Vol. 11 No. 1 February 2023 – May 2023

MEDICINUS

JURNAL KEDOKTERAN
UNIVERSITAS PELITA HARAPAN

Diterbitkan oleh Fakultas Kedokteran, Universitas Pelita Harapan, Indonesia
ISSN 1978 - 3094
E ISSN 2622 - 6995

MEDICINUS

Journal of Faculty of Medicine
University of Pelita Harapan

Vol.11 No. 1
February 2023 – May 2023
ISSN 1978-3094
E-ISSN 2622-6995

Clinical Article

Case Report

Publish: February 2023

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Publish

February – June – October

Association between Anemia and Severe Pneumonia among Children 6-59 Months Old in RSUD Wangaya, Denpasar: A Cross Sectional Study

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Citation: Sukarno Theodora, Suryawan IWB, Sucipta AAM. Association between Anemia and Severe Pneumonia among Children 6-59 Months Old In RSUD Wangaya, Denpasar: A Cross Sectional Study. Medicinus. 2023 February; 11(1):1-5.
Keywords: Anemia; Severe Pneumonia
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Abstract

Background: Severe pneumonia dan anemia happened to many children under five years old. Anemia leads to hypercapnia and slowing down red blood cell maturation and facilitate ischaemic syndrome. In the other side, pneumonia may increase hepcidin that suppressed erythropoiesis, hence anemia could worsen pneumonia. The aim of this research is to find association of hemoglobin level and severe pneumonia under five years old.

Methods: Cross sectional study was done in medical record RSUD Wangaya Denpasar starting from May-August 2022. Data was taken from subject with severe and mild and moderate pneumonia age 6-59 months old that admitted to PICU and Kaswari ward from January 2020-June 2022. Variables processed in this study are gender, pneumonia severity, hemoglobin level, and length of stay

Result: This study admits 56 subjects that fulfilled inclusion and exclusion criteria. Boy and girls subjects are found equally (28 subjects equally in both groups). Severe pneumonia found in 18 (32.1%) subjects and 25 subjects (44.6%) has anemia. Length of stay for severe pneumonia is 4.83 ± 1.54 days. Hemoglobin level in severe pneumonia is 10.93±1,96 mg/dL and subjects with mild and moderate pneumonia is 11.69 ±1.41 mg/dL. The result of chi-square test between haemoglobin level and severe pneumonia is p= 0.26

Conclusions: This study shows that there is no correlation between hemoglobin level and severe pneumonia. Further study is needed since the correlation between them is still controversial.

Introduction

Pneumonia is an acute infection of upper respiration tract that involves one or both lungs, according to WHO. Pneumonia is most commonly caused by virus, bacteria, or fungal organisms.[1] Based on epidemiological study, severe pneumonia is one of the leading causes of morbidity and mortality in children under 5 years old, especially in developing countries. Estimated global incidence of pneumonia is 120 million cases in a year, which account for approximately 1.3 million death. Despite the better prognosis in higher income countries, there is still a substantial burden of this disease.[2] Some studies reported that hospitalized child has significant decrease in their quality of life, due to the restricted leisure time, anxiety, and stress. Similarly, the parents also experienced distress.[3,4]

Severe pneumonia presents as general symptoms with abnormality of respiration rates, wheezing, respiratory retractions, oxygen saturation <95%, and difficulty in swallowing food.[5] Risk factors of severe pneumonia in children under 5 years old includes low birth weight, prematurity, breastfeeding exclusivity, nutritional status, and comorbid diseases.[6] It is known that anemia associated as a risk factor of pneumonia. [7,8,9,10]

Anemia is a condition in which the number of red blood cells, serum iron or the hemoglobin concentration is lower than normal. According to WHO, children under 5 years old is diagnosed with anemia if the hemoglobin concentration is lower than 5 g/dL.[11] Iron deficiency anemia is a progressive condition. On young child, anemia is usually worsen by inadequate dietary iron intake by consuming low iron-rich foods after weaning onto solid foods. Beside iron, vitamin B12 and folic acids are also important diet nutrients that relates to anemia. Anemia causes oxygen deprived brain tissue which will disturb cognitive function, psychomotor growth and development.[8,11] Globally, 43% of children under 5 years old suffer from anemia. Children with anemia are significantly prone to stunting, delay in cognitive development, abnormal immunity, disability, and increased morbidity and mortality.[12]

Furthermore, anemia also causes hypercapnia and delay red blood cell maturation in the bone marrow therefore facilitates ischemic syndrome which worsens pneumonia. In turn, pneumonia leads to inflammatory anemia by increasing serum hispinin which suppresses erythropoiesis.[13]

Anemia may associated with pneumonia as it worsen pneumonia through the hypercapnia mechanism and also slow down the redcell maturation in bone marrow, therefore the hypoxic mechanism will eventually worsen pneumonia. In the other hand, pneumonia could cause or worsen anemia through the increased level of hepcidin that supressed erythropoiesis and will cause inflammatory anemia.[10] Some studies show association between anemia and pneumonia or severe pneumonia, but study done by Alsharkawy shows no association between anemia and severe pneumonia.[14] This study is done to find out the association between anemia and severe pneumonia in children age 6-59 months in Wangaya hospital, Denpasar Bali.

Material And Methods

This cross sectional study aimed to find the relationship between anemia and severe pneumonia in children ranged 6-59 months old in Wangaya Regional General Hospital. Patients were hospitalized between January 2020 and June 2022. The inclusion criteria are 6-59 months old children diagnosed with pneumonia who admitted into inpatient ward (Kaswari ward) or Pediatric Intensive Care Unit (PICU) in Wangaya Hospital. Exclusion criteria includes subject with a history of malignancy, underwent anti-neoplastic therapy, a history of thalassemia, severe malnutrition, other systemic conditions, and incomplete medical record data. Samples needed for this study is minimum 52 samples, while this study use 56 samples. Qualified samples are taken from hospital's medical record with consecutive sampling method, analyzed using SPSS version 27 with univariate and bivariate Chi-square test between anemia (hb <11.0) and severe pneumonia. We extracted patients' gender, pneumonia severity, hemoglobin level, and duration of hospital stay.

Result

Secondary data was obtained from patients admitted to Wangaya Regional General Hospital between January 2020 and June 2022, which was recorded in the hospital's medical record. A total of 56 samples are eligible according to the inclusion and exclusion criterias. Characteristics of the subjects included in this study are shown in **table 1.**

Table 1. Demography of the subjects

Characteristic	Frequency
Gender	
Male	28 (50%)
Female	28 (50%)
Age	
6-48 months	53 (94.7%)
49-59 months	3 (5.3%)
Birth Weight	
<2500 gr	4 (7.2%)
≥2500 gr	52 (92.8%)
Exclusive Breastfeeding	
Yes	38 (67.8%)
No	18 (32,2%)
Diagnosis	
Severe pneumonia	18 (32.1%)
Mild to moderate pneumonia	38 (67.9%)
Hemoglobin level	
Hb<11.0 (anemia)	25 (44.6%)
Hb≥11.0 (not anemia)	31 (55.4%)
Hospital stay	
Severe pneumonia	4.83 ± 1.54 days
Mild to moderate pneumonia	4.45 ± 2.20 days

There are same amount of male and female subjects in this study (28 subjects on both genders). Most of the subjects age 6-48 months (94.7%), meanwhile only 5.3% subjects age 49-59 months old. Among all subjects there are 4 subjects(7.2%) was born with birth weight under 2500 gr, while 52 subjects (92.8%) has birthweight ≥2500 gr. Thirty-eight subjects (67.8%) breastfed exclusively while the rest (32.2%) do not get exclusive breastfeeding. Most of the subjects were diagnosed with mild to moderate pneumonia (67.9%) and the rest of them (31.1%) are diagnosed with severe pneumonia. Almost half of the subjects were classified as anemia (44.6%) while the other half are not (55.4%). The length of stay for subjects with severe pneumonia is longer than those who have mild to moderate pneumonia (4.83 ± 1.54 days and 4.45 ± 2.20 days, respectively).

There was no significant correlation found between hemoglobin level and severe pneumonia (p=0.26), as shown **in table 2**. Moreover, it is worth mentioning that the 95% CI have crossed 1 (0.62 – 5.96), which implies that the odd ratio is not precise. Subjects in the mild to moderate pneumonia group has slightly higher hemoglobin level (11.69 ±1.41) compared to the severe group (10.93±1.96).

Table 2. Hemoglobin level and severe pneumonia distribution

Hemoglobin Level	Pneumonia Severity					
	Severe	Mild to Moderate	Total	p	OR	95% CI
Anemia	10 (55.56%	15 (39.47%)	25 (44.64%)	0.26	1.20	0.62 – 5.96
Not Anemia	8 (44.44%	23 (60.53%)	31 (55.36%)			

Discussion

This study shown that there is no significant relation between hemoglobin level and severe pneumonia (p=0.26; OR= 1.20; 95% CI: 0.62-5.96). Concurrent to the previous study by Alshaekawy, et al, who conducted a case control study that compared vitamin D, serum zinc, and serum iron on the severity of community acquired pneumonia, claimed that they found no significant correlation between both arms (p=0.24). Furthermore, Alshaekawy, et al, observed that the serum zinc and vitamin D is significantly correlated to pneumonia severity, and even found that both are protective factors toward pneumonia in children age 2-59 months old.[14] Several lab results that were correlated with severe pneumonia are abnormal neutrophil, lymphocyte, natrium, albumin, proteinuria, and RSV infection.[15] Meanwhile, a systemic review conducted by Preston, et al, found that only abnormal leukocyte level is significantly related to severe pneumonia, in specific, leukopenia as a mortality predictor of pneumonia.[16]

Anemia and pneumonia are two of the most common pathological diseases in younger population, and they both usually coexist. Children under 5 year old and pregnant mothers are very susceptible to anemia, especially in low income countries. There are various conditions that leads to anemia, such as micronutrients deficiency, acute or chronic infections, low socio-economy, demography, genetics, and immunohematology diseases.[17] Low

hemoglobin has been known to cause hypoxemia, therefore the alveolar macrophage has lower capacity to absorb iron from the red blood cells. This disturbance in the balance of immune system leads to worsening of the lung infections and promotes severe pneumonia.[18] Inflammation of the lung triggers the release of IL-6 and Activin B through STAT 3 and SMAD4 pathway. This pathway also increases the production of hepcidin. Hepcidin is a hormone that acts as regulator of serum iron and free iron in the blood through a mechanism that degrade cellular iron exporter. Abnormal increase in hepcidin causes lower amount of iron in the serum. Another hypothesis also suggested that this acts as the defense mechanism of the host, because serum iron could be an essential element required by the pathogens to multiply.[19]

Prevalence of children under 5 year old with anemia in Indonesia, according to UNICEF, is more than 38%. Another epidemiology data in 2014 suggested that the number could be higher than 60% in 6-35 months old population and as high as 80% in the 6-11 months old population.[20] Anemia and pneumonia are both very common in children under five years old, despite the controversy of its relationship to each another as well as the association with the severity of pneumonia.

There are some limitations of this study. First limitation is the small sample size. Presumably, it may be difficult to determine if the outcome is a true finding. We suggest further study with bigger sample size and longer duration to substantiate this study. The second one is that study did not analyze the association of other variable with the severe pneumonia.

Conclusion

There are no significant correlation between hemoglobin level and severe pneumonia in children aged 6-59 months old.

Acknowledgment

The author thank all the doctors who mentor and gave advice for this manuscript, also thanking all the related parties.

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Comparison of Post-Operative Pain Score Between Open Appendectomy and Laparoscopic Appendectomy on Acute Appendicitis Patient in Siloam Hospital Lippo Village

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Citation: Elsa Mary, Sudirman Taufik. Comparison of Post-Operative Pain Score Between Open Appendectomy and Laparoscopic Appendectomy on Acute Appendicitis Patient in Siloam Hospital Lippo Village. Medicinus. 2023 February. 11(1):6-11.
Keywords: Acute appendicitis; Post-operative pain; Open appendectomy; Laparoscopic appendectomy.
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Abstract

Background: Appendicitis is inflammation of vermiform appendix which can be caused by luminal obstruction. Appendicitis is one of the most common causes of emergency abdominal surgery, with 11 cases per 10.000 person per year. Until today, open appendectomy is still the gold standard for appendicitis treatment although laparoscopic appendectomy has significantly lower post-operative pain.

