date 02/12/2016, number 2016/627). Data regarding epidemiological characteristics (age, gender, history of allergy, insect bite or infection, family history and comorbid diseases), clinical and laboratory findings, organ involvement and treatments used were extracted from patient files. Overall, 416 patients were included into the study. The diagnosis of IgA vasculitis was made according to American College of Rheumatology criteria in patients presented before 2006 while it was made according to Pediatric Rheumatology European Society (PRES) criteria and EULAR/PRINTO/PRES consensus criteria in patients presented after 2006.[8,9]

Skin involvement was defined as presence of symmetrical purpura slightly arising from skin at extensor aspects of skin which doesn't blanch with pressure. Arthralgia was defined as pain alone in any joint while arthritis was defined as presence of one or more findings of swelling, redness, warmth and limitation of movement in the joint regardless of pain. Gastrointestinal involvement was defined as severe, sharp, abdominal colic and/or presence of occult blood in stool, melena or hematochezia.[10]

Renal involvement was defined as presence of gross or microscopic hematuria regardless of proteinuria. Observation of >5 cells in centrifuged urine sample on microscope (x40) or ≥1+ blood reaction in dipstick test was considered as hematuria. Proteinuria was defined as presence of ≥1+ reaction in dipstick test in case of normal urinary density or >4 mg/m^2 protein and >0.2 mg/mg protein: creatinine ratio in 24-hours urine test.[11] Pulmonary involvement was considered in case of pulmonary hemorrhage or interstitial pneumonia that couldn't explained otherwise. The CNS involvement was considered in case of severe headache, seizure, intracranial hemorrhage and encephalopathy that couldn't be explained otherwise.[12]

Anthropometric measurements, blood pressure values, detailed medical history and physical examination findings, urinalysis results, complete blood count values, biochemical parameters (urine and serum), immunoglobulin levels, acute phase reactant levels and complement levels at presentation were recorded. For assessment of proteinuria, protein: creatinine ratio in spot urine and/or 24-hours urine collection was calculated in all patients. Hypertension was defined as systolic or diastolic blood pressure values above 95 percentile according to age, gender and height.[13] After assessment for organ involvement, patients with nephritis were evaluated in a more detailed manner.

The patients with kidney involvement were stratified into 5 categories based on modified Meadow criteria[14] as follows: grade 1, microscopic hematuria; grade 2, persistent proteinuria and/or hematuria; grade 3, nephritic syndrome (hematuria, decrease in glomerular filtration rate, GFR, oliguria, hypertension, and edema); grade 4, nephrotic syndrome (proteinuria >40 mg/m^2 per hour or total protein/creatinine ratio on a spot urine sample>3 mg protein/mg creatinine, hypoalbuminemia with serum albumin < 2.5 g/dl and/or hyperlipidemia/edema), and grade 5, mixed nephritic-nephrotic syndrome.

Renal biopsy results were classified according to International Study of Kidney Disease in Children (ISKDC) parameters.[15] The GFR was calculated according to Schwartz formula.[16] The estimated GFR<60 ml/min/1.73 m^2 was considered as reduction in creatinine clearance.

All given treatments, treatment response and duration of treatment were also recorded. The findings of urinalysis, proteinuria in 24 hour urine collection or protein to creatinine ratio in spot urine at the beginning

of treatment and remission status by treatment were recorded. Remission was defined as complete resolution of clinical and laboratory findings and complete recovery of urinary findings by treatment in patients with nephritis. Partial remission was defined as persistence of abnormal physical examination findings despite resolution of laboratory and clinical presentation, persistence of hematuria and/or proteinuria with partial resolution and need for a second therapeutic modality. Unresponsiveness to treatment was defined as lack of resolution in clinical and laboratory findings despite treatment.[17]

Treatment, urinary findings and biochemical parameters at last follow-up visit were recorded. Prognosis was assessed at the most recent follow-up according to Meadow criteria[14] as follows: state A, normal (normal blood pressure, no proteinuria or hematuria, normal serum creatinine level); state B, minor urinary abnormality (<20 mg/m^2 per hour proteinuria regardless of microscopic or macroscopic hematuria); state C, active renal disease (>20 mg/m^2 per hour proteinuria and/or elevated serum creatinine level); state D, renal failure (GFR<60 ml/min/1.73 m^2).

Statistical analysis

Data were analyzed by SPSS version 22.0. Shapiro-Wilk test was used to assess normal distribution. Data with normal distribution are expressed as mean ± standard deviation while data with skewed distribution are expressed as median (min=max). Student's t test was used to compare data with normal distribution while Mann Whitney test was used to compare data with skewed distribution. Univariate logistic regression analysis was used to identify variables which might be associated to renal involvement. To identify risk factors for renal involvement, variables found to be significant in univariate logistic regression analysis was assessed as independent variables in binary logistic stepwise regression model by backward elimination where renal involvement was dependent variable. A p value<0.05 was considered as statistically significant.

Results

This study was conducted on 426 patients diagnosed as IgA vasculitis (HSP) including 174 girls (40.8%) and 222 boys (59.2%). Mean age at presentation was 8.3±3.2 years. There was history of infection before onset of rash in 189 cases (44.4.0%) while there was a history of insect bite before diagnosis in 13 patients (3.1%). Established drug or food allergy was present in only 3 patients (0.7%). Familial Mediterranean fever and congenital heart disease were determined in seven and four, respectively as a co-morbid disease.

All 426 cases had typical skin manifestations. Joint involvement in 75.1%, GIS involvement in 57.7%, renal involvement in 39.9%, scalp edema in 10.6%, and CNS involvement in 1.6% of patients were detected. There was one patient with life-threatening pulmonary involvement characterized by pulmonary hemorrhage despite intensive immunosuppressive therapy, plasmapheresis and renal replacement therapy.

Table 1 shows laboratory findings of patients with at presentation and the diagnosis of IgA nephritis.

Table 1.
The Laboratory findings of the patients on admission and at the time of the diagnosis of IgA nephritis

Variables	On admission	At the diagnosis of IgA nephritis
Hemoglobin (g/dL)*	12.4±1.5	12.3±1.3
WBC (/µL)*	12060±5287	12416±5392
Platelet (/µL)*	393587±136221	380772±144124
BUN (mg/dl)*	14.3±11.2	17.7±16.4
Creatine (mg/dL) β	0.5 (0.15-5.6)	0.6 (0.2-5.6)
ESR (mm/h)*	34.8±25.7	38.1±27.3
CRP (mg/L) β	16 (2-287)	2 (2-182)
ASO (IU/mL)*	318±291	320±290
C3*	146.4±45.5	142±42
C4*	26.87±10.9	28.7±24.5
IgA*	235.8±103.8	245.9±117.9

* mean ± standard deviation. β median (minimum-maximum)
WBC: White blood cells; BUN: Blood urea nitrogen; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; ASO: Anti-streptolysin O; C3: Complement 3; C4: Complement 4; IgA: Immunoglobulin A

Of 170 patients with renal involvement, there was microscopic hematuria in 94.3%, proteinuria in 55.0% and gross hematuria in 51.8%. The prevalence of dipstick proteinuria ≥(2+), ≥(3+) and ≥(4+) was 46.6%, 44.3% and 9%, respectively. It was found that median micro-protein: creatinine ratio was 1.2 mg/mg (0.17-10.9) while median 24 hour protein excretion was 27 mg/m^2/hour (0.4-510). Since baseline serum creatinine values were unavailable in 5 patients, 154 patients (67 girls and 87 boys) were included to final analysis of renal involvement in IgA vasculitis. Median time from diagnosis of IgA vasculitis to renal involvement was 1.5 weeks (0-68). There was no significant difference in renal involvement between boys and girls (p>0.05). Mean age was 9.1±3.2 years in patients with nephritis whereas 7.8 years±2.9 years in those without nephritis, indicating no significant difference (p>0.05). Mean systolic and diastolic blood pressures were 107.4±16.1 and 68.4±12.7 mmHg, respectively. Mean GFR was found to be 127.6±50.2 mg/min/1.73 m^2. Creatinine clearance was found to be decreased in 8 patients (5.2%). According to modified Meadow scoring at presentation, there was grade 1 disease in 35, grade 2 disease in 45, grade 3 disease in 38 and grade 5 disease in 35 patients. There was no patient with grade 4 disease (**Table 2**).

Table 2.
The distribution of patients on admission based on Meadow classification and clinical outcome according to Meadow's criteria

	State A	State B	State C	State D	Total
Grade 1	26	7	2	0	35
Grade 2	32	12	1	0	45
Grade 3	25	10	3	0	38
Grade 4	0	0	0	0	0
Grade 5	19	10	6	1	36
Total	102	39	12	0	154

Grade 1: Microscopic hematuria***; Grade 2:*** Persistent mild proteinuria (<20 mg/m²/h) and/or hematuria; ***Grade 3:*** Nephritic syndrome (hematuria, low GFR, oliguria, hypertension, edema); ***Grade 4: Nephrotic*** syndrome [proteinüri (>40mg/m²/h), hypoalbuminemia, hyperlipidemia and edema)***; Grade 5:*** Mix (nephrotic-nephritic syndrome). Meadow's criteria: ***A,*** normal (no hypertension, urinary abnormality and protein excretion and normal plasma creatinine concentration); ***B***, minor urinary abnormalities (proteinuria <20 mg/m2/h with or without microscopic-recurrent macroscopic hematuria); ***C***, active renal disease (proteinuria >20 mg/m2/h and or elevated plasma creatinine level); ***D,*** renal insufficiency (GFR below 60 ml/min/1.73 m²)

It was found that GIS involvement was more common in patients with nephritis than those without nephritis (68.6% vs. 53%, p=0.01). No significant difference was detected regarding organ involvement other than GIS between patients with nephritis and those without nephritis. Joint involvement in 115, GIS involvement in 105, scalp edema in 10, scrotal involvement in 7 and CNS involvement in 4 of patients with nephritis were present.

Kidney biopsy was performed in 68 patients and histopathological findings were compatible with stage 1 in 21, stage 2 in 22, stage 3 in 23, stage 4 in 2 and stage 5 in 1 of patients. No patient had stage 6 histopathological changes. Of the patients with nephritis, oral prednisolone therapy was given to 120 patients whereas pulse methyl prednisolone therapy to 62 patients, cyclophosphamide to 5, cyclosporine to 2 and ACE inhibitor to 46 patients. Eculuzimab was given in a child who had a genetic defect on the alternative pathway of complement system. At the end of 3 months of eculuzimab treatment, serum creatinine reduced and proteinuria decreased although we put her eculizumab her repeated kidney biopsy showed sclerosis in 17 of 26 glomeruli and cellular crescent in the rest of the glomeruli. She reached at end-stage renal disease (ESRD).

At last follow-up visit, mean age was 11.7±4.3 years. Median protein to creatinine ratio in spot urine and protein excretion in 24 h urine collection were 0.18 mg/mg (0.05-12.4) and 4.8 mg/m^2/ per hour, respectively. Mean serum creatinine level was 0.59±0.16 mg/dL. Based on Meadow classification at last control visit, there were 102 patients with state A disease, 39 patients with state B disease, 12 patients with state C disease and one patient with state D disease (**Table 2**). As shown in Table 2, it was seen that findings of active disease was persisting at final control in 6 of 36 patients presented with manifestations of nephritic-nephrotic syndrome while in 5.7% 35 of patients presented with microscopic hematuria. In univariate analysis where renal involvement was dependent variable, a positive correlation was detected between renal involvement and age, diastolic blood pressure and GIS involvement (**Table 3**). In binary logistic regression model, these variables were found to be associated to risk for renal involvement. After adjustment according to age by using stepwise regression and backward elimination, it was found that each increase in diastolic blood pressure resulted in one-fold increase while each increase in GIS involvement resulted in 1.8- folds increase in risk for renal involvement (**Table 4**).

