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Case-controlled Study

The association of iron deficiency anemia on chronic suppurative otitis media in children: A case-control study

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ABSTRACT

Background: Chronic suppurative otitis media (CSOM) is the most common infectious disease in the world and the leading cause of hearing loss in children in developing countries. Iron deficiency anemia (IDA) is often found in children with CSOM.

Objective: This study was conducted to determine the association between IDA and the incidence of CSOM in children.

Method: This research is a case-control study using consecutive sampling. Participants were divided into case group which are children diagnosed with CSOM (n = 42) and control group which are children with normal ear (n = 42). All participants were examined for serum iron (FE), hemoglobin (Hb), total iron-binding capacity (TIBC), and ferritin levels. The analysis used in this study includes the chi-square test or fisher extract test and independence *t*-test or Man Whitney test with $p < 0.05$.

Result: The measurement results obtained values of Hb (13.00 ± 1.34 g/dL; $p < 0.001$), FE (95.13 ± 40.84 g/dL; $p < 0.001$), TIBC (354.18 ± 62.44 g/dL; $p = 0.016$), and ferritin levels (17.57 ± 8.55 g/dL; $p < 0.001$). Participants who experienced IDA were 21.43% which in the case group was 31.0% and control group was 11.9% ($OR = 3.32$; $p = 0.033$).

Conclusion: IDA can increase the incidence of CSOM in children.

1. Introduction

Chronic suppurative otitis media (CSOM) is inflammation of the middle ear mucosa and mastoid cavity that lasts more than 2 months characterized by perforation of the tympanic membrane and continuous or intermittent discharge from the ear canal [1]. CSOM is a public health problem worldwide and the leading cause of hearing loss in children, especially in developing countries. In children, this disease can be a risk factor in delays in language and speech development, cognitive disorders, and learning disorders at school [2,3]. According to the World Health Organization (WHO), the prevalence of CSOM in Asian countries was 3.6% in Indonesia, 5.4% in India, 8.1% in Nepal, and 8.4% in Sri Lanka [4]. The prevalence of CSOM in children in Indonesia was 3.4% [5].

The main etiology of CSOM is bacterial and viral infections in the upper airway and middle ear. However, various predisposing factors can trigger the occurrence of CSOM, including Eustachian tube dysfunction and immune system disorders. To create a good immune system various micronutrients are needed. One of the micronutrients needed for the regulation of the immune system is iron [6–8].

Iron is an important element in the body that is needed for various cellular processes [9]. Iron has several important functions, namely as a carrier of oxygen to tissues from the lungs by hemoglobin in red blood cells, as a medium for electron transport in cells, synthesis of deoxyribonucleic acid (DNA), and as an integrated part of important enzyme systems in various tissues [10]. In children, iron is an important nutrient for the growth and function of organs, especially the erythropoiesis system. Iron is needed for the development of the immune system, especially for the proliferation and activation of macrophages, neutrophils, T cells, and B cells. In addition, iron plays a role in the interaction between cell-mediated immunity and cytokines [11,12].

An iron deficiency causes negative effects on the normal functioning of the immune system. In particular, there are two distinct changes of the immune system associated with iron deficiency; the first is the reduced response of T-cell lymphocytes to infectious agents, and the second is the reduced bactericidal action of macrophages and

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neutrophils. Children who have iron deficiency anemia (IDA) are more susceptible to infection than children who do not have IDA [13]. This study aims to analyze the association of IDA on CSOM in Indonesian children.

2. Method

2.1. Participant

The participants in this study were Indonesian children with CSOM aged 1–18 years [5,14]. The diagnosis of CSOM is chronic inflammation of the middle ear and mastoid mucosa in which the tympanic membrane is not intact (perforation or tympanostomy tube) and discharge (otorrhea) [15]. Exclusion criteria were those who had received treatment for iron deficiency anemia, immunodeficiency and haematological disorders, adenoid hypertrophy, craniofacial anomalies, allergic rhinitis, and poor nutritional status.