Methods: This study uses cross-sectional study design with post-open appendectomy and laparoscopic appendectomy patients in Siloam Hospital Lippo Village as the sample population. The Visual Analogue Scale (VAS) is taken from patient's medical record and processed using Mann-U-Whitney test.

Result: From 70 acute appendicitis patients, 36 underwent open appendectomy and 34 underwent laparoscopic appendectomy. The result showed the median score of VAS 1 day post open appendectomy surgery (median = 3, min/max = 2/6 [95% CI = 2,55 – 3,14]) is higher than post laparoscopic appendectomy (median = 2,25, min/max = 0/4, [95% CI = 1,97 – 2,59]), with adjusted p value against age and surgery duration is 0,024. In pediatric patients, median score of VAS 1 day post open appendectomy surgery is the same with laparoscopic appendectomy (median = 3, p value = 0,863). Multivariate analysis showed that surgery duration affects VAS 1 day post appendectomy surgery in pediatric patients (p value = 0,042).

Conclusions:
This study shows that the median score of VAS 1 day post open appendectomy surgery is higher than laparoscopic appendectomy. This result is statistically significant. However, in pediatric patients the median score of VAS 1 day post open appendectomy surgery and laparoscopic appendectomy is the same. VAS 1 day post appendectomy surgery in pediatric patients is affected by surgery duration.

Introduction

Appendicitis is inflammation of the vermiform appendix which can be caused by luminal obstruction.[1] This disease has been one of the most common causes of abdominal surgery with 11 cases per 10.000 people per year.[2]

According to *Profil Kesehatan Indonesia*, there were 596.132 cases in 2009 (3,36%) which then increased to 621.435 cases in 2010 (3,53%).[3]

Appendectomy surgery for acute appendicitis patients can be done in an

open or laparoscopic manner. However, the open appendectomy method has been the gold standard for several decades. Since the founding of laparoscopic appendectomy, this method is now more commonly used since it has better scar healing, faster recovery, better cosmetic result, and a significantly lower post-operative pain according to a lower dose of analgesic used post-surgery.[4,5]

Pain, as described by the Taxonomy Committee of International Association for the Study of Pain (IASP), is a sensory and emotional experience related to true or possible tissue damage. Post-operative pain is categorized as acute pain caused by inflammation and activation of afferent neurons resulted from operative trauma and can be measured using Visual Analogue Scale (VAS).[6]

It is important to recognize post-operative pain as it can disturb patient's comfort, activities, and suppress the immune system which can lead to an increased risk of post-operative infection and worse scar healing.[7] Previous studies done by Fatih Çiftçi (2015) and Gokhan Cipe, et al (2014) found that open appendectomy patients have a significantly higher 6-hour post-operative VAS than laparoscopic appendectomy patients (p = 0,001).[8,9] Although there have been several studies that compare post-open appendectomy and laparoscopic appendectomy pain, however the pain is usually measured using post-operative analgesic dose and only several studies use VAS. There are also not many studies that used population samples from Indonesia.

Material And Methods

This research was 2 groups unpaired numeric comparative analytic study with cross sectional study design, conducted from January 2021 to March 2021. The sample used in this research is 70 acute appendicitis patient post-open or laparoscopic appendectomy in Siloam Hospital Lippo Village, with the inclusion criteria of same group of post-operative analgetic which is NSAID, VAS 1 day post-surgery, and VAS within 0–7,4 range. Data was collected using purposive sampling from patient's medical record. Samples who fulfilled the exclusion criteria, namely laparoscopic appendectomy converted into open appendectomy, perforated appendix, peritonitis, pregnant, and history of abdominal surgery, were removed from the research. With the classification of research variables in the form of independent variables, which were knowledge about open appendectomy and laparoscopic appendectomy, and the dependent variable was post-operative pain, as well as confounding variables namely age, sex, pre-operative pain, anxiety, and surgery duration.

Obtained research data was processed and analysed using Statistical Package for the Social Sciences (SPSS) software version 25. Bivariate statistical analysis was performed using Mann-U-Whitney when the data distribution was not normal and independent t-test when the data distribution was normal. The researcher also calculated the median, minimal value, maximal value, and 95% CI. Multivariate analysis was also done to examine the significancy of types of surgery toward post-operative pain after being adjusted toward confounding variables. This research has received approval from the ethical committee of the Faculty of Medicine, University of Pelita Harapan with the number 189/K-LKJ/ETIK/XII/2020.

Result

According to table 1, this research subjects were mostly female (65,71%) than male (24,39%). The median of pre-operative VAS for open appendectomy was 3 and for laparoscopic appendectomy was 3,25. This difference was not statistically significant as the p value was more than 0,05 (p = 0,356). For the surgery duration, the median for open appendectomy duration was 45 minutes and for laparoscopic appendectomy was 50 minutes. This difference was also not statistically significant (p = 0,473).

Table 1. Demographic of Samples

Variable	Open Appendectomy (n = 36)	Laparoscopic Appendectomy (n = 34)	P value
Sex			
Male, n (%) Female, n (%)	12 (50,00) 24 (52,17)	12 (50,00) 22 (42,83)	0,531
Age (year), median (min/max)	23,5 (5/76)	24,0 (11/84)	0,265
Pre-operative VAS, median (min/max)	3,00 (1,5/7)	3,25 (1/6)	0,356
Surgery duration, median (min/max	45 (30/150)	50 (20/140)	0,473

The median age of subjects that underwent open appendectomy was 23,5-year-old, with the youngest age of 5-year-old and oldest of 76-year-old. Median age of subjects that underwent laparoscopic appendectomy was 24-year-old, with the youngest age of 11-year-old and oldest of 84-year-old. Median of pre-operative VAS for open appendectomy was 3,00, with 1,5 being the lowest score and 7 being the highest score. For laparoscopic appendectomy, the pre-operative VAS median was 3,25, the lowest score was 1, and the highest was 6. The surgery duration of open appendectomy had the median of 45 minute, with 30 minutes as the fastest duration and 150 minutes as the longest duration. For laparoscopic appendectomy, the median was 50 minutes, the fastest duration was 20 minutes, and the longest duration was 140 minutes.

Pain 1-day post-surgery was recorded using VAS from 70 subjects. The distribution of post-operative pain was shown in table 2. Median of VAS 1-day post-open appendectomy was 3,00, with lowest score of 2,0 and highest score of 6,0. For the 34 subjects that underwent laparoscopic appendectomy, the median VAS was 2,25. The lowest score was 0,0 and the highest was 4,0.

Tabulation result shown in table 2 showed that the median of VAS 1-day post-open appendectomy was higher than laparoscopic appendectomy. The results were analysed using Mann-U-Whitney test since the data distribution was not normal and showed that the 95% CI for VAS 1-day post-open appendectomy was 2,55 – 3,14, and for laparoscopic appendectomy was 1,97 – 2,59. The P value for the median difference between open appendectomy and laparoscopic appendectomy was 0,011, which means that the median difference was statistically significant.

Table 2. Distribution of VAS 1 Day Post-Open and Laparoscopic Appendectomy

Surgery type	VAS 1-day post-surgery			
	Median	Min/Max	95% CI	P value
Open appendectomy (n = 36)	3,00	2,0/6,0	2,55 – 3,14	0,011
Laparoscopic appendectomy (n = 34)	2,25	0,0/4,0	1,97 – 2,59	

Multivariate linear regression was done to decide the statistical significance of surgery type difference after being adjusted toward the confounding variables. Variables that were included in the linear regression were the one that had p value <0,25 on the bivariate analysis, which were surgery duration, surgery type, and pre-operative VAS. Pre-operative VAS was then removed from model since it had p value >0,05 on the multivariate analysis and only changed beta less than 10% when removed. The final regression model was shown in table 3. It was found that surgery type still causes statistically significant difference in the median of VAS 1-day post-appendectomy after being adjusted with age and surgery duration.

Table 3. Multivariate Analysis of Independent Variable toward VAS 1 Day Post-Appendectomy Surgery

Variable	Beta	P value
Age	-0,259	0,024
Surgery duration	0,233	0,040
Surgery type	-0,257	0,024

As there were some pediatric patients (0-18 years old), a subgroup analysis of pediatric patients was done. There were 9 pediatric patients that underwent open appendectomy and 7 pediatric patients that underwent laparoscopic appendectomy. Result is shown in table 4 and shows that the median of VAS 1 day post open appendectomy and post laparoscopic appendectomy is the same (median = 3,00). This result is not statistically significant according to Mann-U-Whitney analysis (P value >0,05).

Table 4. Distribution of VAS 1 Day Post-Open and Laparoscopic Appendectomy in Pediatric Patients

Surgery type	VAS 1-day post-surgery			
	Median	Min/Max	5% CI	P value
Open appendectomy (n = 9)	3,00	2,0/4,5	,08 – 3,36	0,863
Laparoscopic appendectomy (n = 7)	3,00	1,5/3,0	,01 – 3,13	

Multivariate linear regression was then done to find out whether there are other variables that affect VAS 1 day post-surgery. Variables that were included in the model were pre-operative VAS and surgery duration. Table 5 showed the final regression model and found that the only variable that affected VAS 1 day post-surgery in pediatric patients was surgery duration.

Table 5. Multivariate Analysis of Independent Variable toward VAS 1 Day Post-Appendectomy Surgery in Pediatric Patients

Variable	Beta	P value
Surgery duration	0,513	0,042

Discussion

According to table 1, this research subjects were mostly female (65,71%) than male (24,39%). The median of pre-operative VAS for open appendectomy was 3 and for laparoscopic appendectomy was 3,25. This difference was not statistically significant as the p value was more than 0,05 (p = 0,356). For the surgery duration, the median for open appendectomy duration was 45 minutes and for laparoscopic appendectomy was 50 minutes. This difference was also not statistically significant (p = 0,473).

Post-operative VAS was then analysed using Mann-U-Whitney test and showed that the median for post-open appendectomy VAS was 3,00 and for post-laparoscopic appendectomy was 2,25, with p value of 0,011. This result means that subjects that underwent open appendectomy had a significantly higher post-operative VAS than subjects that underwent laparoscopic appendectomy.

The result of this research was in line with the researches previously conducted by Gokhan Cipe, et al, and Fatih Ciftci where there were also a statistically significant difference between post-open appendectomy and laparoscopic appendectomy VAS. The research done by Gokhan Cipe, et al, used cohort study design and had 241 subjects. They found that the median of VAS 6-hour post open appendectomy was 4,6 ± 1,3 and for laparoscopic appendectomy was 4,0 ± 1,2 (p = 0,001).[9] Fatih Ciftci, who used cross-sectional design and had 243 subjects, found that the median for VAS 6-hour post-open appendectomy was 4,5 ± 1,2 and for laparoscopic appendectomy was 3,9 ± 1,1 (p = 0,001).[8]

Although the result was in accordance with previous researches, there are slight differences in this research that may affect the result. This research used VAS from 6 hour post-surgery meanwhile the previous researches used VAS from 1 hour post-surgery. Other difference was that the distribution of data was not normal in this research but normal in previous researches. Despite all those differences, this research still suggests that there is a statistically significant difference in post-operative pain between open appendectomy and laparoscopic appendectomy.

There were 16 pediatric patients in this research, with the youngest age of 5-year-old in open appendectomy and 11-year-old in laparoscopic appendectomy. As children may not understand the pain scale well enough, this may cause inaccurate VAS depiction. For that reason, a subgroup analysis of pediatric patients was done and it was shown that the median score of VAS 1 day post-open appendectomy surgery is the same with laparoscopic appendectomy (median = 3,00). Multivariate analysis of pediatric subgroup showed that the only variable that affect VAS 1 day post-surgery score in pediatric patients was surgery duration. Previous researches did not do a subgroup analysis of pediatric patients.