Table 3.
The univariate analysis between kidney involvement and other variables

Variable	OR	95% CI	p
Age	1.146	1.073-1.026	0.001
SBP	1.013	0.999-1.026	0.06
DBP	1.033	1.013-1.053	0.001
Gastrointestinal involvement	1.737	1.152-2.621	0.008
Scalp edema	0.539	0.263-1.107	0.09
Scrotal edema	0.740	0.295-1.856	0.5
ESR	1.008	0.999-1.016	0.07

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; ESR; Erythrocyte sedimentation rate

Table 4.
*The factors affecting kidney involvement (Binary Logistic Regression)**

Variable	OR	95% CI	p
DBP	1.028	1.007-1.050	0.010
Gastrointestinal involvement	1.807	1.105-2.956	0.018

*Variables were adjusted for age; DBP: Diastolic blood pressure

Discussion

In this study, we found that pulmonary involvement was rare but had fatal course. In addition, it was detected that renal involvement was more frequently seen in patients with GIS involvement; that renal involvement had positive correlation with age, diastolic blood pressure and GIS involvement; and that GIS involvement markedly increased risk for renal disease in patients with IgA vasculitis.

IgA vasculitis is slightly more common among boys with varying male: female ratios across the countries in the literature.[18] For instance, in a study from Kuwait, male: female (M: F) ratio was reported as 0.72 in 102 patients.[19] The M: F ratio was found to be 1.35 among 417 patients with IgA vasculitis in a study from Spain[20] while 1.23 among 121 patients in a study from South Korea conducted between 2004 and 2015.[21] In Taiwan, the M: F ratio was reported to be 1.11 in a large series including 2759 patients with IgA vasculitis.[22] In our study, the M: F ratio was found as 1.39. This result is consistent with those reported by others.[20-21]

The distribution of organ involvements in IgA vasculitis varies depending on the definition criteria. Joint involvement has been reported in 50-80%[18,23,24] whereas GIS involvement in 50-75% of cases.[25-27] Arthritis or arthralgia is not the first sign of disease in most cases; however, it may be observed as first sign in 15% of patients.[28] Occasionally, abdominal pain that may be confused with acute abdomen followed by rash can occur. In a retrospective study from Turkey, GIS involvement was reported in 73% of 137 patients.[29] In a study from Spain, GIS involvement was shown in 64.5% of 417 patients.[20] In our study, the distribution of organ involvements was similar to literature. Intussusception was found in 4.5% of 243 patients with GIS involvement. The intussusceptions rate varies from 0.3% to 1.8% in patients with IgA vasculitis across the world.[30,31] In a study on 214 patients from Turkey, GIS involvement it was reported as 1.4%.[32] In our study, the frequency of intussusception was found to be higher than those reported in literature. This may be due to difference of experience between ultrasound operators, who can easily miss or detect small and important signs of intussusceptions. In our center, ultrasound is performed by radiologist.

The severity of renal involvement is one of the most important risk factors affecting long term prognosis in IgA vasculitis.[1,18] In general, renal involvement occurs within 4-6 weeks after onset of disease.[33,34] The incidence of renal involvement varies from study to study based on the definition criteria. In previous studies, it has been reported as 25-55%.[1,17,28,34,35] In our study, median time from diagnosis of purpura to detection of nephritis was

1.5 weeks and renal involvement was detected in 38% of our patients. In our center, we do not perform kidney biopsy in children with minor urine abnormalities. So, 68 of patients with renal involvement underwent kidney biopsy. The distribution of patients based on histo-pathological findings may show variety between studies. Huang et al.[36] evaluated 245 patients with biopsy proven kidney involvement and found that% 90 of patients had stage 2-3 changes based on ISKDC classification. The present study showed almost equal distribution between stage 1, 2 and 3. This finding may be due to the timing of kidney biopsy.

In clinical practice, the identification of early-stage nephritis is pivotal to prevent or delay chronic kidney disease. So, Knowing and guessing about the risk factors associated with renal involvement is crucial.[37] Both the age of onset[7,38,39] and severe abdominal pain were found as risk factors for nephritis.[7,21]

Mao et al.[40] evaluated 535 with IgA vasculitis and found that age of onset>6 years, purpura on the upper limbs or face, and occult blood in stool were risk factors for development of nephritis. In a Finnish study on 223 patients, it was found that presence of severe abdominal pain was a risk factor for nephritis, causing 2.1 folds increase in risk for the development of nephritis.[35] Recently, a meta-analysis has been published by Chan et al.[37] They found that male gender; >10 y old; severe gastrointestinal symptoms (abdominal pain, gastrointestinal bleeding, and severe bowel angina); arthritis/arthralgia; persistent purpura or relapse; WBC>15×109/L; platelets>500×109/L; elevated ASO; and low C3 were associated with renal involvement in children with IgA vasculitis. In our study, GI involvement was found important risk factor for the development of nephritis with 1.8 fold increase in risk for nephritis by GI involvement (**Table 4**, p=0.01). In addition, a positive correlation was detected between age of onset and renal involvement (**Table 3**). In a meta- analysis published by Mao et al.[41] was shown that older age, elevated blood pressure, C3, hemoglobin, urea nitrogen, and hypoalbuminemia were risk factors for renal damage in patients with IgA vasculitis. Authors did not mention the reason of the relationship between high blood pressure at baseline and the development of nephritis. The present study demonstrated baseline diastolic blood pressure is a risk factor for nephritis possibly through an unexplained mechanism. As known, hypertension is seen as part of acute HSP nephritis, with decreased GFR and fluid overload.[1]

Meadow scoring system is a useful tool to assess renal involvement at baseline and prognosis.[14] In a study on 141 patients, Mir et al.[17] evaluated 82 patients (58.1%) with nephritis at baseline and follow-up visits by using modified Meadow criteria. Authors found that baseline findings had effect on prognosis. In that study, 94.5% of the patients with grade 1 and 2 disease according to modified Meadow criteria had better outcome than 62.0% of patients with grade 3-5 disease in long term. In our study, active renal disease or end-stage kidney disease was apparent in patients with grade 5 disease characterized by nephritic-nephrotic syndrome at last follow-up (5% in grade 1-3 vs. 19.4% in grade 5).

In Our cohort, there was a child who was nine years old girl presented with a typical clinical picture of HSPN verified with the kidney biopsy. Her complements levels were normal. She was given prednisolone, cyclosporine, azathioprine, cyclophosphamide, plasmapheresis, and Rituximab. However, she did not give the reasonable response to immunosuppressive medications. Repeated kidney biopsy showed sclerosis in 17 of 26 glomeruli and cellular crescent in the rest of the glomeruli. So, we decided to start Eculizumab for the rescue of renal function with an experience coming from IgA nephritis.[42] Initially, she gave a partial response to Eculizumab. Unfortunately, we could not continue with Eculizumab regularly because of the difficulty to access it. Finally, she reached ESRD. A homozygous mutation in Factor H gene was detected in a study of a complement system. While she was on peritoneal dialysis, she experienced with osteomyelitis on the left foot. She died possibly because of a complication of osteomyelitis.

This study have some limitations including: 1) tissue specimens were obtained in only 68 patients due to failure in performing renal biopsy despite greater number of patients with renal involvement. Limited number of patients having kidney biopsy also restricts number of patients classified by ISKDC system and makes it difficult to establish clinic-pathological association and 2) lack of patients presented with isolated nephrotic syndrome resulted in failure to obtain data regarding prognosis of patients in this group.

Conclusion

IgA vasculitis is a multi-systemic disease. Gastrointestinal involvement is an important finding in prediction of renal involvement. Severity of baseline findings is an important parameter predicting prognosis of disease in patients with renal involvement. We think patients with GI involvement should be closely monitored to detect renal involvement and prevent or delay chronic kidney disease.

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Impact of Intrauterine Growth Restriction Diseases on The Umbilical Cord Blood CD34+ Cell Counts

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Abstract

Different diseases in obstetrics and gynecology can affect the number of CD34+ cells in the umbilical cord blood. This study aimed to evaluate the effect of Gestational Diabetes Mellitus (GDM), Gestational Hypertension (GHT) and Morbidly Adherent Placenta (MAP) on the content of CD34+ cells of umbilical cord blood and to compare the effectiveness of Sysmex XN20 analyzer to the flow cytometry method, which is the gold standard in CD34+ cells. The umbilical cord blood (15 ml) was collected after the birth of the newborns. Peripheral blood mononuclear cells (PBMCs) were isolated by Ficoll-Paque Plus. The cells were stained with Procount ™ Progenitor Cell Count Kit with PE Labeled monoclonal anti-CD34+ antibody then analyzed with Flow Cytometry or Sysmex XN20 without staining, to identify CD34+ cells named as hematopoietic progenitor cells (HPC), respectively.Flow cytometric evaluation revealed a significantly elevated ($p<0.05$) number of cord blood CD34+ cells in GDM and GHT groups compared with healthy controls. MAP patients had comparable CD34+ cells compared with healthy controls. A significant increase in lymphocyte counts was also observed in GDM and GHT groups compared with healthy controls. Sysmex analysis however only revealed an increase in lymphocyte numbers in GHT but picked no differences across groups in HPC. Correlation between Sysmex and flow cytometry results was weak in control, GHT, GDM and MAP groups r: 0570/$p<0.01$, r: 0.5727/p: 0.0708, r:0.2149/p: 0.4779, r: 0.111/p: 0.779, respectively. CD34+ cells were significantly higher in the GHT and GDM groups compared with healthy control cord blood. The correlations between Flow cytometry and Sysmex were not strong.

Keywords: CD34+ cells, gestational hypertension, gestational diabetes, morbidly adherent placenta, umbilical cord blood

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Introduction

Stem cells are self-renewing cells that can differentiate into specialized cells. Hematopoietic stem cells (HSC) s can be obtained from bone marrow (BM) aspirates, mobilized peripheral blood, and umbilical cord blood.[1] HSCs transplantation is an important treatment alternative for hematological, genetic, malignant, neurological, and autoimmune diseases. Recently, there has been an increasing interest in umbilical cord blood transplantation due to its advantages over bone marrow. Umbilical cord blood offers less restrictive criteria for HLA matched donor and has a reduced risk of chronic and acute graft versus host disease (GVHD) due to its naive lymphocyte structure.[2,3] Practical advantages include the abundant supply of donors without any risk, as well as the presence of frozen graft in emergencies such as COVID-19 pandemic, and the less possibility of transmitting infectious agents to the recipient.[4,5]

The success of umbilical cord blood transfusion is associated with the number of total nucleated cells (TNCs) and CD34+ cells transmitted, but insufficient amounts of HSCs in umbilical cord blood are associated with poor recovery, especially in adults and older children those weighs more than 30 kg so this factor is one of the most important barriers to the spread of umbilical cord blood transplantation.[6-8] Because of these restrictive problems, research in the literature has focused on factors altering CD34+ cells product such as maternal age, smoking status, birth weight, gestational age, gender, mode of delivery, preeclampsia.[9-12] Whereas the effect of morbidly adherent placenta (MAP) disease caused by abnormal implantation of the basal plate,[13] reported as 3% in women with previous cesarean history and 60% in women with three previous cesarean histories, MAP's impact on CD34+ cells[14] has not been demonstrated.[15] Also, there are not many articles on the effect of gestational diabetes mellitus (GDM) and gestational hypertension (GHT) diseases on the number of CD34+ cells in the umbilical cord blood, which are important diseases in obstetrics and gynecology practice.