2.2. Ethical approval

We have conducted ethical approval base on the Declaration of Helsinki with the registration of research at the Research Ethics Committee Universitas Padjadjaran, Bandung, Indonesia (1197/UN6.KEP/EC/2020). Informed consent was obtained for all participants.

2.3. Study design

This study is a case-control design with consecutive sampling from June to September 2020. Participants were divided into 2 groups, the case group is a group of children diagnosed with CSOM, and the control group is a group of children with healthy ear on examination. The number of participants was 84 (case group = 42 participants and control group = 42 participants). Data collected from participants including characteristics, and iron deficiency anemia through measurement of haemoglobin (Hb) levels, iron (FE) levels, total iron-binding capacity (TIBC) levels, and ferritin levels. The reporting of this study uses strengthening the reporting of cohort studies in surgery (STROCSS) 2019 guidelines [16].

2.4. Measurement of iron deficiency anemia

IDA is a participant condition in which the number of red blood cells does not meet the body's physiological needs [17]. The number of red blood cells is considered deficient if the Hb value is < 11.0 g/dL [18], Serum FE < 26 g/dL, TIBC >441 g/dL, and ferritin <10 g/dL [10,19]. Participants took ± 3 ml venous blood samples which were stored at a temperature of -20 °C to keep the blood from lysing [20]. Serum was analyzed for IDA (chemiluminescent microparticle immunoassay, Abbott Laboratories, Abbott Park, IL, USA).

2.5. Statistical analysis

The data obtained were first analyzed using the Shapiro Wilk test to determine the distribution of the data. Comparative analysis between case and control groups using a chi-square test or fisher extract test and independence *t*-test or Man Whitney test. Statistical analysis was performed with SPSS 24.0 software (IBM Corp., Armonk, NY, USA). The analysis used to find the correlation between IDA and CSOM was also the same using the chi-square or linear association test. The correlation was considered as significant statistically if p-value < 0.05.

3. Result

3.1. Characteristic of participant

The average age of the participants was 9.14 ± 2.95 years with a median value of 9.00 (6.75–12.00) years. There was no significant age difference between the case (9.17 ± 3.14 years) and the control group (9.12 ± 2.79 years; $p = 0.875$). The youngest participant is 5 years old and the oldest participant is 16 years old. 63 participants (75%) were in the age range of 6–12 of which in the case group there were 31 participants (73.8%) and the control group 32 participants (76.2%; $p = 0.656$). Most of the participants were male with 49 participants (58.33%) of which in the case group there were 24 participants (57.1%) and the control group 25 participants (59.5%; $p = 1{,}000$; Table 1).

Otorrhea is the most complaints experienced by the participants (66.7%). Several participants experienced perforation in the tympanic membrane as follows: marginal 1 participant (2.4%), a sub-total in 24 participants (57.1%), and total perforation in 17 participants (40.5%). In addition, as many as 3 participants (7.1%) were reported to have cholesteatoma.

3.2. Association of iron deficiency anemia on chronic suppurative otitis media

The average Hb value of participants was 13.00 ± 1.34 g/dL with a median value of 13.10 (12.50–13.90) g/dL. The lowest value for participant Hb is 10.20 g/dL and the highest value for participant Hb is 15.00 g/dL. There was a significant difference in Hb values in the case group (12.46 ± 1.25 g/dL) and control groups (13.61 ± 1.16 g/dL; $p < 0.001$). The mean serum FE value was 95.13 ± 40.84 g/dL with a median value of 105.00 (81.75–121.25 g/dL). The range of serum FE is 12.00–162.00 g/dL. There was a significant difference in serum FE values in the case group (75.02 ± 26.14 g/dL) and control group (115.24 ± 35.25 g/dL; $p < 0.001$; Table 2).