There are several shortcomings of this research such as the samples were not as many as previous researches which may cause result that does not represent general population. In addition to that, the data used in this research was a secondary data from medical record which means the data accuracy could not be ensured. In spite of these shortcomings, this research excels with the inclusion of multivariate analysis and subgroup analysis of pediatric patients. Confounding variables of age and surgery duration were taken into consideration in the linear regression model and showed adjusted p value of 0,024, which mean open appendectomy still had a significantly higher VAS 1-day post-surgery.

There are several factors that has not yet been analysed in this study, such as confounding factor anxiety since the data was not found in the medical record, drain usage, and stage of appendicitis which could affect the result, therefore the significancy in this study needs to be researched more in further study with better design such as prospective cohort.

Conclusion

The results showed that the median of VAS 1-day post-open appendectomy was significantly higher than laparoscopic appendectomy. However, in pediatric patients the median score of VAS 1 day post open appendectomy surgery and laparoscopic appendectomy is the same. VAS 1 day post appendectomy surgery in pediatric patients is affected by surgery duration.

Acknowledgment

None.

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Mary Christina Elsa

Factors Associated With Atopic Dermatitis In Elementary School Children In Suburban Area In Indonesia: Original Research

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Citation: Gunawan Catherine, Satriajaya Anthony, Vatvani Akhil Deepak, Waren Kalis, Broto Resza, Kalumpiu Jane Florida, Tan Sylvia. Factors Associated With Atopic Dermatitis In Elementary School Children In Suburban Area In Indonesia: Original Research. Medicinus. 2023 February. 11(1):12-17
Keywords: Atopic dermatitis; Associated Factors; Atopy; ISAAC; Schoolchildren
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Online First : February 2023

Abstract

Background: There was limited data of Atopic Dermatitis (AD) prevalence and its associated factors in Indonesia. Therefore, the aim of this study was to identify and evaluate the AD prevalence and factors associated with AD in elementary school children in suburban area in Banten.

Methods: A cross-sectional study was conducted in 3 elementary schools children age 6–7 years old who were randomly selected. Information was obtained through an Indonesian version of the International Study of Asthma and Allergies in Childhood questionnaire (ISAAC).

Results: From 304 school children in semi-urban area, AD was reported as ever had an itchy rash which was reccurent for at least 6 months in 17.4% of the children, 19.5% of the children had this itchy rash at any time in the past 12 months, and 11.4 % reported doctor-diagnosed AD. The factors found to be associated with an increased risk of AD were allergic rhinitis (OR 2.151 CI: 1.086-4.261), history of premature birth (<37 weeks) (OR 5.306, CI:1.577-17.858), exclusive breastfeeding (OR 3.126 CI:1.314-7.439), and food allergy (OR 2.912 CI:1.386-6.119).

Conclusion: The results of this study showed that allergic rhinitis, history of premature birth (<37 weeks), exclusive breastfeeding, and food allergy were factors associated with AD in Indonesian schoolchildren.

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disorder, characterized by cutaneous dryness, intense itching, scratching, skin damage, and secondary infections. Atopic dermatitis (AD) is one of the most common skin diseases in the world, particularly in neonates, children, and adolescents.[1] AD is caused by a combination of genetic and environmental factors. The disease is closely associated with asthma and allergic rhinitis. Although this disorder is not fatal, it can lead to skin damages, secondary infections, sleep disorders in children and parents, reduced quality of life, high costs, loss of confidence, and reduced functional capacity that can interfere athletic activities and social relationships.[2,3]

As a result of previous studies based on ISAAC, the incidence of AD in the infant population was estimated to be 15–20%, showing an increase in prevalence.

It has also compared the prevalence among the different countries and showed differences in each region.[4] The prevalence of AD is reported to be 17.2% in American children, 15.6% in European Children, 24% in Japanese children aged 5-6 years old, 19.1% in Korea, and 20% in other countries. The prevalence of allergic diseases has increased not only in high income but also in low-to-middle income countries (LMIC), such as Indonesia.[1]

There is a wide spectrum of presentations of atopic eczema, from minimal flexural eczema to erythroderma. The skin of a child with eczema is generally dry. The eczema can occur anywhere, but there are particular patterns that are more common at certain ages. The face is usually the first to be affected. In crawling infants the forearms, extensor aspects of the knees, and the ankle flexures are often the most affected. In older children the flexor aspects of the elbows and the knees are mostly affected. The eczema may be moist and weeping or may be thickened (lichenified) and dry. In children with darker skin the rash may have a papular nature. Scratch marks are always seen. [1]

For primary, secondary and tertiary prevention of childhood AD, it is crucial to determine the factors which are associated with the development or exacerbation of AD. Known associated factors linked to the incidence of AD from previous studies were the presence of asthma or rhinitis symptoms,positive family history for allergic diseases[5], indoor allergens such as dust mite, animal dander and fur[6], environmental tobacco smoke (ETS)[7], exclusive breastfeeding history[8], low birth weight, prematurity, house mould, higher exposure to air pollution, smaller families with less exposure to infections, animal contact in first year of life and within the last year, higher maternal age, consumption of paracetamol in first year of life and within the last year[9], and a wider range of foods.[2,3,10] The association between atopic eczema and food allergy is complex, though it is usually children with severe atopic eczema have food allergy.[2]

There was limited data of AD prevalence and its associated factors in Indonesia. Therefore, the aim of this study was to identify and evaluate the AD prevalence and factors associated with AD in elementary school children in suburban area in Indonesia.

Material And Methods

Study design and subjects

This cross-sectional study was performed in January 2018. A total of 304 children, chosen from a random sample of 3 elementary schools in Tangerang, Indonesia, were included in this study. After coordination with the schools under study, researchers presented letters referred to schools according to ISAAC protocol, and obtain informed consent. Based on ISSAC protocol, after distributing the questionnaires, each question was explained by a trained interviewer. The questionnaires were completed preferably by the parents and by the students themselves if the parents were absent. The data collected were entered into Microsoft Excel.

Questionnaires

Allergic disorders were assessed with a validated questionnaire for age 6-7 years old developed by International Study of Asthma and Allergy in Childhood (ISAAC) which had been translated into Bahasa Indonesia to accommodate local study requirements. AD ever was defined as a positive response to the question “Have you ever had an itchy rash which was coming and going for at least 6 months?” The prevalence of asthma symptoms were obtained from the questions: “Has your child and family member ever had wheeze?” The prevalence of rhinitis symptoms were obtained from the following questions: “Has your child and family member ever had a problem with sneezing or a runny or blocked nose when you (he/she) did not have a cold or the flu?”

An additional questionnaire was administered to obtain demographic data, socioeconomic status, parental education, parental occupation, and other potential associated factors for the development of allergies. The potential associated factors that were investigated included the following: gender, birth weight, delivery time, number of siblings, exclusive breastfeeding history, parental asthma or allergic rhinitis or atopic dermatitis, exposure to animals in the first year of life and within the last year, exposure to tobacco smoke in at home, dampness and mold in the house, food allergy, cooking method in the house, and paracetamol consumption in the first year of life and within the last year.

Written informed consent was obtained from parent or guardian of each child. The study was approved by the Ethical Committee of the Medical Faculty, University of Pelita Harapan (ethical clearance ref: 006/K-LKJ/ETIK/VIII/2017)

Statistical analysis

The collected data were analyzed using SPSS ver.22 (IBM, 2018). To investigate the relationship between associated factors and AD, the analysis was carried out using the *Chi- square* test, and its odds ratio (OR) and confidence interval of 95% were calculated. Statistical significance was set at P<0.05.

Result

Data were collected from 304 school children in semi-urban area. AD was reported as ever had recurrent itchy rash for at least 6 months in 17.4% of the children, 19.5% of the children had this itchy rash at any time in the past 12 months, and 11.4 % reported doctor-diagnosed AD. The associated factors for AD were described in table 1. In this study, the Odd ratio of asthma in patients with AD was 1.08, CI: 0.388-3.006, p value 0.884 and Odd ratio of allergic rhinitis patients with AD was 2.151 CI: 1.086-4.261, p value 0.026. Of the children with AD, 4.8% were born prematurely (<37 weeks), OR 5.306, CI:1.577-17.858, p value 0.003, 61.3% had exclusive breastfeeding (breastfed for 6 months or more), OR 3.126 CI:1.314-7.439, p value 0.007, and 17.2% had food allergy, OR 2.912, CI:1.386-6.119, p value 0.004. Household pets during infancy (in the first year of child's life) was present in 79.9% of the children, OR 0.639, CI: 0.305-1.339, p value 0.233, household pets at present (in the last 1 year) was present in 94.2% of the children, OR 0.432, CI: 0.143-1.306, p value 0.127. The Odd ratio of exposure to cigarette smoke (at present) in children with AD was 1.679, CI:0.894-3.153, p value 0.105. The family income were described in table 2.

The factors found to be associated with an increased risk of AD were allergic rhinitis, history of premature birth (<37 weeks), exclusive breastfeeding, and food allergy. However, gender, asthma, household pets (during infancy), household pets (at present), exposure to cigarette smoke (at present), and family income showed no statistical significance as a associated factor for AD.

Table 1. Factors associated with atopic dermatitis in children

Risk factors	%	OR (95% CI)	p value
gender (female)	47.6 %	1.36 (0.74-2.52)	0.315
asthma	9.6 %	1.08 (0.388-3.006)	0.884
allergic rhinitis	60 %	2.151 (1.086-4.261)	**0.026**
prematurity	4.8 %	5.306 (1.577-17.858)	**0.003**
exclusive breastfeeding	61.3 %	3.126 (1.314-7.439)	**0.007**
food allergy	17.2 %	2.912 (1.386-6.119)	**0.004**
household pets (during infancy)	79.9 %	0.639 (0.305-1.339)	0.233
household pets (at present)	94.2 %	0.432 (0.143-1.306)	0.127
exposure to cigarette smoke (at present)	50.7 %	1.679 (0.894-3.153)	0.105
family income			0.374

Table 2. Family income

Family income	%
< Rp 1,000,000	19.1%
Rp 1,000,000 – 3,000,000	38.1%
Rp 3,000,000 – 5,000,000	28.9%
>Rp 5,000,000	13.9%

Discussion

In our study, factors found to be associated with an increased risk of AD were allergic rhinitis, history of premature birth (<37 weeks), exclusive breastfeeding, and food allergy. However, we did not find any relation between AD and other risk factors including gender, asthma, household pets (during infancy), household pets (at present), exposure to cigarette smoke (at present), and family income. Our finding were consistent with the previous studies which showed that presence of allergic rhinitis, history of premature birth (<37 weeks), and food allergy were associated with increase risk of AD.[10]

Patients with AD have higher rates of allergic diseases than the general population. 80% of children with AD develop asthma and/or allergic rhinitis later in life and referred to as the "allergic march" or "atopic march". The cutaneous manifestations of atopy often represent the beginning of the atopic march. Approximately half of AD patients will develop asthma, particularly with severe AD, and two thirds will develop allergic rhinitis. Epicutaneous sensitization with subsequent migration of sensitized T cells into the nose and airways, causing upper and lower airway disease.[11]

Ten to twenty percent of patients with AD have food-induced urticaria/anaphylaxis compared with 1-3% of the general population.[12] The current hypothesis is that cutaneous sensitization through disrupted skin barrier leads to food sensitization and food allergies. Defects in serine peptidase inhibitor, Kazal type 5 (SPINK5) are associated with food challenge-proven food allergy.[13,14] In addition, skin barrier impairment at birth which is measured by higher transepidermal water loss (TEWL) predicts food allergy at two years of age.[15] Earlier onset (<3 months of age) and more severe AD is associated with high egg, milk, and/or peanut-specific IgE.[16] Patients with AD and concomitant egg, peanut, or dust mite allergy are more likely to have AD that persists beyond five years of age.[17] Infants and young children with AD are more commonly sensitized to foods[18], whereas children over five years and adults are more commonly sensitized to aeroallergens (dust mite sensitization is most prevalent in both children and adults).[19] And vice versa, food allergies play a role in exacerbating AD in up to 33% of patients with severe AD, 10 – 20% with moderate AD, and 6% with mild AD. Elimination of food allergens in patients with AD and confirmed food allergy can lead to significant AD improvement.