The purpose of this study was to investigate the impact of GDM, GHT, and MAP on CD34+ cells count in umbilical cord blood, and additionally, to compare the Sysmex XN20, automated Hematology Analyzers to the gold standard test of Flow Cytometry in the context of these diseases.

Highlight

- CD34 + cells in the umbilical cord blood were significantly elevated in patients with gestational diabetes and gestational hypertension
- No change was observed in patients with morbidly adherent placenta

Materials and Method

Study Subject

Informed consent information was obtained from all pregnant women participating in the study and the research protocols were approved by the Ethics Committee at Erciyes University (Approval date/number: 2018/608). The study population consisted of 18 control pregnant without any underlying disease, 9 MAP, 13 GDM and 11 GHT patients. The delivery type of all of the people in the study is cesarean section. The diagnosis of GDM has been established according to the 75-gram oral glucose tolerance test of American Diabetes Association (ADA). The diagnosis of subtitles of gestational hypertension such as preeclampsia was made according to the American College of Obstetrics and Gynecology (ACOG). The clinical classification of the study population was shown in (**Table 1**).

Umbilical cord blood samples

This is an experimental study carried out on the umbilical cord blood sample which was collected in the delivery room in Gevher Nesibe Medical Faculty, Erciyes University. All blood samples were taken from the umbilical cord after delivery of newborn into EDTA anticoagulated blood tubes. Cord blood samples delivered to the laboratory within 24 hours were processed for mononuclear cell (MNC) isolation using a Ficoll-Paque Plus based on the manufacturer's instructions. After the procedure, the isolated cells were frozen until the sample collection was completed.

HPCs and CD34+ cells enumeration

Frozen PBMCs were resuspended in PBS (500 µl) and HPC was quantified via Sysmex XN20 (Sysmex

Table 1.
Descriptives of the clinical classification of the study population

	Control group (n=18)	GDM (n=13)		Gestational hypertension (n=11)		MAP (n=9)	
	Mean±SEM or N (%)	Mean±SEM or N (%)	p value	Mean±SEM or N (%)	p value	Mean±SEM or N (%)	p value
Maternal age (years)	30.70±1.438	33.64±1.527	0.3686	33.27±1.402	0.4778	33.70±1.274	0.3766
Gestational age (days)	269.9±1.442	263.4±2.129	0.0855	262.9±2.862	0.0601	249.8±2.843	<0.001*
Birth Weight (g)	3394±115.4	3281±158.9	0.9192	2800±203.6	0.0179*	2886±158.5	0.0602
Neonatal gender							
Male	10 (%50)	7 (58.3)	0.944	6 (%50)	>0.9999	8 (88.8)	0.1035
Female	10 (%50)	5 (41.7)		6 (%50)		1 (11.2)	
Birth type							
Vaginal	0 (%0)	0 (%0)		0 (%0)		0 (%0)	
C-section	20 (%100)	12 (%100)		12 (%100)		8 (%100)	

*; p<0.05. SEM; Standard Error of the Mean

Corporation, Tokyo, Japan). The number of HPCs were also quantified by Flow cytometry (FACSAriaIIII). The BD (Becton, Dickinson and Company San Jose, CA 95131 USA) Procount ™ Progenitor Cell Count Kit with PE Labeled monoclonal anti-CD34+ antibody was used to determine absolute numbers and percentages of CD34+ cells. Percentages and absolute numbers of CD34+ cells were analyzed by flow cytometry. Our gate strategy was shown in (**Figure 1A**).

Statistical Analysis

Descriptive analyzes were used for maternal age, gestational age, birth weight, neonatal gender, birth type in clinical classification. Absolute numbers and percentages of CD34+ cells and HPCs between groups were statistically evaluated using the One Way Anova test on Flow Cytometry and Sysmex XN20 analyzers, respectively. The relationship between Flow Cytometry and Sysmex XN20 was established with the Sperman Correlation test. All data were processed with Graphpad Prism version 8.4.2. P-value <0.05 was considered statistically in all analyzes.

Results

The classification of pregnant women and newborns included in the study and the relevant information regarding maternal age, gestational age, birth weight, gender, and type of birth are summarized in **Table 1**. All births that we have collected samples from were cesarean. All groups were similar in terms of maternal age and neonatal gender. Compared to the control group, in terms of gestational age and birth weight, significant results were detected. Gestational age was significantly shorter (?) in the MAP group (p=0.0179). The birth weight of infants was significantly lower (p<0,001) in the group of GHT.

MNCs obtained from umbilical cord blood were analyzed with stem cell markers of a hematopoietic precursor. First, CD34+ stem cell percentages were compared. There was no statistically significant difference across groups (**Figure 1B**). On the other hand, we observed a significant increase (p<0.05) in CD34+ cells count in the GHT and GDM groups compared to controls. The values of the MAP group and the control group were very close and it was not significant (**Figure 1B**). Lymphocyte numbers were also significantly elevated in the GHT and GDM groups compared to controls (p<0.05) (**Figure 1B**).

Next, we compared the CD34 staining results obtained from Sysmex XN20 (Automated Hematology Analyzers) to the result of flow cytometry. The HPCs count achieved from Sysmex XN20 were compared with the control group. Although no significant result was found in any disease group, we gained a trend similar to flow cytometry results. Importantly, we had a significant increase in the numbers of lymphocytes measured by Sysmex XN20 compared to the control group in the GHT group (p<0.05), similar to/just as flow cytometry analysis (**Figure 2**). The differences in the GDM and MAP groups were not significant. The numbers of CD34+ cells, measured by flow cytometry, and HPCs number were compared. There was a significant correlation between the HPC numbers of the control group and the number of CD34+ cells (p<0.01). The Spearman correlation coefficient between the two control groups was r: 0570. We did not observe a significant correlation between HPCs numbers and CD34+ cell numbers of disease groups of GHT, GDM, MAP. Spearman correlation coefficients and P values were r:0.5727/p:0.0708, r:0.2149/p:0.4779, r:0.111/p:0.779, respectively. Our results are shown in (**Figure 3**).

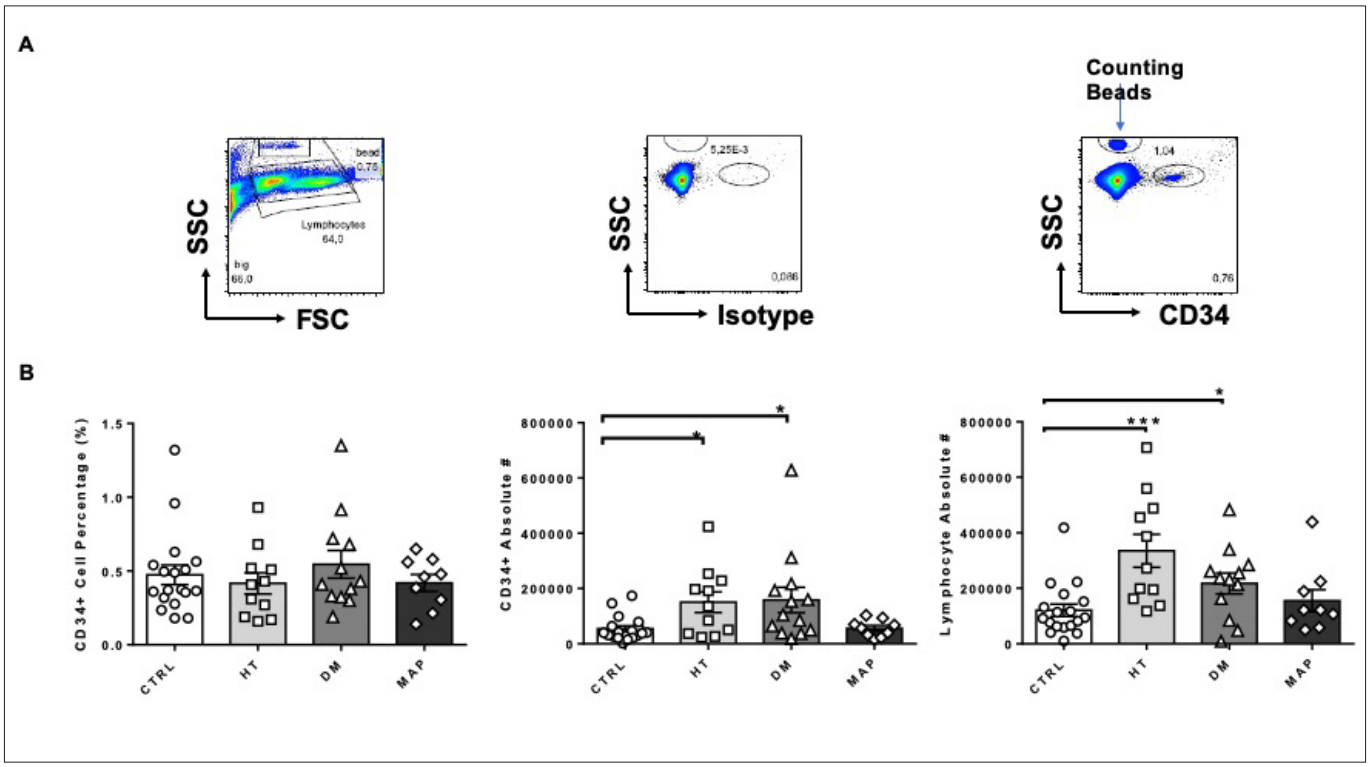

Figure 1. Levels of CD34 + cells and lymphocytes in control, Gestational hypertension, GDM and MAP groups; p>0.05; p<0.001

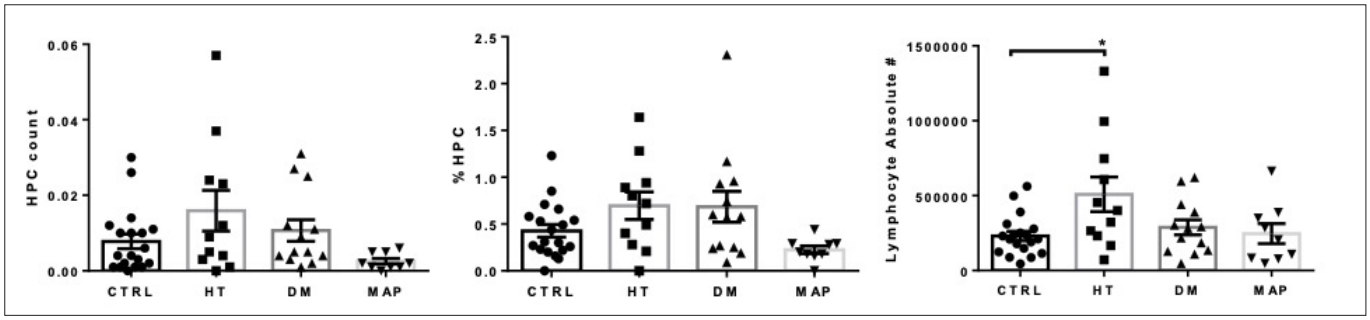

Figure 2. HPCs and lymphocyte level in Control, Gestational hypertension, GDM and MAP groups. p>0.05