Participants' TIBC values obtained an average of 354.18 ± 62.44 g/dL with a median value of 341.50 (309.75–386.25) g/dL. Participants' TIBC values range from 267.00 to 535.00 g/dL. There was a significant difference in the TIBC value of participants in the case group (345.43 ± 73.78 g/dL) and control group (362.93 ± 47.86 g/dL; $p = 0.016$). The ferritin value of the participants was 17.57 ± 8.55 g/dL with a median value of 14.90 (13.40–25.50) g/dL. There was a significant difference in ferritin values in the case group (12.37 ± 4.58 g/dL) and control group (22.18 ± 8.64 g/dL; $p < 0.001$; Table 2).

In this study 18 participants (21.43%) experienced IDA, of which 13 participants (31.0%) in the case group and 5 participants (11.9%) in the control group. There is a significant relationship between IDA and CSOM with $p = 0.033$ and $OR = 3.32$ (Table 3).

Table 1
Characteristic of participant.

Characteristic	Participant		*p*
	Case group (%)	Control group (%)	
Category			
1–5 years	4 (9.5)	5 (11.9)	0.656
6–12 years	31 (73.8)	32 (76.2)	
13–18 years	6 (14.3)	5 (11.9)	
Gender			
Male	24 (57.1)	25 (59.5)	1.000
Female	18 (42.9)	17 (40.5)	
Parents' educational level			
Primary school	3 (7.1)	1 (2.4)	0.927
Middle school	0 (0.0)	0 (0.0)	
High school	31 (73.8)	28 (66.7)	
Bachelor	8 (19.0)	13 (31.0)	
Parents' income			
Low income	2 (4.8)	0 (0.0)	0.927
Middle income	35 (83.3)	32 (76.2)	
High income	4 (9.5)	7 (16.7)	
Very high income	1 (2.4)	3 (7.1)	

Table 2
Comparison between case and control group in the biomarker of iron deficiency anemia.

Biomarker	Groups		*p*
	Case	Control	
Hb	12.46 ± 1.25	13.61 ± 1.16	<0.001**
Serum FE	75.02 ± 26.14	115.24 ± 35.25	<0.001**
TIBC	345.43 ± 73.78	362.93 ± 47.86	0.016*
Ferritin	12.37 ± 4.58	22.18 ± 8.64	<0.001**

Note: HB = haemoglobin; FE = iron; TIBC = total iron-binding capacity; *significant <0.05; **significant <0.001.

Table 3
The association of iron deficiency anemia on CSOM in Indonesian children.

IDA	Group		*OR*	*p*
	Case	Control		
Yes	13 (31.0)	5 (11.9)	3.32	0.033*
No	29 (69.0)	37 (88.1)		

Note: IDA = iron deficiency anemia; OR = odds ratio; *significant <0.05.

4. Discussion

The results of this study are the following study conducted by Anggraeni et al., in 2019 that the age group affected by CSOM was 6–12 years [5]. Another study stated that at the age of >4 years, CSOM was found in South Korea [21]. Several other studies have also found the incidence of CSOM is more common at the age of 5–12 years, which is a group having more risk to upper respiratory infection. According to the literatures risk of CSOM in this group age related to inadequate diet and intake cause a decrease in immune system, mucosal damage, impaired growth, and development in children. This is related to disturbances in cell-mediated immunity, decreased neutrophil function, and myeloperoxidase activity against invading pathogens in the middle ear [12,13,22]. In this study CSOM frequently found at school age, and is more common in males, this result is similar a study conducted by Jain et al. which found the highest incidence of CSOM in males as much as 60% [23]. This is due to the craniofacial anatomy in men and women having differences in men having tubal angle the eustachian tube which is larger and more horizontal than the female, the length of the mastoid cavity, intercochlear distance, and thickness of the eustachian tube in males are greater than in females [24].