Relation of breast-feeding with IgE as allergic marker in childhood is complex and early production of food-specific IgE is associated with an elevated risk for allergic outcomes. Among children of mothers with high IgE levels, breast-feeding was associated with elevated IgE levels relative to never breast-fed children in that maternal IgE strata. Thus exclusive breastfeeding cause immediate, continuing, and high-volume exposure to antigens, including bacteria and allergens, which might alter inherited predisposition toward IgE production. Other explanation is that breast-feeding associated with lower infections in early life which might stimulate the infant immune system toward an allergic (TH2) rather than an antimicrobial (TH1) response and encourage persistence of the TH2 immunity, particularly in the context of a genetic predisposition toward IgE production.[20] Premature birth (<37 weeks) infants might have higher risk of AD because they have immature skin barrier that cause increased permeability and transepidermal water loss.[21]

Exclusive breastfeeding, household pets during infancy and at present effects on AD is still controversial, where exclusive breastfeeding, household pets (during infancy), and household pets (at

present) were found as both risk and protective factors of AD. Previous studies showed that female gender, asthma, exposure to cigarette smoke (at present), and high family income were significant risk factor for AD, which were not in agreement with our result.

The limitation of this study was our study design was a cross-sectional survey which cannot identify the causal relationship. In addition, the diagnosis of AD was based on a questionnaire, not by detailed history and physical examination. Further investigation by prospective cohort study is required to prove the causal relationship between the development of AD and risk factors in Indonesian children. Because AD might be an 'entry point' for the subsequent development of asthma or allergic rhinitis, children with AD need proper management to prevent epicutaneous sensitisation leading to systemic immune response. There was no conflict of interest in this study.

Conclusion

The results of this study showed that allergic rhinitis, history of premature birth (<37 weeks), exclusive breastfeeding, and food allergy were factors associated with AD in Indonesian schoolchildren.

Acknowledgment

The authors thank the team from Faculty of Medicine, University of Pelita Harapan, preceptors, and most of all the study participants from these elementary schools, Tangerang, Indonesia.

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Lactate Dehydrogenase A as a Target of Cancer Therapy

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Citation: Neolaka Gladies Mercya Grameinie. Lactate Dehydrogenase as a Target of Cancer Therapy. Medicinus. 2023 February. 11(1):18-24
Keywords: LDH; Lactate; Cancer; Therapy
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Online First : February 2023

Abstract

Lactate dehydrogenase (LDH) is an enzyme that catalyzes the conversion of pyruvate to lactate and on the contrary lactate to pyruvate. LDH is a tetramer consisting of two types of subunits M (LDHA) and H (LDHB). LDHA catalyzes the conversion of pyruvate to lactate, while LDHB converts lactate to pyruvate. LDHA increases its expression in cancer cells and is associated with cancer aggressiveness. Lactate that continues to increase gives the effect of an acidic microenvironment so that there is sufficient availability of oxygen for metabolism, which increases anaerobic glycolysis and decreases oxidative phosphorylation. Inhibition of LDHA can provide hope in cancer therapy because many studies have shown that inhibition of LDHA reduces cancer growth. This review will describe several cancer treatment approaches using LDH as a cancer therapy target until now.

Introduction

Lactate dehydrogenase (LDH) is an enzyme that catalyzes the conversion of pyruvate to lactate and on the contrary lactate to pyruvate. Pyruvate which is converted to lactate indicates the occurrence of anaerobic glycolysis due to reduced oxygen availability in cells.[1] LDH is a tetramer consisting of two types of subunits M (LDHA) and H (LDHB). The H type is more prominent in the heart, while the M type is more prominent in skeletal muscle and in the liver. These subunits combine to form five types of tetramers, namely H4, H3M1, H2M2, H1M3 and M4. LDHA has a higher affinity for pyruvate and a high Vmax for pyruvate reduction than LDHB. LDHA catalyzes the conversion of pyruvate to lactate, while LDHB converts lactate to pyruvate.[1,2]

LDHA increases its expression in cancer cells and is associated with cancer aggressiveness. The increase in LDHA is due to the high oxygen consumption due to the very fast proliferation rate of these cells so that the cells experience hypoxia.[3] Hypoxic conditions allow the action of LDHA to convert pyruvate to lactate. The increase in lactate gives an acidic microenvironment, so that even though there is sufficient oxygen, the metabolism that occurs is increased anaerobic glycolysis and decreased oxidative phosphorylation. This phenomenon is called the Warburg phenomenon.[2,4]

High levels of lactate production are an indicator of metastasis and a poor prognosis in cancer patients. Lactate has now become a marker for tumor malignancy.[4] While the increase in LDH enzymes in cancer patients can be the main target in cancer therapy.[5] Inhibition of LDHA can provide hope in cancer therapy because many studies have shown that LDHA inhibition reduces cancer growth. This paper will describe several cancer treatment approaches using LDH as a cancer therapy target.

Structure, Isozyme and Function of LDH

The LDH enzyme (LDH, EC 1.1.1.27) has a tetrameric form with a molecular

weight of 144 kDa containing four subunits. Each monomer is formed by a polypeptide chain consisting of 334 amino acids.[6] Each subunit has a different active center.[7] The LDH enzyme is a dehydrogenase enzyme that has isozymes. Isozymes are enzymes that have different structures but catalyze the same reactions.[8] Differences in the structure of isozymes from one another are caused by differences in amino acid sequences, modification of covalent bonds and conformational changes in three-dimensional structures.[9]

The LDH enzyme consists of five isozymes composed of two types of H sub-units (LDHB) and M sub-units (LDHA). These subunits combine to form four types of tetramers namely LDH1 (H4); LDH2 (M1H3); LDH3 (M2H2); LDH4 (M3H1) and LDH5 (M4).[6,9] Sub-units B and A are encoded by two different genes, namely for sub-unit B by the LDH-H gene located on chromosome 12p12.2-p12.1, while for sub-unit A is coded by the LDH-M gene located on chromosome 11p15. 4. The difference between subunits A and B can be seen in the LDH-M and LDH-H sequences.[6,9]

These five isozymes have distribution in several types of organs such as the heart, liver, brain skeleton, kidneys and red blood cells. H4 (LDH1) and H3M (LDH2) isozymes are mainly present in the heart but to a lesser extent in the liver, skeleton and kidneys. The M4 (LDH5) isozyme predominates in the liver and skeletal muscle, but to a lesser extent in heart muscle, brain and red blood cells.[1,4] This difference in distribution has physiological significance. Organs whose metabolism is aerobic are found to contain a lot of LDH isozymes rich in subunits H is shown by the heart. On the other hand, organs capable of anaerobic metabolism contain isozymes rich in slow-moving M subunits such as HM3 (LDH4) and M4 (LDH5) isozymes.[4]

The H subunit has a higher affinity for lactate than for pyruvate. This compound will be immediately converted by the LDH isozyme into pyruvic acid which can then be converted into acetyl-CoA to enter the Krebs cycle which takes place aerobically. Most tissues have the H2M2 (LDH3) isozyme. Under normal circumstances, the LDH present in the blood are LDH2, LDH1, LDH3, LDH4 and LDH5. Normally, red blood cells contain more LDH2 than LDH1.[8] The H subunit is more acidic because it has a residue. There are fewer basic amino acids that have a negative charge compared to the M subunit which has basic amino acids. Therefore, this second property can be utilized in electrophoretic separation. LDH1 migrates faster than LDH5.[2,8]

Lactate dehydrogenase (LDH) is an enzyme that plays an important role in glycolysis. Lactate dehydrogenase catalyzes the conversion of pyruvate to lactate while simultaneously oxidizing NADH in the final step of anaerobic glycolysis. LDH enzyme can catalyze the reversible reaction of pyruvate to lactate. The LDH enzyme can be detected by its ability to catalyze the reduction of pyruvate in the presence of NADH or to catalyze the oxidation of lactate in the presence of NAD+.[9] The structure of LDH can see in this figure 1 below.

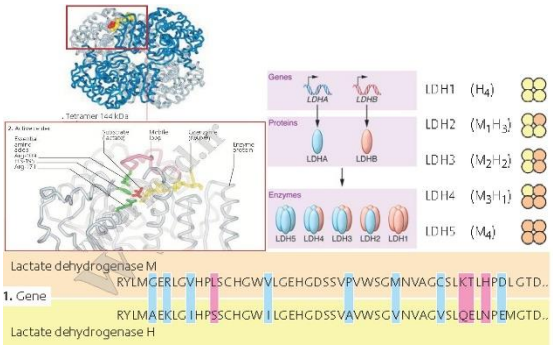

Figure 1. Structure, isozymes and gene of Lactate Dehydrogenase.[8]

Metabolism of LDH in Cancer Cells

Cancer is a disease that results in unrestrained cell proliferation and propagation, which invades and destroys other tissues and eventually kills the organism due to its spread to other areas of the body.[2] Exogenous factors such as chemicals, radiation, viruses and endogenous factors such as immunodeficiency and genetic alterations can lead to the development of cancer.

These changes are basically the result of mutations that benefit oncogene function and eliminate the function of cancer suppressor genes.[11] Cancer formation is a multilevel stage with four to seven steps that occur until the change of normal cells into malignant cells.[4] Cell proliferation is an increase in the number of cells as a result of cell growth and development. Uncontrolled cell growth and development is a hallmark of cancer. Failure of regulation results in phenotypic changes in cancer.

Cancer cells perform a different metabolism than normal cells. In 1920 Warburg discovered that cancer cells metabolize glucose differently in the presence of oxygen. Glucose is converted to pyruvate, but the pyruvate produced is not used for oxidative phosphorylation because pyruvate is converted to lactate. This phenomenon initiates metabolic changes in cancer cells. The changes that occur provide an advantage for cancer cells to survive and carry out cell proliferation and advanced development.[12,9] Metabolic changes create conditions for an acidic extracellular environment At the start of tumor cell expansion, the cells will take oxygen around them so that the cells experience hypoxia and initiate the activation of the transcription factor Hypoxia-inducible transcriptional 1-α (HIF1-α).[9]

Gene Expression of HIF is a solution to overcome cells in hypoxic conditions and reduce dependence on aerobic respiration, as well as oxidative phosphorylation and prioritize anaerobic glycolysis. Therefore, cancer cells experience increased expression of glycolytic enzymes, glucose transport and inhibition of mitochondrial respiration. HIF also stimulates angiogenesis by regulation of several factors including vascular endothelial growth factor.[5,9] HIF-1α induces LDH protein with M-Subunit. LDH-M is also called LDH5 and is encoded by the LDHA gene whereas LDH-H is encoded by LDHB (not regulated by HIF). Both LDH-M and LDH-H are expressed under normal conditions, but in cancer cells LDH5 has increased expression.[10,2]

Other metabolic changes make proto-oncogenes able to become oncogenes by mutations that result in changes in protein structure and increase in protein concentration. This is due to the loss of protein regulation and stability which makes its existence and activity in the cell longer. Several signals are given to activate oncogenes.[9] Ras signals are received when mutations occur and promote glycolysis and then the AKT kinase affects the signal to insulin to take up glucose which is used for regulation of cancer cells. The transcription factor Myc is also upregulated for various metabolisms. Loss of p53 protein prevents expression of the gene encoding SCO2 to synthesize cytochrome C which functions in mitochondrial respiration. The p53 protein also regulates metabolic regulation that depends on the transcription factor NF-Γb.[6,9]

The regulation of glucose metabolism involves various transcription factors. Myc and HIF-1α can regulate LDH expression at the transcription and translation stages. Myc and HIF-1α will attach to the hypoxia response element (HRE) 5'-CACGTC-3' and 5'-GACGTGCG-3' (respectively) which are the sites of the LDHA promoter. HIF-1α will be activated by phosphatidylinositol 3 kinase (P13K) which initiates glycolytic enzymes including LDHA.[6,12]

ErbB2(Her2/neu) is an oncogene that is highly expressed in breast cancer and is indicated for a poor prognosis. If it is related to LDHA expression, its activation is through P13K which can activate HIF-1α and regulate LDHA gene regulation. In addition, heat shock factor 1 (HSF1) also plays a role in the expression of the LDHA gene by attaching directly to the LDHA promoter region.[12,13] Another factor is pyruvate kinase isozyme M2 (PKM2) epidermal growth factor. PKM2 is a transcription coactivator that interacts with HIF-1α. PKM2 induction is carried out by prolyl hydroxylase 2 which promotes HIF-1α and attaches to HRE thereby exerting p300 coactivators, histone acetylation, and converting oxidative phosphorylation to glycolysis. PKM2 is also a β-catenin coactivator to induce Myc expression.[9,12] The regulation of signaling between LDH, Myc and HIF1 in metabolism cancer can shown at figure 2.