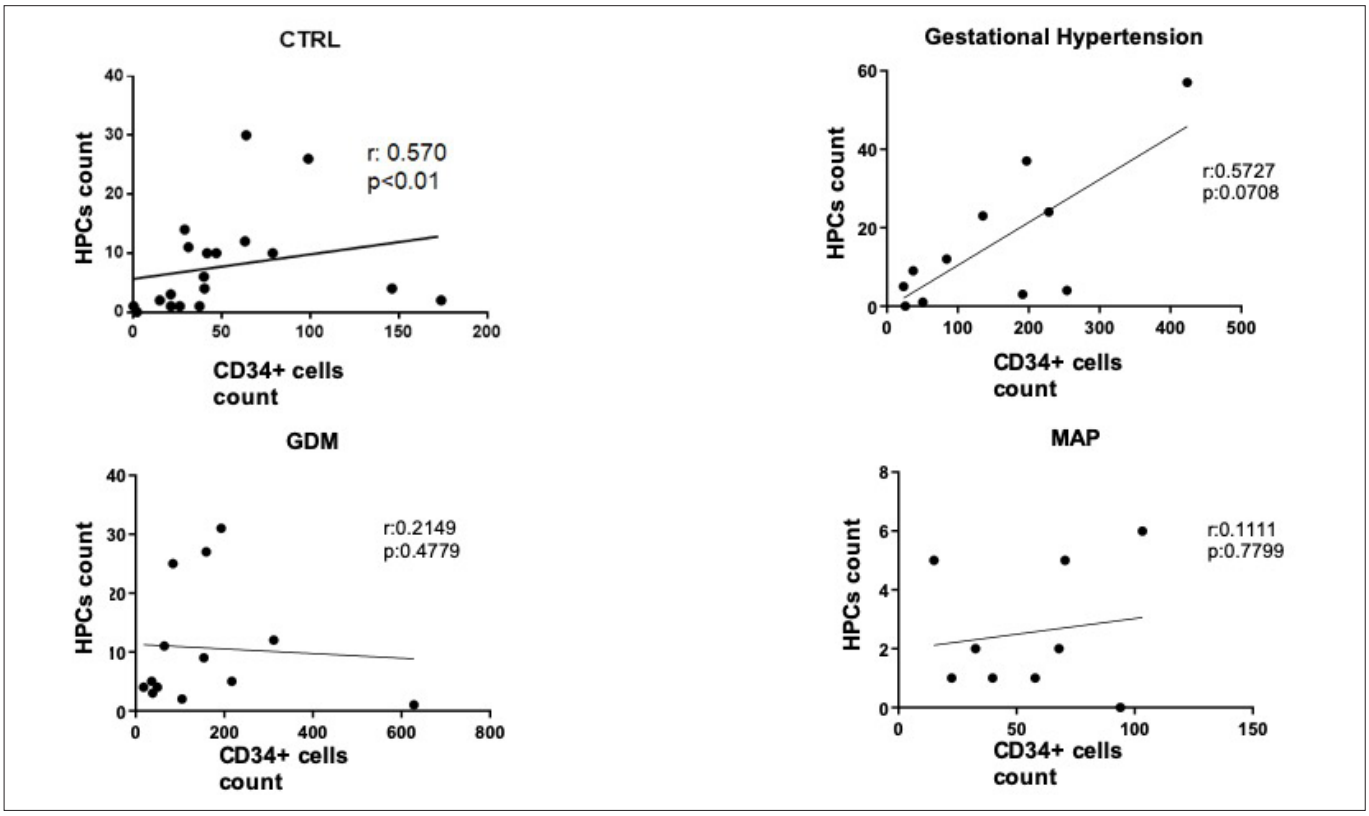

Figure 3. Correlation between HPCs and CD34 + cells. p>0.05 r;correlation coefficient

Discussion

In this study, the effects of GHT, GDM, MAP on CD34+ cell counts, and the correlation between Sysmex XN20 and flow cytometry results were investigated. CD34+ cell percentages between the groups were not statistically significant. However, the GDM and GHT groups had significantly increased CD34+ cells as well as lymphocyte numbers. For the control group, a significant correlation was confirmed between flow cytometry and Sysmex XN20 analysis, but the correlation coefficient was low (P<0.01, r:0.579). The correlation coefficients between Sysmex XN20 analysis and flow cytometry and of the remaining disease groups were poor (r:0.5727/ p:0.0708 for GHT, r:0.2149/p:0.4779 for GDM, r:0.111/p:0.779 for MAP).

As mentioned above, all samples were obtained from a C-section birth, gestational age was significantly shorter in the MAP group, and birth weight was significantly lower in the group of gestational hypertension. Lim et al.[17] and Dimitriou et al18 showed that type of birth had no significant effect on CD34+ cells in umbilical cord blood. Other studies state that cesarean deliveries have more CD34+ cell contents in the umbilical cord compared to vaginal delivery.[19,20] Al-Sweedan et al.[11] demonstrated normal vaginal delivery was associated with 0.18 times more yield of CD34+ cells compared to cesarean sections in the multivariate model. Cervera et al.[21] showed that there was not a significant relationship between CD34+ cell numbers and gestational age. Lin et al.[22] demonstrated elevated CD34+ cells content in premature babies. Ballen et al.[10] and other investigators [23-25] reported the opposite. Many of the previous reports revealed a positive correlation between birth weight and CD34+ cells count.[9-11,16] In light of divergent results from several studies, differences between groups should be taken into account when evaluating the results.

The increase of CD34+ cells in the preeclampsia by Benian et al.[26] and Al-Sweedan et al.[11] is in line with our results. However, in three previous studies, a decrease in the number of CD34+ cells in the preeclampsia group compared to the non-preeclampsia group was reported.[27-29] This difference may be due to our population size, which is less than two previous studies.

Alternatively, although our patient group has pathologies of the same origin, our GHT group includes six pregnancy hypertension and five preeclampsia patients.

Hadarits et al.[30] evaluated the cord blood of neonates born from mothers with GDM and the cord blood of neonates born from non-diabetic mothers. In concordance with our results, they noted that the neonates of gestational diabetic mothers had proportionally more CD34+ cells in cord blood compared to the control group. They also showed CD34+ cells were proportionally higher in the cord blood of neonates of diabetic mothers who were diet-regulated and insulin-regulated.

To our knowledge, This is the first study to investigate the effects of MAP on the number of CD34+ cells in umbilical cord blood. Our study population with MAP consists of placenta accreta, placenta percreta diseases. One reason we could not reach statistically significant results may be the limited size of our study groups. However, this does not lower the specificity of the study, and it guides the literature in the context of the effects of these diseases on CD34+ cell numbers and shows that further studies are needed to determine whether these patients will be good candidates for umbilical cord blood transplantation units. It is noteworthy that cesarean section birth rate is increasing and the incidence of these diseases increases with cesarean section.

In the literature, many publications were using HPCs data measured by the white precursor channel. Furundarena et al.[31] compared the flow cytometry and Sysmex XN analysis at different times in the autologous group as pre-apheresis, post apheresis, and a day before apheresis. Correlation coefficients were (r=.9775), (r=.9285) (r=.5744), respectively. The most familiar to our results is the day before the apheresis. Park et al.[32] in the study conducted in 31 patients with stem cell transplantation, the correlation coefficient between Sysmex XN and flow cytometry was found (γ= 0.548), (γ=0.652) concerning to the percentage and numbers of CD34+ cells, respectively. These results resemble our findings, thus showed a weak correlation. Additionally, Tanosaki et al.[33] showed that there is a strong correlation between HPCs and CD34+ cells in pre-apheresis (R2=0.919) peripheral blood samples and apheresis products (P=0.729). One reason that the correlation coefficient revealed in the above-mentioned publications is higher than our results may be the use of mobilizing agents to increase stem cell production from peripheral blood. Increased number of stem cells in the peripheral blood may help to obtain better correlation. Other reasons may be that our sample population is less than other studies, or that PBMCs isolated from blood are analyzed on the Sysmex XN20 instead of a blood sample directly. Besides, no study comparing flow cytometry analysis with Symex XN20 in the GHT, GDM, and MAP disease group have been published. One of the biggest reasons for not achieving an adequate correlation between the flow and Sysmex results in the disease groups is that our patient population is small, but our study still proves that disease groups with a larger population are needed to understand whether Symex XN20 is a good candidate to demonstrate the content of umbilical cord blood.

Conclusion

While gestational diabetes and gestational hypertension had a positive effect on CD34+ cells in umbilical cord blood, no change was observed in the MAP group examined by us for the first time, in future studies, especially the MAP group population should be expanded. Correlation between flow cytometry and Sysmex XN 20 is low based on is of diseases and it is needed to be studied in larger groups.

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Ethics Committee Approval: The Ethical Committee of Erciyes University, Faculty of Medicine , approved this study (Number: 2018/608).

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Author Contributions: EMT wrote the manuscript. EU, MSK, AE designed the study. EMT, SE, AB, FZO, AO performed experiments. SZU and MSK provided patient samples. All authors read, revised the manuscript. AO and EU provided funding.

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Does Clarithromycin Use in Acute Viral Bronchiolitis Shorten Length of Hospital Stay?

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Abstract

Acute bronchiolitis is the most common cause of hospitalization among infants. Although antibiotics are not recommended in the absence of secondary bacterial infection, rates of antibiotic usage is high rate in clinical practicesTo test the hypothesis that clarithromycin use in infants with acute viral bronchiolitis shortens length of hospital stay.One hundred sixty-seven patients aged 1-24 months hospitalized for treatment with a diagnosis of acute viral bronchiolitis at pediatric clinic between April 2017 and May 2018 were investigated retrospectively. The patients were divided into two separate groups, Group A (122 patients), using clarithromycin therapy during hospitalization, and Group B (45 patients), which did not receive clarithromycin (Group B). Demographic and clinical data, treatments received, and duration of hospital stay were obtained from patients' records.The rate of clarithromycin use in this study was 73%. No statistically significant difference in length of hospital stay was determined between patients receiving clarithromycin and those receiving no antibiotic therapy. However, length of hospital stay decreased with age. Clarithromycin use elicited no statistically significant decrease in hospital stay in patients with acute viral bronchiolitis.The routine use of clarithromycin is not recommended in acute viral bronchiolitis in the light of its cost and side-effects, and the fact is has no impact on clinical status and hospital stay.

Keywords: Acute bronchiolitis, infant, clarithromycin

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Introduction

Bronchiolitis is a severe, life-threatening lower respiratory tract infection generally affecting infants.[1,2] Acute bronchiolitis is the most common cause of hospitalization among infants younger than six months.[3] The most common agent is respiratory syncytial virus (RSV).[4] It can also be caused by rhinoviruses, influenza virus, parainfluenza viruses, coronaviruses, metapneumovirus, and rarely by other respiratory tract viruses. Antibiotics are not recommended in the absence of secondary bacterial infection.[5,6] However, antibiotic use rates of 34-99% are reported even in non-complicated acute bronchiolitis. Antibiotic use rates of 34%, 45% and 99% have been reported in hospitalized infants who do not need mechanical ventilator support.[7-10] One outpatient clinic study reported that antibiotics were used by 53% of children with bronchiolitis.[11]

Highlight

- Antibiotic use rates of 34-99% are reported even in non-complicated acute bronchiolitis.
- Clarithromycin use elicited no statistically significant decrease in hospital stay in patients with acute viral bronchiolitis.
- The routine use of clarithromycin is not recommended in acute viral bronchiolitis.

