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Original Research Article

Association of ferritin level with attention deficit hyperactivity disorder in children

Ni Putu Wirantari*, I. Gusti Ayu Trisna Windiani, Dyah Kanya Wati, I. Gusti Lanang Sidiartha, I. Putu Gede Karyana, I. Wayan Gustawan

Department of Child Health, Medical School of Udayana University, Sanglah Hospital, Denpasar, Bali, Indonesia

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***Correspondence:**
Dr. Ni Putu Wirantari,
E-mail: ariwirantari@yahoo.co.id

ABSTRACT

Background: Dopamine is an important component in the pathophysiology of ADHD. Dopamine synthesis is regulated by the enzyme tyrosine hydroxylase and influenced by iron deposits in the brain. Several studies have shown that low ferritin levels in children with ADHD and iron supplementation are said to show good clinical outcomes, but this study has never been conducted at Sanglah General Hospital.
Methods: This study used an observational analytic study design with unpaired case control design. Research held in Policlinic RSUP Sanglah from July 2018 to April 2019.
Results: In a total of 25 children with ADHD and 25 children without ADHD, median ferritin level was 43.7(7.9-77.0) in the case group and 68.2(33.1-319.0) in control group. Bivariate analysis of ferritin level categories using the chi-square test showed significantly different results. Low ferritin levels (<45 ng/mL) was obtained in 56% of the case group and 16% in the control group. Odd ratios determine the relationship between ferritin and the incidence of ADHD at 6.7 (95% KI 1.8-25.2). The results of multivariate analysis showed that adjusted OR was 6.5(95% KI 1.2-34.6) and was statistically significant with p value 0.027.
Conclusions: There was correlation between ferritin levels and ADHD in children.

Keywords: ADHD, Ferritin, Children, Without ADHD

INTRODUCTION

The pathophysiology of attention deficit hyperactivity disorder (ADHD) is a complex and uncertain process. Attention deficit hyperactivity disorder is a heterogeneous syndrome with a multifactorial hypothesis, including environmental, genetic and biological factors. Some studies suggest that dopamine is an important element in the pathophysiology of ADHD. Dopamine plays a role in the process of modulation of psychomotor and executive activity, which is the main clinical picture in ADHD children.[1]

Dopamine synthesis is influenced by the enzyme tyrosine hydroxylase. Tyrosine hydroxylase converts tyrosine to L-dopa which then undergoes a decarboxylation process to dopamine. Iron deposits in the brain affect dopamine synthesis, which in turn affects various behaviors, especially in ADHD children.[1] Research by Cortese et al, showed significantly lower brain ferritin levels in ADHD children.[2]

Research by Juneja et al, obtained a low serum ferritin level in 92% children with ADHD. Konofal's research obtained low ferritin levels in children with ADHD (84%) compared to children without ADHD (18%). An RCT study comparing iron supplementation with placebo for 12 weeks showed a significant reduction in ADHD scores in ADHD children.[3] At present iron supplementation has not been routinely carried out as a

management of children with ADHD so it is important to do research on ferritin levels especially in Sanglah General Hospital.

Research by Tumbelaka et al, Agustina et al, in Jakarta and Susanti et al, in Yogyakarta however obtained insignificant results between ferritin levels and clinical ADHD.[4-6] Weaknesses in Susanti et al, and Agustina et al, include taking groups of children without ADHD as a comparison group not from the same population and no other investigations was done to exclude anemia and inflammation.[5,6] The high prevalence of iron deficiency in school children could make a bias in which the proportion of children who are deficient in non-ADHD children groups became insignificantly different from the ADHD group. Besides, ferritin levels could also be normal or high due to inflammatory conditions, so they did not reflect iron deposits in the body.

Research on serum ferritin levels in children with ADHD has been widely reported. Data on serum ferritin levels in ADHD children is still controversial, there are those who report low serum ferritin levels with significant differences, there are also those who get results with insignificant differences. Referring to the findings regarding ferritin levels in children with ADHD, it is important to examine them by considering weaknesses in previous studies. Ferritin levels are expected to be used as an additional indicator that needs to be considered in children with ADHD.

METHODS

This study was analytic observational study which was conducted in pediatric policlinic Sanglah hospital. Which was done from July 2018-April 2019 and the data was analysed at May 2019.