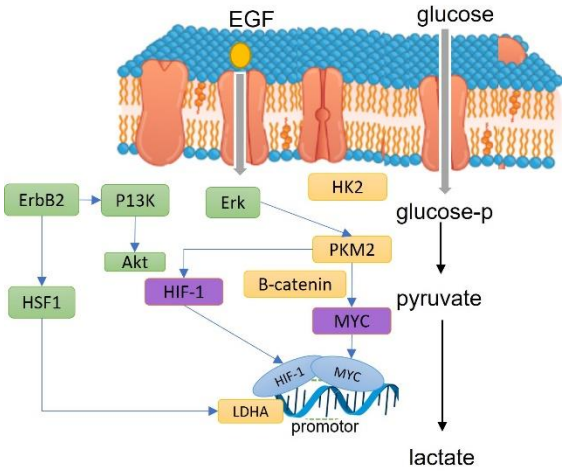

Figure 2. Regulatory Relationship between LDH-A, Myc and HIF-1α in glucose metabolism.[2,6,10,12]

Lactate Dehydrogenase as a Target Cancer Therapy

Based on explanation above, LDH has an important role in metabolism of cancer cells. Which is catalyzing the reaction of pyruvate into lactate and producing NAD+ which is needed to maintain the continuity of the glycolysis process so that allows cancer cells to develop and metastasize. Therefore the current direction of development is more emphasis on finding LDH enzyme inhibitors. Genetic studies show that LDH may be a good strategy for regulating metabolism in cancer cells. As a result of the development of several researchers, there are several ways to use LDH as a cancer therapy, as will be described below.

- *Inhibitory compounds*

Until now, researchers have developed assays and methods to identify LDH inhibitors, especially LDHA. The selected compounds need to have chemical similarities and if used do not cause other reaction disturbances and of course still maintain the stability of LDHA. The use of inhibitor compounds was evaluated through the level of lactate production, oxygen consumption and 13C NMR spectroscopy. In addition, changes in metabolism, cell proliferation and apoptosis also need to be seen. The compound used as an LDHA inhibitor is 3-((3-carbamoyl-7(3,5-dimethylisoxazol-4-i)-6 methoxyquinolin-4-yl) amino) benzoic acid as NADH-competitive. The results obtained are inhibitory compounds that have the potential to inhibit as little as 2-3 nM and at LDHB 10-80 times their inhibition. Rapid rates of lactate production can be inhibited in liver and breast cancer cell lines. The most consistent LDHA inhibition was when cells were subjected to hypoxic conditions and LDHB expression was still low. In addition, there was an increase in oxygen consumption in hepatocellular carcinoma cells at a dose of 3 microM, because higher concentrations would inhibit mitochondria.[14]

In addition, there are other compounds that can inhibit LDH development, namely 1-(phenylseleno)-4 (Trifluoromethyl_ Benzene (15) and galloflavin (5) which suppresses tumor growth through apoptotic cell death interfering by inhibiting LDHA by increasing the potency of LDHB thereby interfering with cell proliferation.[15,16]

- *Inhibition of Shuttle Lactate*

Lactate is a product produced from the pyruvate breakdown reaction by the LDH enzyme. The lactate produced can be a precursor for the formation of glucose in a lack of oxygen. In cancer cells, lactate is produced higher than normal cell production, therefore lactate will be removed from the cell. Lactate is released from the cell through a transporter, namely Monocarboxylate Transporter (MCT). The MCT mechanism occurs in simport, namely when lactate is released, protons will enter, this happens to maintain cell balance. It has been reported that the transporters that act on cancer cells are MCT 1 and MCT 4. Uptake of lactate by tumor cells occurs through the MCT 1 transporter which has a high affinity for lactate. Meanwhile, lactate is released via the MCT 4 transporter which has a low affinity for lactate[17]. Inhibition of MCT1 can provide a choice for tumor cells to use glucose, thereby reducing the

amount of glucose thereby providing hypoxic conditions to tumor cells and causing tumor cells to die. Inhibition of MCT4 can provide a direct potential for tumor cells to experience hypoxia so that tumor cells can die due to the accumulation of lactic acid in the cells.[17]

- *Inhibition RNAi*

RNAi is an interference RNA that is used to inhibit the occurrence of a gene expression. The LDH inhibition approach using RNAi aims to prevent LDH from being produced because it inhibits transcription and allows the degradation of the LDH gene. It has been reported that inhibition of LDHA mRNA with RNAi induced cell death in cancer cell lines with wild-type p53, mutant and without p53 and indicated that the endogenous LDHA formed impairs cancer cell defense. From the results of this study it was found that p53 can regulate NAD+ and reduce NADH. P53-dependent as an inhibitory molecule in cancer cell lines that helps the silencing of LDHA by RNAi. P53 inhibits by decreasing the activity of NAD+-dependent deacetylation of sirtuin 1 (SIRT1) and increasing the acetylation of p53 in cancer cells. Both of these occur due to the increased activity of NADPH-dependent oxidoreductase NQO1. Therefore, the combination of inhibiting the use of RNAi and adding p53 status to cancer cells can be used as therapy.[6,18]

- *Inhibition with LDH Acetylation*

Acetylation is the process of adding an acetyl group. Acetylation of LDH means adding an acetyl group to LDH. LDH acetylation has been reported to play an important role in pancreatic tumors. Through spectophotometric analysis it was suspected that there were eight acetylation sites, and the results of further studies found that acetylation occurred at lysine 5 (K5) which inhibited LDHA catalytic activity. Lysosomes.[19]

- *Inhibition of tyrosine phosphorylation*

Tyrosine phosphorylation is the process of attaching phosphate to tyrosine residues. It has been reported that the receptor tyrosine kinase oncogene FGFR1 directly phosphorylates LDHA. Phosphorylation at Y10 and Y83 gave activated LDHA by prolonging the binding of LDH to NADH. In addition, Y10 phosphorylation in LDHA is associated with the activation of the tyrosine kinase oncogene. Y10 saves cells by reducing cell proliferation and ATP when cells are hypoxic.[20]

Several tyrosine kinase inhibitors have been found and are effective as antitumor agents, namely imatinib mesylate (STI571; Gleevec), gefitinib (Iressa), erlotinib (OSI-1774; Tarceva), lapatinib (GW-572016), canertinib (CI-1033), semaxinib (SU5416), vatalanib (PTK787/ZK222584), sorafenib (BAY 43-9006), sutent (SU11248), and leflunomide (SU101). Inhibition of tyrosine kinase can interfere with signaling pathways and thereby interfere with the development of malignant cells. The ability of new tyrosine kinase inhibitors also continues to develop to solve cancer problems.[20]

Conclusion

LDHA plays an important role in the growth of cancer cells. By inhibiting LDH from the gene to protein level, it can be used as a target for cancer therapy. Inhibition of LDH expression and suppression of lactic acid will affect cancer cell proliferation and growth thereby interfering with cancer development.

Acknowledgment

The acknowledgment is a form of appreciation for the contribution of an institution or an individual who is not considered as the writer for example an institution or an individual who provides the research funding of this publication. Individuals with direct involvement in the study but not included in authorship may be acknowledged. The source of financial support and industry affiliations of all those involved must be stated.

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(Gladies Mercya Grameinie)

Relationship Between Clinical Factors of lymphoma DLBCL GCB and Non-GCB Subtype with Ki-67 Proliferation Index in Siloam Karawaci Hospital 2014 - 2018

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Citation: Kristiani Erna, Marisca Stephanie, Qurro Tri, Kweeswara Natasya, Chandra Amos. Relationship Between Clinical Factors of lymphoma DLBCL GCB and Non-GCB Subtype with Ki-67 Proliferation Index in Siloam Karawaci Hospital 2014 – 2018. Medicinus. 2023 February. 11(1):25-29
Keywords: DLBCL; GCB; Non-GCB; Proliferation index Ki-67; Age; Gender; Location; Stadium.
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Online First: February 2023

Abstract

Background: Non-Hodgkin large cell B-lymphoma (DLBCL: Diffuse Large B-cell Lymphoma) were classified into two subtypes of Germinal Center B-Cell Like (GCB) and non-Germinal Center B-Cell Like (non-GCB), which GCB has a better prognosis. The Ki-67 antigen is one of the most reliable markers of cell proliferation. This research aims to establish the relationship between proliferation index Ki-67 with DLBCL subtypes and to evaluate the utility of Ki-67 proliferative index as a predictive marker for predicting stages of lymphoma.

Methods:
We obtained 60 cases of patient samples DLBCL in Siloam Hospital Lippo Karawaci in 2014-2018. Clinical and pathological data were obtained from medical records. Chi-square methods were used to analyze data.

Result: There were more ≤60 years compared to >60 years. In this study, there were more male patients than female patients. lymphoma provided in extranodal were higher than lymphoma in nodal form.

Conclusions: There is a relationship between Ki-67 proliferation index with lymphoma GCB and non-GCB subtypes and stage of lymphoma, which can be used as a predictive factor in predicting the stage of lymphoma.

Introduction

Lymphoma is one of many types of hematological malignancy. Compared with the incidence of leukemia, lymphoma has a higher incidence rate. Lymphomas occur due to malignant changes in lymphoid tissue, usually local but can spread systemically.[1] Histologically, lymphoma is divided into Hodgkin's Lymphoma and Non-Hodgkin Lymphoma (NHL). Epidemiologically, Hodgkin's disease is relatively rare compared to NHL in Asia.[2] Evidence shows that NHL has an incidence rate of 90% of lymphoma that occurs.[3]

Diffuse Large B-cell Lymphoma (DLBCL) is the most common type of Non-Hodgkin Lymphoma and is highly heterogeneous, both clinically and morphologically. DLBCL is divided into two subtypes i.e. Germinal Center B-Cell Like (GCB) and non-Germinal Center B-Cell Like (non-GCB), where GCB has a better prognosis.[4]

DLBCL is the most common malignant tumor of lymphoid tissue originating from B cells. Based on DLBCL

location, DLBCL is divided into nodal and extranodal, where nodal is found in lymph nodes, while extranodal is found in abdomen, skin, brain, and bone and often metastasizes to bone marrow.[4]

Ki-67 is one of the most reliable cell proliferative markers. Ki-67, a nuclear non-histone protein, is synthesized early in cell proliferation. Ki-67 expressions have been widely used in clinical practice as an index for evaluating activity of lymphoma proliferation. High Ki-67 expression is strongly associated with worse overall survival (OS) for NHL. Nevertheless, the relationship between Ki-67 and results with DLBCL lymphoma are still contradictory and inconclusive in various studies. Ki-67 expression is related to differentiation degree in most tumors. Few studies show Ki-67 expression is highest in poorly differentiated carcinoma.