Reported outcomes of the use of antibiotics in acute viral bronchiolitis in previous studies include no significant difference in severity of symptoms (decreased respiratory difficulty, feeding difficulty, and respiration rate, or restoration of social smiling), no statistically significant difference in terms of mean length of hospital stay, and no acceleration of healing, while unnecessary antibiotic use was also described as a financial burden leading to iatrogenic side-effects and resistant micro-organisms.[12-15] However, one study reported significant decreases in oxygen and intravenous fluid support requirements in patients receiving clarithromycin compared to placebo. The duration of beta-2 agonist use was also shorter in the clarithromycin group, and repeat hospitalization rates were lower.[16]

This study determined the incidence of clarithromycin use in acute viral bronchiolitis and compared patients using clarithromycin with those not receiving it in terms of duration of hospitalization.

Materials and Methods

Patients with a diagnosis of acute viral bronchiolitis at pediatric clinic between April 2017 and May 2018 were investigated retrospectively. Demographic and clinical data, treatments received, and duration of hospital stay were obtained from patients' records. One hundred sixty-seven patients aged 1-24 months, diagnosed with acute viral bronchiolitis on the basis of clinical and physical examination findings (history of fever, nasal discharge, cough, respiratory difficulty, and feeding difficulty, and presence of tachypnea, tachycardia, and rhonchi at physical examination), laboratuar findings and if necessary chest Xray, hospitalized. Patients who received inhaler beta 2 agonists, intravenous (IV) fluid support, and inhaler or oral steroid therapy, and with no chronic disease were included in the study. Acute bronchiolitis classified mild, moderate and severe.[17] All patients were selected from among subjects recorded as having mild-moderate acute viral bronchiolitis. Patients with chronic heart disease, asthma, pneumonia, cystic fibrosis, or prematurity-related bronchopulmonary dysplasia, or aged over two years or under one month were excluded.

No mechanical ventilator or advanced oxygen support were required. Oxygen saturations were measured using pulse oximetry. Patients discharged in a healthy condition were enrolled.

The patients were divided into two groups. Group A, using clarithromycin therapy during hospitalization, and Group B, which did not receive clarithromycin. Two groups were first established on the basis of clarithromycin use (yes/no).

Ethical Committee Approval

Approval for the study was granted by Trabzon Kanuni Education And Research Hospital Ethical Committee (No:2018/07).

Statistical analysis

Univariate associations between medication use and patient characteristics were assessed using the Mann-Whitney U or chi-square tests, based on the structure of the data. A Poisson regression model was then applied to compare the predictive ability of medication use on length of stay in hospital, after adjusting for age, gender and season. Poisson regression is appropriate when the dependent variable consists of numerical data (e.g. length of stay). The analyses were performed using the Statistical Package for Social Sciences 25.0 for Windows (SPSS Inc., Chicago, Illinois, USA). The results were assessed at a level of $p < 0.05$ significance.

Results

Boys constituted 99 (59.2%) of our patients and girls 68 (40.8%). The patients were divided into two separate groups, Group A (122 patients), using clarithromycin therapy during hospitalization, and Group B (45 patients), which did not receive clarithromycin (Group B). Mean age for Group A was 12.6±6.6 months and 13.3±5.0 months for Group B. Mean length of hospital stay was 4.2±2.4 days for Group A and 4.3± 2.1 days for Group B. The rate of clarithromycin use in this study was 73%. Seventy-three percent of one hundred sixty-seven patients with acute viral bronchiolitis, aged 1-24 months and admitted to hospital, were started on clarithromycin therapy. Univariate analysis was used to identify any significant relation between clarithromycin use and patient characteristics [length of hospital stay (days), age (months), gender, season] (**Table**). No statistically significant difference was determined in terms of length of hospital stay between patients using clarithromycin and those using no antibiotic. We revealed no significant relation between clarithromycin use and patient characteristics. Medication use was not a statistically significant predictor of the length of hospital

stay. Neither gender nor season exhibited statistically significant correlation with length of hospital stay.

Table.
Univariate Analysis of Clarithromycin Use and Patient Characteristics

	Clarithromycin		
Patient characteristics	**No (n=45) B**	**Yes (n=122) A**	**p**
Length of stay (days)			0.387
Mean (SD)	4.3± 2.1	4.2±2.4	
Median(IQR)	4.0±2.5	3.0±2.0	
Age (months)			0.302
Mean (SD)	13.3± 5.0	12.6±6.6	
Median(IQR)	13.0± 6.0	12.0± 9.3	
Gender, n (%)			0.410
Female	16 (35.6)	52 (42.6)	
Male	29 (64.4)	70 (57.4)	
Season, n(%)			0.283
Spring	5 (11.1)	7 (5.7)	
Summer	2 (4.4)	12 (9.8)	
Fall	23 (51.1)	51 (41.8)	
Winter	15 (33.3)	52 (42.6)	

Continuous variables are expressed as mean±standard deviation and median±interquartile range, and groups were compared using the Mann Whitney U test. Categorical variables were expressed as frequency (percentage) and were compared using the chi-square test.

Multivariate analysis using Poisson regression was used to determine whether clarithromycin use is a statistically significant predictor of length of hospital stay. Neither gender nor season was correlated with length of stay. However, age had a significant effect on length of hospital stay. We observed a 2.1% decrease in length of hospital stay for each increasing month of age (p=0.001, 95 CI% for eβ : 0.966, 0.991).

Discussion

Several retrospective and prospective studies comparing patients with acute viral bronchiolitis using antibiotics such as azithromycin, clarithromycin, erythromycin, and ampicillin with patients not using antibiotics have shown that antibiotic use makes no positive contribution to clinical improvement or length of hospitalization.

Pinto LA, et al. compared azithromycin and placebo in 184 infants and reported that azithromycin had no effect on clinical improvement or length of hospital stay in patients with acute bronchiolitis. Routine use is not recommended in patients with acute bronchiolitis since this can cause drug resistance.[18] In agreement with that study, clarithromycin did not affect length of hospitalization in patients with acute viral bronchiolitis in our study.

In a study of 52 infants, Field et al.[12] observed no difference in terms of severity of symptoms between patients using ampicillin and those using placebo. They concluded that antibiotic use did not accelerate healing, and also emphasized that unnecessary antibiotic use resulted in cost problems, iatrogenic side-effects and resistant micro-organisms. Similarly, we observed that clarithromycin made no positive contribution to patients' clinical status and had no effect on length of hospital stay.

Kneyber et al.[13] reported that approximately half of 71 infants hospitalized due to RSV bronchiolitis received parenteral antibiotic therapy but that antibiotic use did not shorten length of stay in mild or moderate RSV bronchiolitis. No statistically significant difference was observed in mean length of hospital stay between patients using azithromycin and those using placebo. We also observed no decrease in mean length of hospital stay with oral/iv clarithromycin use in our study of 167 patients with mild and moderate acute viral bronchiolitis.

In their randomized controlled study of 126 patients aged 1-2 months and hospitalized with viral bronchiolitis, Mazumder et al.[14] divided their subjects into three groups – receiving IV ampicillin, oral erythromycin, or no antibiotics. No significant difference was observed between these three groups in terms of clinical findings (decreased respiratory difficulty, feeding difficulty, and respiration rate, and return of social smiling). Kabir et al.[15] compared three groups using parenteral ampicillin, oral erythromycin, and receiving no antibiotics. They also determined to difference in terms of clinical outcomes and lengths of hospital stay. Hamid et al.[19] examined 100 patients with acute viral bronchiolitis in a retrospective study. No positive contribution to healing at clinical follow-up or significantly significant difference in length of hospital stay was observed between the group using iv or oral antibiotics and the no antibiotic group. McCallum et al.[20] compared patients receiving a single dose of azithromycin with a placebo group, and determined no significant variation in patients' clinical improvement or length of stay at hospital. Our findings were compatible with those of these previous studies.

In a letter to a medical journal, McCallum et al.[21] reviewed seven different studies and suggested that prospective studies examining the relation between acute viral bronchiolitis and macrolide use in infants were henceforth unnecessary. However, we think that retrospective studies are still needed in order to emphasize that macrolides or other antibiotics are not required in acute viral bronchiolitis.

Only one study reported positive effects of clarithromycin in acute RSV bronchiolitis. In a study of 21 patients with RSV bronchiolitis published in 2007, this study reported that lower oxygen and intravenous fluid support requirements in patients receiving clarithromycin compared to placebo.[16] In this study also reported shorter beta-2 agonist use in the clarithromycin group, together with a lower repeat hospitalization rate. However, that study was limited by its low patient numbers. In our study, the agents involved in acute viral bronchiolitis were unknown, and clarithromycin had no effects on length of hospitalization.

The rate of clarithromycin use among patients hospitalized with a diagnosis of acute viral bronchiolitis in our study was quite high, at 73%. In agreement with most studies in the literature, we determined that clarithromycin did not shorten length of hospital stay compared to patients not receiving it. Despite the many studies showing no benefit from clarithromycin, it continues to be widely used, particularly in developing countries. The reasons for overprescription of antibiotics

by physicians include concerns over the risk of not using them, variations in culture and therapeutic customs, patient expectations, and health policies. In the light of costs, antibiotic resistance, potential side-effects, and the fact that clarithromycin makes no positive contribution to the disease, its use in acute viral bronchiolitis is not recommended.

Acute viral bronchiolitis in this study was diagnosed on the basis of clinical findings. The limitations of the study include the fact that information was obtained retrospectively from patient records. However, the statistically adequate patient numbers in our study represent a particular advantage.

Conclusion

The widespread use of clarithromycin in acute viral bronchiolitis is of no benefit to the patients, and results in increased costs, antibiotic resistance, and undesirable side-effects. This is a problem to which a solution needs to be found, particularly in developing countries.

Ethics Committee Approval: The Ethical Committee of Erciyes University, Faculty of Medicine, approved this study (Number: 2018/07).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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Peripheral Lymphadenopathies in Childhood: Experience at a Pediatric Oncology Department in Turkey

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Abstract

Palpable lymph nodes are very common physical examination findings in childhood, and sometimes it can be challenging to say if it is benign or malignant.This retrospective study evaluated 157 children admitted to an oncology department because of lymphadenopathy and aimed to determine the clinical, laboratory, and epidemiologic data valuable for differential diagnosis.One hundred fifty-two cases were analyzed, which were defined as either malignant or benign by the etiology. The benign cases were also defined to three groups as ‘viral lymphadenopathy’, ‘bacterial lymphadenopathy’, and ‘other reactive lymphadenopathy’.A specific cause for lymphadenopathy was documented in 61 (40,1%) cases. Of 152 cases, benign causes were detected in 133 (87,5%), and malignant causes were detected in 19 (12,5%) cases. The most frequent cause in the benign group was reactive hyperplasia (59,8%) and in the malignant group was lymphoma (7,3%). A biopsy was performed from 19 of the cases for diagnosis. Malign causes were detected in 12 (58%), and benign causes were detected in the remaining 7 (42%). In terms of differential diagnosis, some symptoms, physical findings, and laboratory tests showed meaningful differences between the case groupsThe following findings were determined as being important to alert physicians about the probability of a malignant disorder: location of lymphadenopathy, number of associated systemic symptoms, size of lymph node, abnormal laboratory findings, abnormal chest X-ray.