Most of the patients in this study had unilateral CSOM which was following previous studies that obtained 78.95% unilateral CSOM patients [25]. In this study, it was found that most CSOM patients complained of otorrhea which was similar to a previous study that 19.6% of CSOM patients complained of otorrhea [3]. Otorrhea is the most common symtomp complain by CSOM patients caused by a long-lasting inflammatory process in the middle ear increasing proinflammatory cytokines such as TNF-α and IL-8 causes mucus cell metaplasia/hyperplasia resulting in increased secretion of fluid in the middle ear [26,27]. A study by Singh et all found 25% of CSOM patients had subtotal tympanic membrane perforation [28]. Tympanic membrane perforations in CSOM withot cholesteoatoma were commonly found in pars tensa which is the largest of the tympanic membrane [29]. Cholesteatoma is more often seen in attic and marginal perforation. In the current era of antibiotics, complications of CSOM are rare because early antibiotics and surgery play an important role in preventing complications in CSOM patients [11].

The study conducted by Elemraid et al. found that 46.5% of CSOM patients experienced an iron deficiency and the duration of infection became longer [11]. Previous studies stated that there was an association between IDA and CSOM found that there was an increase in iron levels after iron supplementation in children with CSOM and a decrease in the incidence of CSOM recurrence ($p < 0.001$) [8]. Another study stated that the majority of iron-deficient children had CSOM as much as 95.6% and received iron supplements of 15 mg for children <2 years and 50 mg for children >2 years [30]. In the literature, there is a correlation between IDA and an increased risk of infection in the pediatric population. This association is related to a decrease in the immune system, namely a decrease in the function of neutrophils, macrophages, and lymphocytes. IDA causes disturbances in the growth and differentiation of immune cells through effector pathways and cytokine activity, as well as disturbances in modulating the innate immune response and adaptive immune response [13,31].

In the journal Kubivilla et al., it was stated that a decrease in the function of neutrophils and macrophages, as well as a decrease in the activation of B cells and T cells Iron deficiency, causes a decrease in the levels of the anti-inflammatory cytokines IL-1ra, IL-2, IL-4, IL-10, IL-13, and TGF-β and an increase in the secretion of the proinflammatory cytokines IL-6, IL-8, and TNF-α [3]. This inflammatory process causes extensive mucosal cell proliferation and mucosal metaplasia in the middle ear, resulting in the secretion of fluid in the middle ear. In addition, the inflammatory process in the middle ear due to iron deficiency causes oxidative stress. Oxidative stress is an imbalance between pro-oxidants and antioxidants. Oxidative stress conditions occur through the activation of proinflammatory cytokines, especially IL-8. Oxidative stress occurs due to pathogenic bacteria in the middle ear mucosa penetrating epithelial cells and directly activating the nicotinamide adenine dinucleotide phosphate (NADPH) enzyme which produces reactive oxygen species (ROS). Reactive oxygen species (ROS) are proxies and are produced from the inflammatory process. Excessive reactive oxygen species (ROS) will cause oxidative stress and tissue damage through peroxidation of cell membrane lipids, resulting in cell death in the form of apoptosis or necrosis [6,28].

Many researchers have identified several risk factors for CSOM, but iron deficiency has never been considered a risk factor. In this study, 31% of the case group had IDA while in the control group, 11.9% had IDA and the correlation was statistically significant with $p = 0.033$ and $OR = 3.3$.

5. Conclusion

Iron deficiency anemia increases 3.3 times risk of CSOM in children compared to normal. Therefore, iron deficiency anemia should be considered in children with CSOM so that the treatment and prevention of CSOM can be carried out thoroughly.

Ethical approval

We have conducted an ethical approval base on the Declaration of Helsinki at the Health Research Ethics Committee in Dr. Hasan Sadikin General Hospital, Bandung, Indonesia.

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Author contribution

All authors contributed toward data analysis, drafting and revising the paper, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

Registration of research studies

1. Name of the registry: Research Ethics Committee Universitas Padjadjaran, Bandung, Indonesia.
2. Unique Identifying number or registration ID: 1197/UN6.KEP/

EC/2020.

3. Hyperlink to your specific registration (must be publicly accessible and will be checked): -.

Guarantor

Lina Lasminingrum is the person in charge for the publication of our manuscript.

Consent

We have explained the aim and benefits of our reporting to parents or guardians in which they are willing to fill out the consent form consciously.

Provenance and peer review

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Declaration of competing interest

The authors declare that they have no conflict of interest.

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