Based on the data above, this study aims to see the relationship between clinical factors of lymphoma DLBCL subtype GCB and non-GCB with a Ki-67 proliferative index at Siloam Hospital in 2014-2018 and to evaluate the utility of Ki-67 proliferative index as a predictive marker for predicting stages of lymphoma.

Study Methods

Population and Sample Research

This study is a cross-sectional retrospective analytical study. All data were taken from the medical records of DLBCL lymphoma patients at General Hospital Siloam Lippo Karawaci, Tangerang from 2014-2018. Samples with incomplete clinical data, as well as patients who did not undergo the Ki-67 examination were excluded. The sampling technique was carried out sequentially.

Staging and Ki-67

Ann Arbor Staging System was used to classify the stage of lymphoma in this study. High Ki-67 proliferative index is defined by > 70 proliferative index, while low Ki-67 proliferative index is defined by < 70 proliferation index.

Study Analysis

This study was conducted with a total of 60 subjects consisting of GCB and Non-GCB DLBCL patients at Siloam Hospital, Karawaci from 2014 to 2018. The statistical data obtained were analyzed using the Chi Square test. Relationship between Ki-67 proliferative index and stage of the lymphoma used Chi Square Test for Independence or Cross Tabulation analysis. All analyses were done in SPSS 23.0.

Result

Subject Characteristic

Table 1. Frequency and Percentage Based on Characteristic of Study Subjects lymphoma Patients at Siloam Hospitals Karawaci in 2014-2018

Subject characteristic (n=60)		Frequency	Persentage (%)
Age	≤60	40	66.7
	>60	20	33.3
Sex	Male	32	53.3
	Female	28	46.7
Location	Extranodal	34	56.7
	Nodal	26	43.3
Stage	I	3	5.0
	II	9	15.0
	III	24	40.0
	IV	24	40.0

Table 1. shows characteristics of participants enrolled in the study. Age, sex, location and stage were shown in the table above

Table 2. Distribution of descriptions of age, sex, location, stadium with subtypes of lymphoma of DLBCL and Ki-67

		GCB	Non-GCB	Ki-67 high	Ki-67 low
Age	≤60	22 (55.0%)	18 (45.0%)	29 (72,5%)	11 (27,5%)
	>60	12 (12 (60.0%)	8 (40%)	18 (90.0%)	2 (10.0%)
Sex	Male	18 (56.2%)	14 (43.6%)	22 (68.8%)	10 (31.2%)
	Female	16 (57.1%)	12 (42.9%)	25 (89.3%)	3 (10.7%)
Location	Extra nodal	21 (61.8%)	13 (38.2%)	26 (76.5%)	8 (23.5%)
	Nodal	13 (50.0%)	13 (50.0%)	21 (80.0%)	5 (19.2%)
Stage	I	3 (100%)	0 (0.0%)	0 (0.0%)	3 (100%)
	II	9 (100%)	0 (0.0%)	0 (0.0%)	9 (100%)
	III	20 (83.3%)	4 (16.7%)	23 (95.8%)	1 (4.2%)
	IV	2 (8.3%)	22 (91.7%)	24 (100%)	0 (0.0%)

GCB: Germinal Center B-Cell Like, Non-GCB: Non-Germinal Center B-Cell Like

Table 2. shows the distribution of lymphoma subtypes (GCB and non-GCB) and Ki-67 proliferative index level among the characteristics of participants enrolled in the study.

Statistical Test Results

Table 3. Results of Analysis of Age, Gender, Location, Stadium with Ki-67

Subject characteristic (n=60)		Ki-67		P-Value
		High	Low	
Age	≤60	29 (72.5%)	11 (27.5%)	0.186
	>60	18 (905)	2 (10%)	
Sex	Male	22 (68.8%)	10 (31.2%)	0.066
	Female	25 (89.3%)	3 (10.7%)	
Location	Extra nodal	26 (76.5%)	8 (23.5%)	0.760
	Nodal	21 (80.0%)	5 (19.2%)	
Stage	I	0 (0.0%)	3 (100%)	0.000
	II	0 (0.0%)	9 (100%)	
	III	23 (95.8%)	1 (4.2%)	
	IV	24 (100%)	0 (0.0%)	

Table above shows those with stage I 0 (0%) subjects have a high Ki-67 proliferation index and 3 (100%) subjects had a low Ki-67 proliferative index. In stage II, all 9 subjects have a high Ki-67 proliferative index. Stage III included 23 (98.5%) subjects who had a high Ki-67 proliferation index value. Subjects who have stage IV include 24 (100%) subjects who have a high Ki-67 proliferation index value and 0 (0%) subjects who have a low Ki-67 proliferation index value. Through these data, a p-value of 0.00 can be obtained, indicating a significant relationship between the proliferation of Ki-67 with the stage.

Table 4. Analysis lymphoma Subtype DLBCL with Proliferation Index Ki-67

	Ki-67		P-Value
	High	**Low**	
GCB	21 (61.8%)	13 (38.2%)	0.000
Non-GCB	26 (100%)	0 (0.0%)	

Table 4 above shows lymphoma of the GCB subtype which has a high Ki-67 proliferation index value as many as 21 subjects or equivalent to a percentage of 61.8% and those with a low Ki-67 proliferation index value as many as 13 subjects or equivalent to 38.2%. The Non-GCB Subtype lymphoma which had a high Ki-67 proliferation index value were 26 subjects or equivalent to a percentage of 0%. From these data, a p value of 0.000, indicates that there is a significant relationship between GCB and Non-GCB lymphoma subtypes with Ki-67 proliferation.

Discussion

From the study analysis above, it indicates that the age group ≤60 years old has a higher percentage of lymphoma than the age group >60 years old. In another study, it was found that the average age of LNH patients in this study was 53 years. This result is the same as findings reported by Mozaheb (2012). This study reported that the average age of diagnosed LNH was 45-55 years old. Similarly, results presented by Yasmin, et al (2005) reported that the average age of diagnosed LNH patients was 50-55 years old.[6,7]

From the result of this study, there were more cases of lymphoma in males. Based on the theory that has been described in the literature review in accordance with the results of the analysis where men are more susceptible to lymphoma than women. Lifestyle or habits that can increase the risk of lymphoma, such as drinking alcohol and smoking are more common habits much favored by men.[5]

From the results of this study, it shows extranodal located lymphoma are more numerous than nodal located lymphoma, this result is in line with the research conducted by Megko S Kennedy, et al.[8]

From the results of this study, it indicates that the Non-GCB subtype lymphoma has a higher stage than the GCB subtype lymphoma, and has a significant relationship with the Ki-67

proliferation index (p value <0.05). The results of this study indicate that the Non-GCB subtype lymphoma has a Ki-67 proliferation index which is higher than the GCB subtype lymphoma. Research conducted by Youssef, et al also showed the same results. Proliferative index value limit of 70% is a value to distinguish bad prognosis and vice versa, so it can be concluded that Non-GCB subtype DLBCL lymphoma has a worse prognosis than GCB DLBCL lymphoma.[9]

The results of this study can be concluded that the p value of clinical factors of age, sex, location, has no relationship with the Ki-67 proliferation index. While the clinical factor stage has a p value <0.05, namely (p: 0.0000), it can be concluded that the stage has a relationship with the Ki-67 proliferation index. Based on a literature review, high Ki-67 is associated with the stage of lymphoma and can be a determinant factor of prognosis for DLBCL lymphoma patients. Other clinical factors such as age, gender, location did not have a significant relationship to Ki-67. According to Kramer, et al. the difference in results obtained was caused by several factors including differences in the size of the sample used, the way of interpreting Ki-67 differences, as well as errors in assessing the expression of Ki-67. In addition, there is no international agreement in determining how to assess the expression of Ki-67 and determine the limit value of Ki-67.[10]

This study was conducted in a cross-sectional manner, data were collected retrospectively and no follow-up was performed for the patients. Therefore, this study cannot be used to search for causality and the mechanism of the relationship between the Ki-67 proliferation index and the DLBCL subtype. Randomized clinical trials are needed to determine the effectiveness of the Ki-67 proliferation index with DLBCL subtype as a diagnostic tool.

Conclusion

There is a relationship between Ki-67 proliferation index to the stage of lymphoma GCB and non-GCB subtypes. There was no significant relationship between age, gender, and tumor location with the Ki-67 proliferation index. As evidence shows high Ki-67 proliferative index correlates with higher lymphoma stage, therefore Ki-67 biomarker can be used as a predictive factor in predicting the stage of lymphoma.

Acknowledgment

None.

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A Case Report: Combined Sciatic Nerve and Lumbar Plexus Nerve Block in A Patient with Acute Decompensated Heart Failure Undergoing Lower Extremity Surgical Debridement

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Citation: Tantri Irma, Saroso Natalia. Case Report: Combined Sciatic Nerve and Lumbar Plexus Nerve Block in Patient with Acute Decompensated Heart Failure Undergoing Lower Extremity Surgical Debridement. Medicinus 2023. February; 11(1):30-35
Keywords: Lumbar plexus block; Sciatic nerve block; Heart failure; Lower extremity surgery; CSLPB
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Online First: February 2023

Abstract

Background: Peripheral nerve block for lower extremity surgeries requires a minimum of two block injections. Although the combination of the lumbar plexus block and the sciatica block is a procedure that requires large doses of local anesthetic, which may induce cardiotoxicity, a recent study suggests that change in the hemodynamic system is not clinically significant.

Case Description: We report a case of a 53-year-old male presenting with a worsened shortness of breath two days before hospital admission. He also experienced a sudden high fever and pain on his right thigh. The patient had a history of Heart Failure (EF 28%) and Congestive liver disease and was diagnosed with right femur cellulitis with right phlegmon. Surgical debridement was planned to treat sepsis. Right lumbar plexus block and right sciatica block were performed as surgical anesthesia. The surgery duration was one hour, and the patient was transferred to the PACU. The patient was treated in ICU before being admitted to the general ward and was discharged on day three post-surgery.

Conclusion: The combination of Sciatic nerve and lumbar plexus nerve block is an effective anesthesia and analgesia technique for lower limb surgery in individuals with a severe heart condition.

Introduction

Peripheral nerve block is becoming a widely used regional anesthesia technique with aid from ultrasound guidance.[1]

A minimum of two block injections of the lower extremity peripheral nerve block are required in, the lower extremity peripheral nerve block. This combination of two blocks requires a high dose of anesthesia drugs which may induce cardiotoxicity.

Anatomically lumbar plexus is located mainly in skeletal muscle; thus, injection of local anesthetics may increase the risk of high systemic absorption. The combination of lumbar plexus block and sciatic nerve block may also cause hemi-sympathectomy and vasodilation in the corresponding extremity that has been anesthetized. The decrease in arterial blood pressure may influence the cardiac index. Referring to de Leeuw's study, although this decrease was statistically significant, the arterial blood pressure

varied by less than 10%; thus, it does not correspond with the cardiac index. Therefore, this can be concluded that the change in the hemodynamic system is not clinically significant.[2]

Case Description

A 53-year-old male presenting with a worsened shortness of breath two days before hospital admission. He became persistently breathless, and the symptom worsened with activities. He complained of chest pain, palpitation, and yellowing on his skin and eyes. Recently he also experienced a sudden high fever and pain in his right thigh. His past medical history showed that he had a history of coronary artery disease (CAD) and underwent Percutaneous coronary intervention (PCI) three months prior.

The patient appeared dyspneic,icteric and was in pain. His temperature was 38.7 C, RR 26 breaths/min, PR 76 beats/min, and SpO2 was 93% without O2 supplementation. His physical examination revealed a murmur on the tricuspid valve and a gallop on cardiac auscultation. There was swelling and redness on the right lower extremity that was warm and tender to the touch.

Electrocardiography showed normal response Atrial Fibrillation (AF). Laboratory results demonstrated leukocytosis (16.640/µL), hyperbilirubinemia, prolonged APTT, and also increased Procalcitonin (6.53ng/mL) and CRP (43.4 mg/L). Echocardiography revealed LVH (Left Ventricular Hypertrophy) concentric EF (Ejection Fraction) 28% with decreased systolic function. The abdominal ultrasound findingwas congestive liver disease, while the right lower extremity ultrasound displayed diffuse cutaneous–subcutaneous edema seen on the posteromedial proximal femur, anteromedial distal femur, and posterolateral distal femur suggestive of cellulitis.