Keywords: Childhood, etiology, lymph node, lymphoma, peripheral lymphadenopathy

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Introduction

Peripheral lymphadenopathy (LAP) is a frequently encountered physical finding in childhood. A palpable lymph node on physical examination poses a distressing situation for both the parents and the physician following the child. This study aims to determine the epidemiologic properties, clinical and laboratory findings, and etiologic distribution of patients with peripheral lymphadenopathy. These findings are featured in different case groups.

Highlight

- Lymphadenopathy in children is common and in the majority of cases are benign.
- It should be a sign of a serious disease.
- An appropriate history and examination, careful observation and appropriate investigations should help to decide which children require a biopsy or further treatment.

Materials and Methods

Informed consent information was obtained from all parents of participating childen in the study and the research protocols were approved by the Ethics Committee at Ankara University (Approval date/number: 08 June 2015/10-419-15). The cases that applied to the departments of pediatric oncology of the Medical Faculty of Ankara University between January 2013 and January 2015 were evaluated. The epidemiologic properties, clinical and laboratory findings of the cases were assessed retrospectively. The cases were defined as either malignant or benign by the etiology. The benign cases were also defined to three groups as 'viral lymphadenopathy', 'bacterial lymphadenopathy' and 'other reactive lymphadenopathiy'. Patients who had upper respiratory tract infection findings and had no antibiotic response or had a viral infection diagnose with serological tests were included in the viral lymphadenopathy case group. Patients who had an antibiotic response had group A β-hemolytic streptococcus (GAS) infection and had lymphadenitis according to the biopsy results in the bacterial lymphadenopathy case group. Patients with no systemic symptoms except for lymphadenopathy and had no antibiotic response were diagnosed with biopsy as reactive hyperplasias. They were included in the other reactive lymphadenopathy case group.

Lymph node enlargements were classified according to the size, extension, and duration of the LAP according to the following criteria:

- Size of lymp node: <1 cm, 1-3 cm, >3 cm
- Extention of the lymph nodes: localized LAP (a single or multiple but adjacent lymph node involvement) and generalized LAP (two or more lymph node involvement without neighborliness)
- Duration of lymph node enlargement: acute (<4 weeks) and chronic (≥4 weeks)

Patients who had a lymph node biopsy were also classified into the early biopsy group (went to biopsy within the first two weeks after its presentation) and late biopsy group (after the first two weeks of presentation). LAP features like size, location, extension, duration, mobility were evaluated. Other physical examinations and laboratory findings, radiological tests, and biopsy results were compared between the case groups. The data were analyzed by using the Statistical Package fort he Social Sciences Software Package (SPSS) (version 11.5). Comparisons between groups were made using appropriate statistical methods (Pearson chi-square and Student's T-test). A p-value of less than 0,05 was considered significant.

Results

Epidemiologic and clinical data of 157 cases were evaluated. Lymphadenopathy-like mass was detected in 5 cases after the examination, and they were excluded from the study, which was a dermoid cyst, cystic hygroma, inguinal hernia, focal fat necrosis, and fibroma. The data of the remaining 152 cases were analyzed. The cases were defined as either malignant or benign by the etiology. The benign cases were also defined to three groups as 'viral lymphadenopathy', 'bacterial lymphadenopathy', and 'other reactive lymphadenopathy'. The classification of the case groups according to the definitive diagnosis is shown in **Table 1**.

Table 1.
The classification of the case groups according to the definitive diagnosis

Biopsy results	n	%
Granulamatous infection	2	10.5
Chronic lymphadenitis	1	5.2
Kikuchi disease	1	5.2
Reaktive hyperplasia	2	10.5
Florid follicular hyperplasia	1	5.2
Salivary gland	1	5.3
Hodgkin lympoma	8	42.3
Non Hodgkin lymphoma	3	15.7
Total	19	100.0

Of 152 cases, when 5 cases admitted with a lymphadenopathy-like mass were excluded, 133 cases (87.5%) were diagnosed with lymphadenopathy due to benign etiology. Malignant causes were detected in 19 cases (12.5%). No specific etiology was found in 91 patients (59.8%), and specific etiology was found in 61 (40.1%). Of all groups, 58 (38,2%) children were female, and 94 (62,8%) children were male. The male gender was dominant in both malignant and benign subgroups. The average age of the patients was 6,48±4,39 years; it was 8,85±5,89 years in the malignant group and 6,13±4,05 years in the benign group. The benign subgroups' average ages were similar to each other. There is no malignant lymphadenopathy between 0-2 years old, and for four groups, most cases were between 2-12 years old. 12-18 years old cases dominated malignant lymphadenopathies. Detailed information is given in **Table 2**.

Table 2.
Gender and age range of case groups

Physical examination/ laboratory findings	Viral	Bacterial	Other	Benign	Malignant	Total	p*	p**
	n (54) %	n(40) %	n (39) %	n (133) %	n (19) %	n (152) %		
Dispnea	1 1.9	0 0.0	0 0.0	1 0.8	4 21.1	5 3.3	<0.01	<0.01
Hepatomegaly	8 14.8	5 12.5	1 2.6	14 10.5	10 52.6	24 15.8	<0.01	<0.01
Splenomegaly	7 13.0	2 5.0	0 0.0	9 6.8	9 47.4	18 11.8	<0.01	<0.01
Anemia	2 3.7	3 7.5	2 5.1	7 5.3	13 68.4	20 13.2	<0.01	<0.01
Leukopenia	3 5.6	2 5.0	2 5.1	7 5.3	3 15.8	10 6.6	<0.01	0.003
Leukositosis	6 11.1	1 2.5	1 2.6	8 6.0	6 31.6	14 9.2	<0.01	0.003
Trombositopenia	0 0.0	1 2.5	0 0.0	1 0.8	6 31.6	7 4.6	<0.01	<0.01
Trombositosis	2 3.7	3 7.5	1 2.6	6 4.5	3 15.8	9 5.9	<0.01	<0.01
Atipic +virocit + downey	6 11.1	5 12.5	6 15.3	17 12.7	0 0.0	17 11.1	<0.01	<0.01
Blast	0 0.0	0 0.0	0 0.0	0 0.0	9 47.4	9 5.9	<0.01	<0.01
ESR> 20 mm/sa	19 35.2	14 35.0	9 23.1	42 31.6	16 84.2	58 38.2	<0.01	<0.01
CRP> 3 mg/L	15 27.8	10 25.0	7 18.4	32 24.2	14 73.7	46 30.5	<0.01	<0.01
ALT >41 IU/L	6 11.1	2 5.1	2 5.1	10 7.6	0 0.0	10 6.6	0.214	0.336
AST >45 IU/L	9 16.7	4 10.0	5 12.8	18 13.5	4 21.1	22 14.5	0.384	0.658
LDH> 200 IU/L	39 72.2	21 52.5	17 43.6	77 57.9	16 84.2	93 61.2	0.028	0.004

p*: Evaluation of benign-malignant lymphadenopathies
p**: Evaluation of viral-bacterial-other reactive hyperplasia-malign lymphadenopathies

Some systemic symptoms, pathologic physical examination findings, and characteristics of lymphadenopathies are given in **Table 3**. Most of the patients (82.8%) have to swell in the neck. The acute process was typical in viral cases; bacterial cases and other reactive groups were mostly chronic. No significant difference was detected in terms of duration between malignant and benign cases. Seventy-five (49.3%) patients had upper respiratory tract infection, and it was the most common examination finding for all groups, followed by fever. Fever ($p<0.01$), weight loss ($p<0,05$), skin eruption ($p<0.01$), leg pain ($p<0.01$), abdominal swelling ($p<0.01$) were statistically significant findings as well as in comparing the four groups and the comparison of the benign-malignant groups. The presence of systemic symptoms ($p<0.01$), upper respiratory tract infection ($p<0.01$) were significant findings only in benign and malignant comparison. Also, the malign cases had an increasing number of symptoms.

Of 152 cases, 47 (%30.9) of them had recurrent infection stories, 34 (22.4%) of them had a chronic disease, and 3 (2%) patients had a vaccination story. Chronic diseases included asthma (9), adenoid hypertrophy (12), hypochondroplasia (1), Kawasaki disease (1), Hashimoto thyroiditis (4), familial mediterranean fever (1), psoriasis (1), chronic kidney failure (1), ataxia-telangiectasia (1), and allergic rhinitis (2). Bilateral cervical lymphadenopathy (59,5%) was the most frequent generalized lymphadenopathy type. Cervical+inguinale (20.6%) and cervical+axillar+inguinale (7.6%) followed that. 101 (66.4%) patients had cervical lymphadenopathy. This was the most common area for all case groups. Of 5 supraclavicular nodes, 4 of them were malignant. The mean diameter of the malign lymph nodes was 3.29±2.18 cm (cervical: 3.3±2.2 cm, axillar: 2.2±2.1 cm, inguinal: 0.6±0.3). In the benign group, the mean diameter of the lymph nodes was 1.63±1.07 cm (cervical: 1.6±1.02 cm, axillar: 1.1±1.1 cm, inguinal: 0.5±0.3 cm). Malign lymph nodes were bigger than benign lymph nodes. 47.4% of the malignant lymph nodes were fixed, and 95.5% of the benign lymph nodes were mobile and this was statistically significant ($p<0.01$).