This study population was children diagnosed with ADHD and children without ADHD. The inclusion criteria was children (age <18 years old) diagnosed with ADHD as case group and children without ADHD as control group. Children with chronic disease, severe malnutrition, obesity, austism, restless leg syndrome, learning disorder, getting iron therapy, history of trauma and history of heavy metal exposure were excluded**.**

Samples were selected by consecutive sampling using a large sample estimation formula for the proportion of a population. With an error rate set at 5% for $Z\alpha = 1.96$ and 20% for $Z\beta = 0.842$. The minimal sample size was set as many as 25 subjects for each group.

The data of the subjects used in this study were gender, age, nutritional state, and laboratory results in the form of hemoglobin, c-reactive protein level and ferritin level. The data obtained are presented in the form of narratives and tables. Categorical data were presented in numbers and percentage. Numerical data were in median (minimum-maximum) according to the normality of data distribution and further analyses, such as chi square test and logistic analysis.

Approval of the ethical feasibility of the study was given by the research ethics commission of the medical school of Udayana University/ RSUP Sanglah Denpasar with a permit number of 809/UN14.2.2/PD/KEP/2018.

RESULTS

This research was conducted from July 2018 to April 2019 at the Department of Children's Pediatric Clinic Department of Child Health Sanglah Hospital Denpasar. Of the 58 children netted in the study, 52 children whose parents agreed to participate in the research process by signing the research approval sheet. From history taking of 52 children whose parents agreed to participate, 50 children met inclusion and exclusion criteria (25 children with ADHD and 25 children without ADHD).

Table 1: Characteristics of research subjects.

Characteristics	Group	
	ADHD	**Not ADHD**
Age (year), mean (SD)	5.4±1.8	6.2±1.5
Sex, n (%)		
Boy	21(84.0)	17(68.0)
Girl	4(16.0)	8(32)
Nutritional status, n(%)		
Under nourish	1(4.0)	4(16.0)
Well nourish	20(80.0)	19(76.0)
Overweight	4(16.0)	2(8.0)
Hb (gr/dL), mean (SD)	12.3±0.8	12.8±1.1
CRP (mg/L), median (min-max)	0.3 (0.3-3.9)	0.6(0.3-7.9)
Ferritin (ng/mL), median (min-max)	43.7(7.9-77,0)	68.2(33.1-319.0)

Table 2: Bivariate analysis.

Variabel	Kelompok		OR	95% CI	p value
	ADHD (n=25)	**Not ADHD (n=25)**			
Kadar feritin					
<45 ng/mL, n(%)	14(56)	4(16.0)	8.7	1.8-25.2	0.003
≥45 ng/mL, n(%)	11(44)	21(84.0)			

OR: odd ratio; CI: confidence interval; p: probability

A total of 25 ADHD children and 25 children without ADHD. The characteristics of the research subjects are shown in Table 1. Median ferritin levels in the case group was 43.7(7.9-77.0) while in the control group it was 68.2 (33.1-319.0). Bivariate analysis in Table 2 showed ferritin level categories using the chi-square test showed significantly different results. Low ferritin levels (<45 ng/mL) obtained in 56% of the case group and 16% in the control group. Odd ratio determined the relationship

between ferritin and the incidence of ADHD at 6.7(95% KI 1.8-25.2). Multivariate analysis in Table 3 showed that adjusted OR was 6.5(95% KI 1.2-34.6) and was statistically significant with p value 0.027.

Table 3: Multivariate analysis.

Variable	Adjusted RO	95% CI	p value
Feritin (<45 ng/mL)	6.5	1.2-34.5	0.027
Age	1.3	0.8-2.1	0.238
Sex (boy)	3.4	0.6-21.2	0.187
Nutritional states	0.5	0.1-2.5	0.404
Hb	1.7	0.8-3.7	0.197
CRP	1.3	0.6-2.6	0.524

OR: odd ratio; CI: confidence interval; p: probability

DISCUSSION

The average age of subjects with ADHD in this study was 5.4 years. Children in this age range are often epidemiologically experiencing ADHD. School-age children are said to experience ADHD more often than other age groups. Male was the most subject experienced GPPH (84%). Disorder concentration and hyperactivity was reported 2.5 times more often in boys than girls. A study explained that the anatomy of men with a slightly larger head size was more prone to experience a head injury at birth. Skeletal bone immaturity in boys also causes more susceptibility to damage and increased chance of experiencing ADHD.[7]

The mean hemoglobin level in the case group was 12.3±0.8 while in the control group it was 12.8±1.1. In this study there was no subjects experiencing anemia both in the case and control groups. Iron deficiency anemia is the most common type of anemia in the world, especially in developing countries.[8] Iron acts as a cofactor of tyrosine hydroxylase (a neurotransmitter synthesis enzyme) which plays a role in the pathophysiology of ADHD.