The patient was diagnosed with right femur cellulitis with right phlegmon, sepsis, Acute decompensated heart failure, Parenchymal icterus et causa congestive liver disease, normal response AF and stabilized CAD. The patient was symptomatically treated with analgesics and antipyretics. Pharmacological treatment included Digoxin, Aspirin, heparin, diuretics (Spironolactone, Furosemide), and Intravenous broad-spectrum antibiotics (Ampicillin-Sulbactam). The cardiologists advised treating sepsis immediately and suggested cardiac ablation or implantable cardioverter-defibrillator (ICD) placement on an outpatient basis for the management of the normal response Atrial Fibrillation. The surgeon scheduled a drainage incision on the cellulitis to clear the source of infections. Antiplatelet and anticoagulant were stopped temporarily five days before surgery.

The patient was fully conscious and cooperative on the day of surgery. Vital signs were within normal range. ECG revealed normal response AF.

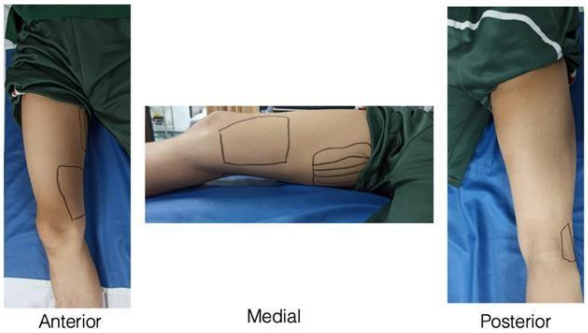

Figure 1. Patient's wound area

The patient was given an O2 supplementation using 3 lpm nasal cannula. He was monitored with NIBP (Noninvasive Blood Pressure), ECG 3 lead, and pulse oximetry. Central Venous Catheter (CVC) and arterial blood

pressure monitoring were established under local anesthetic. The combination of the lumbar plexus block and the right sciatic block was performed using portable ultrasonography with 2-5MHz (Sonosite M-Turbo) transducer curved, nerve stimulator Pajunk MultiStim Sensor, 22G 10cm insulated needle (Stimuplex Ultra 360, B.Braun, Germany).

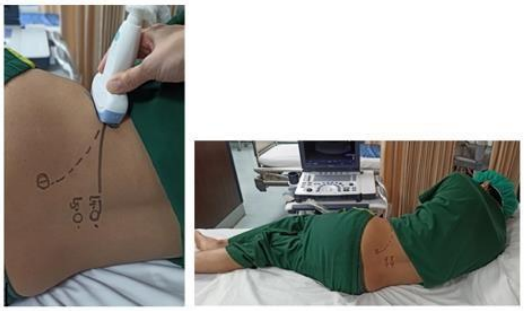

Figure 2. Right lumbar plexus block with shamrock method

Table 1. Lumbar Plexus Nerve and Sciatic Nerve Block

	Right Lumbar Plexus Block	Right Sciatic Block
Method	Shamrock method	Subgluteal approach
Position	Lateral decubitus (right foot above left foot)	Lateral decubitus
Probe location	Paramedian transverse scan above right iliac crest	Subgluteal (as level as greater trochanter and ischial tuberosity)
Needle insertion	In plane	In plane
Nerve stimulator	Quadriceps muscle twitch (+) 0.2-0.5 mA	Hamstrings muscle twitch (+)
Anesthetic agent	0.25% bupivacaine isobaric 20ml with epinephrin 1:200.000	0.25% bupivacaine isobaric 20 ml with epinephrin 1:200.00

The patient was placed in the lateral decubitus position. After aseptic antiseptic was given, local anesthetic using lidocaine 1% 2ml was injected into the insertion area.

The lumbar plexus block was performed using shamrock method. The ultrasound probe was placed above right iliac crest with the paramedian transverse scan technique. The needle is inserted with an in-plane approach at depth where transverse process is contacted.Nerve stimulator showed twitch response of the quadriceps muscle is elicited at 0.2-0.5 mA.Isobaric bupivacaine 0.25%20 ml with epinephrine 1 : 200,000 were injected through a 22G insulated needle.

The right sciatic block was performed with the subgluteal approach. The ultrasound probe was placed transverse on the right gluteal crease to visualize the area between greater trochanter and ischial tuberosity. The needle is inserted in-plane from the lateral aspect of the ultrasound probe, and advanced toward the sciatic nerve. Nerve stimulator showed Hamstrings muscle twitch.

Isobaric bupivacaine 0.25%20 ml with epinephrine 1 : 200,000 were injected through a 22G insulated needle once the needle tip is positioned adjacent to the nerve.

After the procedure was successfully performed, the patient denied palpitation, chest pain, or shortness of breath. The patient was monitored 20 – 25 minutes after; it was found that the blood pressure had decreased to 80/40mmHg, and there was an AF rapid response with a heart rate of 125 – 140 bpm found on ECG. The patient was given a bolus of 200 ml crystalloid and dobutamine drip with titrated dose. After that, the blood pressure increased to 90/60mmHg with ECG AF rapid response, and the heart rate decreased (105 – 110 bpm). The duration of the surgery was one hour, and then the

patient was transferred to the PACU (Post Anesthesia Care Unit).

In the PACU, vital signs were stable, and complaints were denied. The patient was treated in ICU before being admitted to the general ward and was discharged on day three post-surgery.

Discussion

According to the dermatomal,wound at the lower limb at the anterior, medial and posterior side are innervated by these nerves as follows, a) anterior: anterior cutaneous branch of the femoral nerve (anterior rami, posterior division of the Lumbar II – IV nerve root), b) medial: anterior division of the obturator nerve (anterior rami, ventral division of the Lumbar II – IV nerve root), and c) posterior part of the common peroneal nerve (anterior rami of the Lumbar IV – Sacral II nerve root). In this case Lumbar Plexus Block have the coverage of the anterior branch of the femoral cutaneous nerve and anterior division of the obturator nerve. Meanwhile the sciatic block will cover the common peroneal nerve.

According to study from Jogdand (2019), combination of the psoas compartment block (posterior plexus block) and sciatic block have the efficacy to block the sensory that is equivalent to continuous spinal anesthesia in the operation of the lower limb. Post operation analgesia also has a longer duration of pain relief in psoas compartment and sciatic block when compared to spinal anesthesia.[3] Demirel et al (2014) also found that with the combination of L1 paravertebral, psoas compartment block and sciatic block have an extended initial time of analgesia need.[4]

According to the literature, combination of the lumbar plexus block and sciatic block, have a better hemodynamic status when compared to the patient received spinal anesthesia.[4,5] In this patient, 20 – 25 minutes after block, there is a decrease in blood pressure from 146/62 mmHg to 80/40 mmHg. Patient's ECG also showed a change from normal response atrial fibrillation with a heart rate of 82x/min into rapid response atrial fibrillation 125 – 140x/min.

This event may be caused by the pre-existing congestive liver disease that patient had, that the local anesthesia agent disposition. Congestive liver disease itself related to the heart failure that patient had that cause patient's stroke volume is low that caused the hemodynamic to be unstable. Lowered blood circulation will cause the vascularization to the liver decreased and hepatocellular dysfunction. In addition to that, big volume of the local anesthesia agent and block at the highly vascularized area will cause increase in the local anesthesia agent absorption. Other probability that may cause the hypotension in the patient is the probable epidural spread that following the lumbar plexus block. However, previous study showed that Shamrock technique in the lumbar plexus block is a technique that will reduce the risk of epidural spread. This technique increased the visibility, and the position of the needle tip does not head to the neural foramina so it will reduce the risk of epidural distribution. One of the disadvantages of the CSLPB (Combined Sciatic Nerve and Lumbar Plexus Nerve Block) is the required time to the anesthesia preparation. Adali et al (2011) compared the required time to prepare for lumbar plexus block and sciatic block compared to spinal anesthesia in patients underwent lower limb orthopedic operation and it showed that in patients with spinal anesthesia had a significantly shorter time for preparation ($p < 0.001$).[5]

Another study by Demirel et al (2014) also showed that in patients receiving combination of the lumbar plexus, sciatic block and paravertebral L1 block has a longer time for preparation compared to spinal anesthesia in patients underwent

hemiarthroplastyoperation ($p < 0.001$).[4] On the other hand, Adali et al (2011) shows that even though it took a longer time for preparation, it has a comparable surgeon-patient's satisfaction in the two groups.[5]

Lumbar plexus block and sciatic block have a highly vascularized area, so we need to add epinephrine 1:200.000 local anesthetic agent to detect early intravascular injection. Local anesthetic agent is given slowly with a repeated aspiration every 5 ml. To prevent local anesthetic toxicity in the patient, local anesthetic agent administration in a big volume (20 ml) at each lumbar plexus and sciatic block has been calculated and should not exceed 3 mg/kg (Bupivacaine).

According to the study to find the prospective dose-finding in patients with ASA I, II or stable ASA III that used Dixon's up-and-down sequential method. In patient receiving lumbar plexus block with Ropivacaine 0.5% 20.4 ml will be effective in 50% patients, meanwhile 36.0ml will be effective in 95% patients. If the motoric block of the femoral nerve is not mandatory,25.8 ml (95% CI 18.6 – 33.1) is adequate to block the sensory in 95% patients.[7]

There is two plane that can be used in lumbar plexus block with ultrasound guidance, sagittal and transverse plane. According to the expert, anatomically transverse plane is better in visualizing the structure. Paramedian transverse (PMTS) and Shamrock techniques use the transversal plane with ultrasound guidance. Pangthipampai et al (2019) compared the PMTS and Shamrock technique in visualizing the related anatomy. The Shamrock technique significantly can visualize the lumbar plexus (89.1%) compared to PMTS (60.9%) ($p = 0.002$). Advantage of the PMTS technique is that it could visualize the articular process more clearly compared to Shamrock technique. However in the Shamrock technique, other than the lumbar plexus, we could see other structure such as inferior vena cava, quadratus lumborum muscle clearly.[8]

There are several approach to sciatic nerve block, such as anterior approach, parasacral, transgluteal, infragluteal, lateral, posterior subgluteal, infra-gluteal-parabiceps, proximal femur of the popliteal fossa.[9] In this patient, the chosen method is the subgluteal approach. Subgluteal space, where the sciatic nerve located is a distinct bordered space. Subgluteal space can be identified with ultrasound as level as greater trochanter and ischiadicum tuberosity as a hypoechoic area between the perimysium of the gluteus maximus and quadratus femoris muscle. Local anesthetic agent that is injected to the subgluteal space with ultrasound guidance is effective to block the sciatic nerve. There is also several other advantages in using subgluteal approach, such as 1) easier to insert the needle into the subgluteal space with the ultrasound guide, 2) needle tip position can be confirmed using 2- 3 ml saline to see the distension of the subgluteal space, 3) easier to insert continuous catheter to the subgluteal space, 4) subgluteal injection can also block the posterior cutaneous femoral never that innervates the sensory of the posterior aspect of the femoral regionand 5) in this area, there is no main blood vessels to minimize the vascularcomplications.[9]

Conclusion

The combination of Sciatic nerve and lumbar plexus nerve block is aneffective anesthesia and analgesia technique for lower limb surgery in individuals with a severe heart condition. (ASA III).

This procedure should be performed under ultrasound guidance and nerve stimulator to identify the targeted nerve that is located deep and the structure around it so that it will reduce the complication risk (intravascular injection).

The determination of volume, local anesthetic agent concentration, and block approach should be tailored according to the patient's condition to reduce the risk of its toxicity and spread to the epidural space, especially in patients who underwent lumbar plexus block.