Table 3.
Some systemic symptoms and characteristics of lymphadenopaties

		Viral	Bacterial	Other	Benign	Malignant	Total	p*	p**
		n (54) %	n (40) %	n (39) %	n (133) %	n (19) %	n (152) %		
Duration	Acute	32 59.3	15 37.5	16 41	63 47.3	9 47.4	72 47.4	0.158	0.154
	Chronic	22 40.7	25 62.5	23 59.0	70 52.7	10 52.6	80 52.6		
Systemic symptoms	Have a symptom	42 77.8	28 70.0	7 17.9	77 57.9	15 78.9	92 60.5	0.079	<0.01
	Fever	12 22.2	10 25.0	1 2.6	23 17.3	10 52.6	33 21.7	<0.01	<0.01
	Weight loss	2 3.7	4 10.0	2 5.1	8 6	5 26.3	13 8.6	0.003	0.019
	Night sweat	1 1.9	4 10.0	3 7.7	8 6.0	4 21.1	12 7.9	0.023	0.058
	Flu symptoms	40 74.0	23 57.5	1 2.5	64 48.1	11 57.9	75 49.3	0.425	<0.01
	Itching	3 5.6	0 0.0	3 7.7	6 4.5	0 0.0	6 3.9	0.345	0.237
	Skin eruption	3 5.6	0 0.0	0 0.0	3 2.3	6 31.6	9 5.9	<0.01	<0.01
	Tooth decay	8 14.8	8 20.0	5 12.8	21 15.8	1 5.3	22 14.5	0.223	0.497
	Leg pain	0 0.0	0 0.0	0 0.0	0 0.0	2 10.5	2 1.3	<0.01	0.003
	Abdominal swelling	0 0.0	0 0.0	0 0.0	0 0.0	2 10.5	2 1.3	<0.01	0.003
Number of symptoms	No symptom	12 22.2	12 30.0	32 82.1	56 42.1	4 21.1	60 39.5	<0.01	<0.01
	+1 symptom	28 51.9	19 47.5	4 10.3	51 38.3	5 26.3	56 36.8		
	+2 symptom	11 20.4	7 17.5	1 2.6	19 14.3	0 0.0	19 12.5		
	+3 symptom	3 5.6	0 0.0	2 5.1	5 3.8	5 26.3	10 6.6		
	>3 symptom	0 0.0	2 5.0	0 0.0	5 3.8	5 26.3	10 6.6		
Extension	Localizated	6 11.1	4 10	8 20.5	17 12.8	4 21.1	22 14.4	0.584	0.354
	Generalizated	48 88.9	36 90.0	31 79.5	115 86.5	15 78.9	130 85.5		
Localization	Preairucular	0 0.0	0 0.0	1 2.6	1 0.8	0 0.0	1 0.7	0.705	0.405
	Postairicular	0 0.0	0 0.0	3 7.7	3 2.3	1 5.3	4 2.6	0.444	0.073
	Submental	1 1.9	0 0.0	1 2.6	2 1.5	0 0.0	2 1.3	0.591	0.712
	Submandibular	34 63.0	27 67.5	15 38.5	76 57.1	4 21.1	80 52.6	0.030	0.010
	Cervical	39 72.2	25 62.5	23 59.0	87 65.4	14 73.7	101 66.4	0.475	0.473
	Supraclavicular	0 0.0	0 0.0	1 2.6	1 0.8	4 21.1	5 3.3	<0.01	<0.01
	Axillar	9 16.7	3 7.5	7 17.9	19 14.3	6 31.6	25 16.4	0.057	0.135
	İnguinal	14 25.9	8 20.0	14 35.9	36 27.1	7 36.8	43 28.3	0.376	0.347
Size	<1 cm	9 16.7	3 7.5	12 30.8	24 18	6 31.6	30 19.7	<0.01	<0.01
	1-3 cm	41 75.9	35 87.5	26 66.7	102 76.7	2 10.5	104 68.4		
	>3 cm	4 7.4	2 5.0	1 2.6	7 5.3	11 57.9	18 11.8		
Mobility	Fixed	1 1.9	3 7.7	2 5.1	6 4.5	9 47.4	15 9.9	<0.01	<0.01
	Mobile	53 98.1	37 92.5	37 94.9	127 95.5	10 52.6	137 90.1		

p*: Evaluation of benign-malignant lymphadenopathies
p**: Evaluation of viral-bacterial-other reactive hyperplasia-malign lymphadenopathies

The diagnostic tests and abnormal physical examination findings are given in **Table 4**, comparing data between the case groups. Dyspnea, hepatomegaly, splenomegaly, anemia, leukopenia, leukocytosis, thrombocytopenia, thrombosis, atypical lymphocytes, virocytes, Downey cells or blasts in peripheric blood smear, elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels were significant findings as well as in comparing the four groups and the comparison of the benign-malignant groups. Anemia (13.2%) was the most common abnormal CBC result. Not only anemia but also other pathological CBC results and elevated ESR, CRP, LDH levels were significant in malignant cases. Elevated LDH levels were also significant in viral LAPs. Also, elevated lactate dehydrogenase (LDH) enzyme level was significant at the benign and malignant comparison. Elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels have seen mostly malignant and viral lymphadenopathies. We performed an excisional biopsy to 19 (12.5%) patients; 15 (78.9%) of them were early biopsy. Nine (81.8%) cases who underwent early biopsy had been diagnosed as having a malignant disorder. Histopathologic examination showed 11 lymph nodes were lymphoma, 2 of them granulomatous infection, one chronic lymphadenitis, 1 Kikuchi disease, two nonspecific reactive hyperplasias florid follicular hyperplasia, one salivary gland. Bone marrow aspiration was performed in 28 cases, and 35.7% of them was diagnosed as a malignant disorder. All cases had a chest X-ray; 6 (3.9%) patients had mediastinal adenopathy, and 5 of those patients were diagnosed with malignancy. 58 (39.2%) had abdominal ultrasonography (USG); it resulted as normal (51.7%), splenomegaly (10.3%), hepatomegaly (8.6%), hepatosplenomegaly (8.6%), mesenteric lymphadenitis (13.8%), hypoechoic lesion in spleen (3.4%), hypoechoic lesion in liver (1.7%). Three patients who had a hypoechoic lesion in the spleen or liver received the diagnosis of malignant. Superficial USG was performed in 101 (71.1%) patients; it resulted as reactive lymphadenopathy (92%), suspicious for malignancy (4%), granulomatous infection (1%), lymphadenitis (2%), solid mass (1%). Of 4 suspicious for malignancy cases according to USG, 2 of them were Hodgkin lymphoma, one patient had reactive hyperplasia, and one patient had a GAS infection. Ectopic sinüs was found in two patients, and a colloid cyst of the thyroid was found in two patients in addition to lymphadenopathy.

Table 4.
Physical examination and laboratory findings

		Diagnosis	n	%
Malignant		ALL	7	4.6
		Hodgkin lymphoma	8	5.3
		nonHodgkin lymphoma	3	2.0
		AML	1	0.7
		Group total	**19**	**12.5**
Benign	Viral lymphadenopaties	Viral reactive hyperplasia	30	19.7
		EBV	18	11.8
		CMV	6	3.9
		Group total	**54**	**35.5**
	Bacterial lymphadenopaties	Bacterial reactive hyperplasia	25	16.4
		GAS	6	3.9
		Acute lymphadenitis	6	3.9
		Chronic lymphadenitis	1	0.7
		Granulomatous lymphadenitis	2	1.3
		Group total	**40**	**26.2**
	Other reactive lymphadenopaties	Nonspesific reactive hyperplasia	35	23.0
		Florid follicular hyperplasia	1	0.7
		Kikuchi disease	1	0.7
		Toxoplasma infection	1	0.7
		Scabies	1	0.7
		Group total	39	25.8
		Total	**152**	**100**

Table 5.
Biopsy results

		Viral	Bacterial	Other	Benign	Malignant	Total	p*	p**
		n (54) %	n (40) %	n (39) %	n (133) %	n (19) %	n (152) %		
Gender	Male	16 39.6	15 37.5	19 48.7	50 37.6	8 42.1	58 38.2	0.444	0.303
	Female	38 70.4	25 62.5	20 51.5	83 62.4	11 57.9	94 61.8		
Age	0-2 years	6 11.1	5 12.5	9 23.1	20 15	0 0	50 32.9	0.010	0.040
	2-12 years	44 81.4	30 75	26 66.7	100 75.2	13 68.4	64 42.1		
	12-18 years	4 7.4	5 12.5	4 10.3	13 9.8	6 31.6	38 25.0		

p*:Evaluation of benign-malignant lymphadenopaties
p**: Evaluation of viral-bacterial-other reactive hyperplasia-malign lymphadenopaties

Discussion

Palpable lymph nodes are common physical examination findings in childhood. That usually causes anxiety for parents. Finding and understanding the cause of the lymphadenopathy is also important for clinicians. A good anamnesis and physical examination occur the basis of the diagnosis. The laboratory tests and radiological imaging methods can be used if necessary.

In our study, lymphadenopathy like mass was detected 5 cases after the examination; these were dermoid cyst, cystic hygroma, inguinal hernia, focal fat necrosis, and fibroma, and there is no dominancy between the masses. Yarıs *et al.* studied 126 lymphadenopathy cases, and 28 (22%) of them were lymphadenopathy like mass, and lymphangioma was the most common one(21.4%).[1] Taiseer evaluated 2063 children with neck masses, and 252 (12%) of them were congenital neck masses, which were mostly thyroglossal cysts (53%).[2] Finally, the data of the remaining 152 cases were analyzed. 87.5% were benign, and 12.5% were malignant LAPs. In 61 patients (40.1%), we found a specific etiology, 19 cases were malignant disorder, 41 cases had infectious causes, and one patient was Kikuchi disease. The most frequently seen malignant disease was Hodgkin lymphoma (5.3%). If there is no inflammation story, negative laboratory tests, progressive minimalization in 6 months period, it is nonspecific reactive hyperplasia.[3] Peripheral lymph nodes were palpable 44% of healthy children and 64% of sick children.[4] In Kumral's study[5] only 46.5% of cases had a specific etiology, which was 39% in Oguz's study[6] Empiric antibiotic therapy and limited viral tests may be causing that situation; moreover, clinicopathologic supplementation does not need for the diagnosis.[7]

All malignant cases referenced or consulted; none of them applied itself. In the literature, the malignancy rates are significantly low in family practice, the first step.[8,9] In oncology clinics, malignancy rates are higher. In Kumral's study, 30% of the cases had malign disorder.[5] In Lake's study[10] which was a biopsy serial, 17% of cases were malignant. In this study, 12.5% of cases were malignant.

In this study, the average age was higher in the malign group, and these findings were similar to the other studies.[1,6,11,12] 0-2 years, the other reactive lymphadenopathies (23.1%) was the most common case group, while malignant LAPs were never seen in this age range.

The duration of the LAP was similar to benign and malignant cases. The acute process was typical in viral cases; bacterial and other reactive groups were chronic mostly. According to most studies, malignant LAPs were chronic,[5,6] although Karaman found malignant LAPs were acute and benign LAPs were chronic mostly.[11]

Generalized LAP was more frequently encountered in all case groups. Extension of lymph nodes did not help us evaluating whether it was benign or malignant LAP. Evaluating the localization of lymph nodes, cervical nodes (66.4%) were the most frequently involved localization for malignant and benign subgroups. Axillar LAP was more common in malignant nodes (31.6%) than benign nodes (14.3%). 80% of the supraclavicular nodes were malignant in our study. According to the literature, epitrochlear, supraclavicular, and popliteal lymph node palpation is not common in any age, and supraclavicular nodes are abnormal.[13] Supraclavicular localization of the lymph node is always warranted for physicians.[14] Furthermore, the posterior cervical triangle[15] and postauricular area in older ages[4] are important for malignancy.

The size of the node was not diagnostic when it was between 1 and 3 cm. Nodes that were smaller than 1 cm were common in other reactive LAPs, which was a benign subgroup (30.8%) and malignant LAPs (31.6%). 57.9% of the malignant LAPs were bigger than 3 cm. These findings were compatible with relevant studies.[1,5,6] Most of the benign LAPs were mobile (95.5%), and most of the malignant LAPs were fixed (47.4%); this was similar to other studies.

Upper respiratory tract infection symptoms (49.3%) were more frequently encountered in all case groups. Although upper respiratory tract infection was more significant in viral LAPs, fever and B symptoms were common in malignant LAPs. Malignancy was getting significant when the number of symptoms increased. According to the studies, fever is the most detected symptom accompanying the LAP.[5,6,16] In Oguz's study[6] night sweats and weight loss were seen mostly in malignant LAP and fever in benign LAP. However, in Kumral's study[5] weight loss was seen mostly in malignant LAP; fever and night sweat in benign LAP.

Dyspnea, hepatomegaly, splenomegaly were significant examination findings in terms of malignancy. Hepatomegaly and splenomegaly are also significant in viral LAP. Abnormalities in chest X-ray and abdominal ultrasonography were suggestive of a malignant disorder. In Knight's study[14] which lymphadenopathies researched, 56% of patients with hepatomegaly and 77.7% of them with an abnormal chest X-ray had a malign disorder. According to Saltztein[17] big mediastinal LAPs are often caused by malignancy or granulomatous diseases. In Jing Fu Wang's study[18] 13 of the 168 patients with LAP (7,7%) had an abnormal chest X-ray.

Ultrasonography is a beneficial method for screening palpable peripheral lymph nodes. It is easily accessible, cheap, has no radiation, needs no sedation, and does not use contrast. It gives many ideas about solid-cystic separation and size, nature, replacement of the lymph node. Also, doppler USG gives us information about the vascularization of the nodes.[19] Niedzielska evaluated 87 patients with LAP and diagnosed reactive hyperplasia 57.5% of them with USG.[16] Ingolfsdottir evaluated 18 of 43 lymphadenopathies by USG, and five suspected malignancy; however, 4 of these patients gave false-positive results. Besides, USG gave false results in 2 of 3 patients who were diagnosed as malignant histologically. This study argues that ultrasonography is not a reliable method in the benign-malignant differentiation of lymphadenopathy.[20] In Fu's study[21] USG was a lodestar method distinction between malignant and benign LAPs. Lymph node structure, central hiler vascularity, absence of the hilum, peripheral vascularization were significant

markers for malign LAPs. In the literature, we can conclude that ultrasonography, in general, is a useful method that helps to get an idea about the structure of lymphadenopathy, is frequently used by physicians and can be used in diagnosis and follow-up; however, it should be kept in mind that it can give false positive and negative results in distinguishing malignancy. In our study, the vast majority of patients who underwent USG were reported as reactive hyperplasia, which was higher than the literature. The agreement between ultrasonographic diagnosis and histopathological diagnosis was similar to the general literature.

Excisional biopsy is the gold standard in lymphadenopathies with suspected malignancy. The biopsy results show that a good history, physical examination, and laboratory tests, and if necessary, to decide on a biopsy after giving antibiotics seems to be the best decision. In Koçak's study[22] 18 (24%) of 74 patients with lymphadenopathy had lymph node biopsy; 11 (61%) of these cases were diagnosed as malignant, and 7 (39%) were benign. The most common malignant cause was non-Hodgkin's lymphoma, and the most common benign cause was reactive lymphoid hyperplasia. In Knight's study,[14] 239 children with peripheral lymphadenopathy were biopsied; Reactive lymph node hyperplasia in 52% of cases, a granulomatous disease in 32%, malignant disease in 13%, chronic lymphadenitis in 3%. We found a malignant disease in more than half of our patients, whom we followed within the framework of a similar algorithm and made a biopsy decision. However, reactive hyperplasia, which could not be specifically diagnosed after biopsy, was present in our study and the literature.[10,15,18,24] Our study was compatible with the literature to detect the most benign causes in etiology and the most common reactive lymph node hyperplasia among these benign causes.[1,5,6,24,25]

Immune suppression and immune deficiencies are communicated with malignancy in some conditions. Especially EBV is a human virus that is a known relationship between malignancy.[26] One patient was ataxia-telangiectasia, and the other had an EBV infection, which was diagnosed as non-Hodgkin lymphoma later.

In cases presenting with peripheral lymphadenopathy, after a history and physical examination, it should be considered whether lymphadenopathy is a symptom of severe disease. To determine the etiology, firstly, non-invasive tests should be selected after a good history and physical examination, complete blood count and peripheral blood smear should be the tests that should be performed in the first plan. If the patient is considered a nonspecific infection, the patient should be treated with 7-10 days of empirical antibiotic therapy. If a specific infection is considered first, chest radiography, serological tests, or specific diagnostic methods of the disease should be used in addition to the above tests. If this diagnosis and post-treatment do not make a specific diagnosis, if the size of lymphadenopathy does not decrease or shrink or grow, lymph node biopsy should be performed to make a definitive diagnosis without wasting time.

Ethics Committee Approval: The Ethical Committee of Ankara University, approved this study (date: 08.06.2015, number: 10-419-15).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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: The authors have no conflict of interest to declare.

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Image Corner

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A Rare Cause of Joint Pain: Synovial Haemangioma

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A 17-year-old girl was admitted with complaints of recurrent pain, swelling and tenderness in her left knee since she was 3 years old. The swelling of the knee has occasionally increased. She was diagnosed as chronic arthritis and non-steroidal anti-inflammatory drugs were recommended before admission. With non-steroidal anti-inflammatory drugs, her pain was relieved initially but only partially resolved. On admission, physical examination was unremarkable for arthritis. There was localized swelling measuring 3,5x4 cm in diameter on the upper part of left knee. Acute phase reactants and antinuclear antibodies were negative. Magnetic resonance imaging showed synovial haemangioma characterized by a well-circumscribed contour with a lobule filling the left suprapatellar bursa and space- filling formation with heterogeneous intense contrast enhancement after contrast agent administration (**Figure 1**). It was required open total synovectomy and mass resection (**Figure 2**), and histopathological findings were compatible with cavernous haemangioma. Joint pain in children can be result from a variety of acute and chronic diseases.[1] Synovial hemangioma, a benign tumor that occurs in children and young adults, is a non-common cause of recurrent nontraumatic pain and swelling in the knee.[2,3] It can cause cartilage erosion and degenerative joint disease in untreated cases. Therefore, early diagnosis is essential.[4] Tumor and tumor like lesions such as synovial haemangiomas should be kept in mind in patients with extraordinary findings in single joint. In case of doubt, imaging methods should be used for early diagnosis and prevent long term sequel especially for intra-articular lesions.

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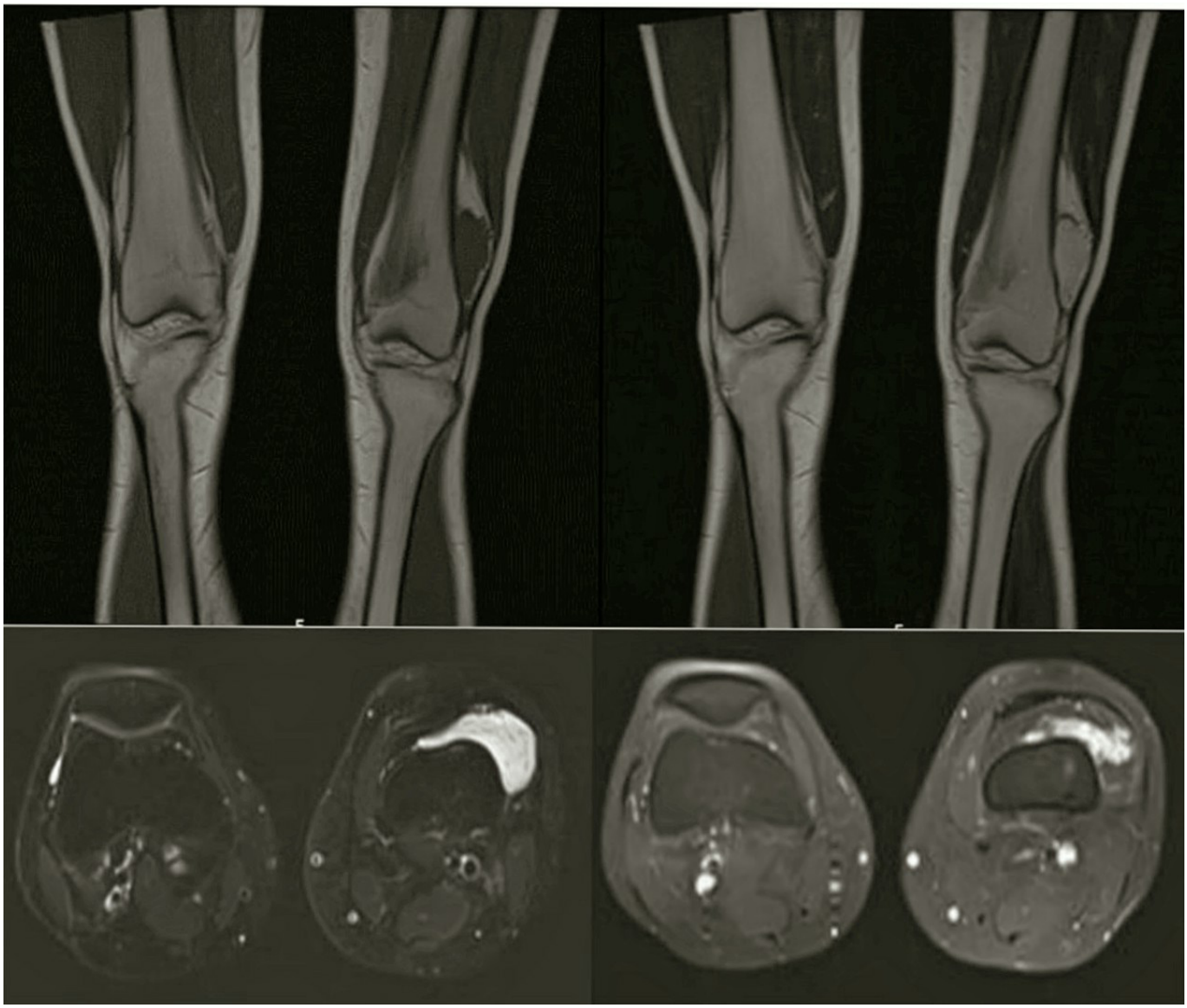

Figure 1. The intra articular nodular soft tissue mass filling the suprapatellar bursa was seen T1-weighted image isointense, T2-weighted image hyperintense, fat-suppressed T2-weighted image hypointense and had contrast enhancement.

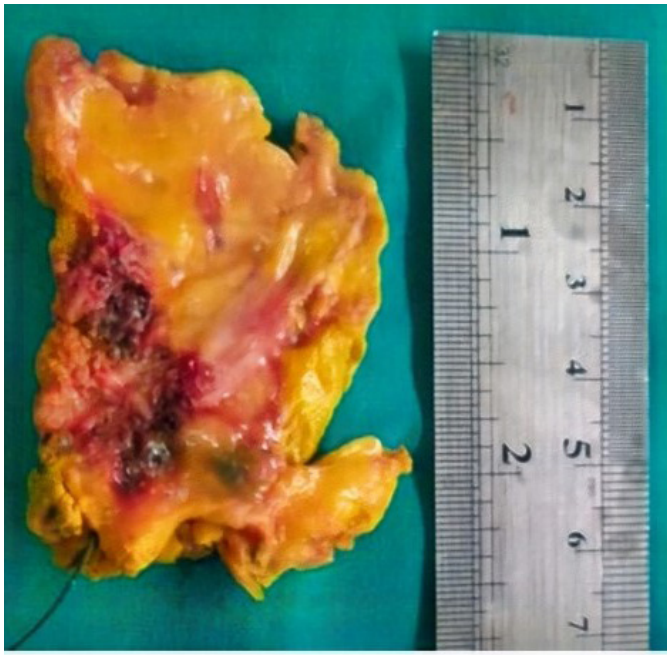

Figure 2. The mass of approximately 6 cm in size was resected with open total synovectomy.

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