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Irma Lusiana Tantri

Concomitant Chylothorax and Chyloperitoneum with Newly Diagnosed: B-Cell Lymphoma: A Case Report

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Citation: Siahaan Sylvia, Prasetya Ignatius, Pradhana Cindy. Concomitant Chylothorax and Chyloperitoneum with Newly Diagnosed: B-Cell Lymphoma: A Case Report. Medicinus. 2023 February. 11(1): 36-40
Keywords: Chylothorax; Chyloperitoneum; Lymphoma
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Online First: February 2023

Abstract

Chylothorax and Chyloperitoneum are an infrequent condition, characterized by the accumulation of chyle in the pleural and peritoneum cavity. We report an uncommon presentation of concomitant chylothorax and chyloperitoneum caused by diffuse B-cell Lymphoma. A 60-year woman was admitted with progressive shortness of breath, abdominal fullness, cough when lying down on one week duration. She also complains progressive non painful neck lump, night sweats, and weight loss. Chest radiograph showed right pleural effusion. CT scan abdomen with contrast revealed ascites with lobulated mass and multiple lymphadenopathy. Thoracocentesis and paracentesis were performed, revealed exudative with yellow and milky appearance and elevated triglyceride. Histopathologic confirmed diffuse large B-cell lymphoma. Chylothorax concomitant with chylous ascites is rarely encountered. Serous effusion occur often in malignant lymphomas. Management of chylothorax and chyloperitoneum is conservative measures and treat the aetiology. Effusion often becomes a chronic problem that persist although the lymphoma has been treated.

Introduction

Chylothorax and Chyloperitoneum are an infrequent condition, characterized by the accumulation of chyle in the pleural and peritoneum cavity. Etiology of chylothorax and chyloperitoneum classified into traumatic and non-traumatic. Non traumatic chylothorax is primary caused by malignancy, such as lymphoma or metastatic carcinoma. We report a previous case with uncommon presentation of concomitant chylothorax and chyloperitoneum caused by diffuse large B-cell Lymphoma.

Case Illustration

A 60-year woman with no significant past medical history was admitted with progressive shortness of breath, abdominal fullness, cough when lying down on one week duration. She also complains progressive non painful neck lump in the last two months, night sweats and weight loss in the last one year. On review system, she denied any fever and chills. Her medical history included previously diagnosed diabetes mellitus type 2 on medication and no history of tuberculosis.

On physical examination, she was underweight (BMI 15.8 kg/m^2), respiratory rate 40 times per minute, oxygen saturation 92% on room air. Chest examination revealed dullness and decreased breath sound in the right hemithorax. Abdominal distension with fluid wave and shifting dullness was also noted. She had palpable lymph nodes in right submandibular, left supraclavicular region, and multiple in the left iliac and lumbar region.

Laboratory examination revealed thrombocytosis (Platelet 663K/μL). Hemoglobin, white cell count, liver function tests, and renal function tests were within normal limits. Chest radiograph posteroanterior (PA) view showed right pleural effusion and opacity in left lower lobe and serial chest radiograph was performed (**Figure 1**). CT scan abdomen with contrast revealed ascites with lobulated mass with contrast enhanced in para-aortic, pericaval, common and internal para-iliac, mesentery, and liver hilum measuring 12.3 x 15.8 x 21.9 cm, multiple mesenteric lymphadenopathy (size 1,3 – 2,3 cm), and bilateral pleural effusion with mass in right hemithorax measuring 1.2 x 2.7 x 1.5 cm suspect right diaphragm lymphadenopathy (**Figure2**).

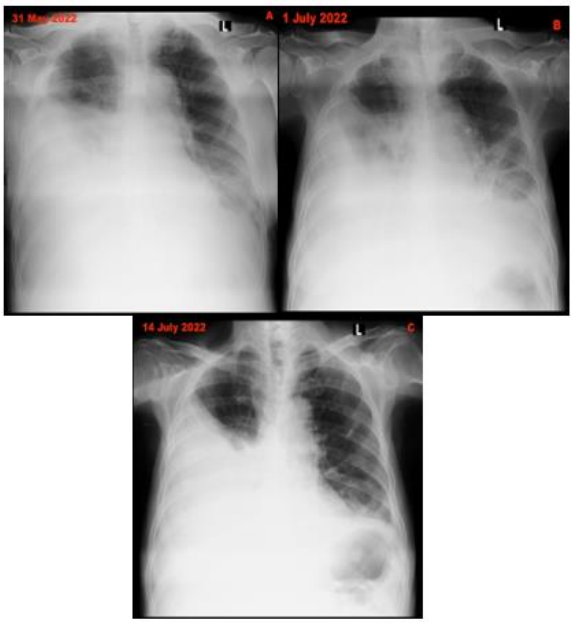

Figure 1. A. Posteroanterior chest radiograph on admission showed unilateral pleural opacity
B. Before chemotherapy showed bilateral pleural opacity
C. 10 days after chemotherapy showed unilateral pleural opacity which is slightly improved

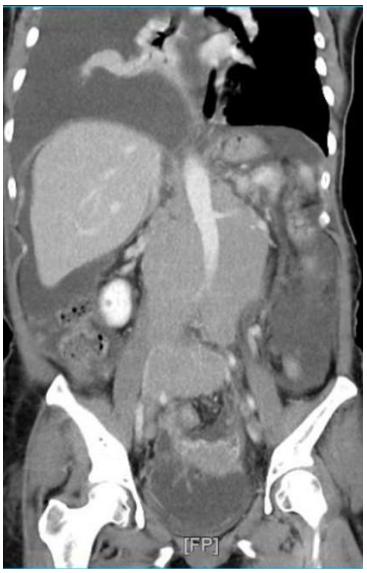

Figure 2. CT scan whole abdomen with contrast showed lobulated mass, multiple lymphadenopathies, bilateral pleural effusion

Thoracocentesis and paracentesis were both performed. Pleural fluid was milky and yellowish-coloured, protein level 6.35 g/dL, lactate dehydrogenase 505 U/L, LDH ratio 0.89 consistent with exudate, triglyceride 323 mg/dL, and mononuclear cell were dominant. Peritonealfluid was also yellow, milky appearance, and exudative. Pleural fluid cytology showed lymphocyte predominance, atypical cells with reactive mesothelial. Biopsy was performed for neck lymph node with result suspect diffuse large B-cell lymphoma. The result of imunohistochemistry:
CD20: positive with noduler dan diffuse pattern
CD 3, CD 5: negative
CD 10: positive in some cells
CD 21: positive in follicular dendritic cell
Mum-1: negative
Ki-67: positive ± 70%
Cyclin D1: negative/ non spesific
Conclusion: Follicular Lymphom, high grade with fiffuse large B-cell lymphoma.

She was consulted to oncologist for chemotheraphy with regimen RCHOP (Cylcophospamide 1000 mg, Doxorubicin 70 mg, Vincristine 2 mg, Prednison 100 mg/day). After one cycle of chemotherapy, the pleural effusion still re-occurred one week later and thoracocentesis was performed. Unfortunately, she went to her home at Kalimantan for next treatment.

Discussion

Chyle is milky fluid that consist of lymph and lipid formed in small intestine and taken up by lymph vessels. Chyle is naturally alkaline, bacteriostatic, nonirritating that contains immunoglobulin, white blood cell, protein, and electrolytes. Chylothorax refers to the presence chyle to pleural cavity due to obstruction or leakage of thoracic duct. Chyloperitoneum or Chylous ascites is uncommon for ascites, defined as extravasation chyle to peritoneal cavity as a result of obstruction of injury lymphatic system. Chylothorax and chyloperitoneum are classified to traumatic and non-traumatic causes. As a cause of chylothorax and chyloperitoneum, multiple aetiologies have been described, and the underlying aetiology determines the ongoing evaluation and management. More than half of all chylothorax caused by with lymphoma accounting for thevast majority. The commonest etiology of chyloperitoneum are malignancy, cirrhosis, tuberculosis, and filariasis leading to lymphatic fluid stasis.[1-4]

Statistics show that in patients with non-Hodgkin's lymphoma (NHL) and Hodgkin's disease (HD), 20-30% will develop a pleural effusion, while pericardial and peritoneal effusions are uncommon. The main cause of pleural effusion in Hodgkin disease has been identified as thoracic duct obstruction. However in NHL, the primary consideration was shown to be direct pleural infiltration. Chylothorax concomitant with chyloperitoneum is rarely encountered. The reported incidence of the concurrent of chylothorax and chylous peritoneum has varied from 9% to 55% of chylous effusion. [1,5-8]

The majority of patients with chylothorax present with dyspnea but the severity depend on the rate of chyle accumulation as well as the aetiology. Chylous effusions are always caused by an obstruction of the lymphatic trunks. Disruption of thoracic duct between T4 and T6 levels may produce bilateral chylothorax, while disruption above and below this point maylead to left and right chylothorax. In the present case, the pleural and abdominal effusions were identified to be chylous, strongly indicating that the effusions originated in the lymph trunks. Possible reasons for the effusions may be that the metastatic lymphoma cells blocked the lymph tunnels leading to obstruction and further impairment of these tunnels, and can occurs due to transdiaphragmatic fluid migrationfrom chylous peritoneum. Another method to identify thesource of chylothorax by injection of ^{99m}Tc-sulfur colloid into peritoneal space or lymphangiography, but we did not perform in our case. [1,5-8]

Thoracocentesis and paracentesis are necessary for diagnosis chyllus as it will reveal turbid, milkyfluid and characterized by elevated triglycerides > 110 mg/dL or the presence of chylomicrons. Measurement of triglyceride and cholesterol levels in the pleural fluid should be the initial lipid tests performed in patients with suspected chylothorax. The chylous fluid is lymphocyte predominant exudative fluid. In our case, pleural and ascitic fluid reveal yellow and milky, exudative fluid with mononuclear cell dominance and elevated triglyceride, which fulfil chylous fluid. Moreover, the fluid that are collected from pleural and abdominal cavities may be used to relief symptoms and improve our understanding for aetiology such as infections and malignant cells.[5]

In our case, cytology showed lymphocyte predominance, atypical cells with reactive mesothelial and culture showed no growth of bacteria. CT scan abdomen was performed to evaluate abdominal lymphadenopathy, in our patient showed multiple lymphadenopathy that suggest lymphoma, ascites, and large lobulated mass and incidental finding of thorax revealed pleural effusion and lymphadenopathy in right hemithorax. In consequence of multiple lymphadenopathy in neck region, biopsy was performed in supraclavicular lymph nodes revealed diffuse large B-cell lymphoma, confirmed by IHK. Serous effusions in lymphoma are generally associated with a poor outcome. Management of chylothorax and chyloperitoneum is conservative measures and treat the aetilogy. Effusion often becomes a chronic problem that persist although the lymphoma has ben trated. Repeated peritonal and pleural taps are often needed for symptomatic tratmnt. Pleural drainage such as chest tub, indwelling catheter, or pigtail catheter are recommended for massive pleural effusion to relieve symptom and to measure the accumulation of pleural fluid. But, in this case, the patient preffered to do thoracosintesis periodically, rather than insert the pigtail. Thoracocentesis is a different strategy in patients who are not thought to have rapid fluid reaccumulation, patient preference, or poor prognosis.[1,9-12]

She was referred to oncologist for chemotherapy RCHOP regimen. According to ESMO recommendation, she is high risk category based on International Prognostic Index.

Conclusion

The combination of chyloperitoneum and chylothorax is infrequent complications of lymphoma, despite effusion in lymphoma are common. Lymphoma is the most common non traumatic aetiology for both Chylothorax and chyloperitoneum result from thoracic duct damage with chyle leakage to cavity. The diagnosis was made by fluid analysis. Management is mainly conservative along with treatment of underlying aetiology in order to disease's improvement.

Acknowledgment

The acknowledgment is a form of appreciation for the contribution of an institution or an individual who is not considered as the writer for example an institution or an individual who provides the research funding of this publication. Individuals with direct involvement in the study but not included in authorship may be acknowledged. The source of financial support and industry affiliations of all those involved must be stated.

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