The median CRP in the case group was 0.3 (0.3-3.9) while in the control group it was 0.6 (0.3-7.9). In this study CRP levels were evaluated to rule out the condition of infection because ferritin concentrations could increase if there was an acute infection. The nutritional status of the GPPH in the case group was mostly good (80%). Nutritional intake especially iron intake can affect the results of the study. Obesity and malnutrition can affect iron status in these children. In this study not all children's nutritional status was included. Children with obesity and malnutrition were excluded.

In this study the mean ferritin level of the GPPH group was lower than the group without ADHD and was statistically significant. The median ferritin level in the ADHD group was 43.7 ng/mL, while the median ferritin level in the no-GPPH group was 68.2 ng/mL. Serum ferritin levels used in various studies have varied cut-off values. Research conducted by Juneja et al, in India in 2010 using a cut off value of <12 ng/mL in their study, found 92% of groups of children with ADHD had low ferritin levels. Lahat et al, used ferritin levels cut off <20 ng/mL, found 56% with ADHD had low ferritin levels.[1] Konofal et al, used ferritin levels cut off <30 ng/mL, finding 84% of ADHD children had low ferritin levels and 18% in non-ADHD groups with a p <0.001.[4] Cortese et al, using ferritin levels <45 ng/dL as a cut off to get 60% of children with ADHD.[2]

The cut off value of different serum ferritin levels illustrates the normal range in the population but does not describe the biological conditions in the body so that it evaluates a person's ferritin levels. A study that used bone marrow examination as the gold standard, showed that peripheral iron reserves would not be fully filled until serum ferritin levels were reached >50-100 ng/mL. Peripheral iron deposits can reach the central nervous system by penetrating the brain barrier and will affect the degree of saturation of iron reserves. Normal normal ferritin levels for the synthesis of hemoglobin and myoglobin may not be enough to maintain brain neurotransmitter function. When iron reserves are depleted (generally described as <12-45 ng/mL) there will be a decrease in hemoglobin synthesis, attention disorders and delay in psychomotor development.[9]

Research conducted by Cortese et al, using ferritin levels <45 ng/dL as a cut off used by researchers as a reference. Our research found 56% children with ADHD had ferritin level <45 ng/dL. Tumbelaka et al, also used this cut-off and using this cut-off and found 42% subject with low ferritin level (14 of 33 children with ADHD).[4]

Research conducted by Cortese et al, found children with ADHD aged 6-14 years with an average age of 9.1 years and male sex as much as 82%.[2] Tumbelaka et al, found children aged 5-12 years with a median age of 7 years in children with ADHD (70% of male subjects).[4] This study found children with ADHD aged 2-8 years with a mean age of 5.4 years (84% of male subjects).

Iron is an important element in biological processes, including several brain functions. Some of the hypotheses raised about iron deficiency in ADHD children. Iron is a cofactor of enzymes needed for the synthesis and catabolism of neurotransmitters that have implications for the pathophysiology of ADHD. Iron is needed for the synthesis of various enzymes involved in the formation of neurotransmitters, namely tryptophan hydroxylase (serotonin) and tyrosine hydroxylase (norepinephrine and dopamine).[2,10] The results of multivariate analysis found ferritin levels <45 ng/mL at risk of having ADHD of 6.5 times with 95% CI 1.2-34.6 (p value 0.027). This result is consistent with the research conducted by Juneja et al, who found that ferritin levels were lower in children with ADHD compared to controls and were statistically significant. Konofal's research et al, found that low serum

ferritin levels were significantly associated with the severity of symptoms of ADHD.

This study consider hemoglobine and CRP levels to rule out anemia and inflammation. Ferritin is the best indicator for assessing iron reserves and has a high specificity for iron deficiency, but ferritin levels are influenced by many factors such as inflammatory conditions and anemia. Ferritin levels tend to rise in inflammatory conditions and decrease in anemia.

Iron deficiency anemia is the most common type of anemia in the world, especially in developing countries.[8] In this study there was no subjects experiencing anemia both in the case and control groups. The mean hemoglobin level in the case group was 12.3±0.8 while in the control group it was 12.8±1.1. Attention Focusing Disorders and Hyperactivity are thought to occur due to changes in the levels of neurotransmitters. Iron acts as a cofactor of tyrosine hydroxylase (a neurotransmitter synthesis enzyme). Iron deficiency can cause changes in dopamine levels in substantia nigra and putamen. Iron deficiency can also cause ADHD.[11]

Ferritin concentrations can increase if there is an acute infection. Increased serum ferritin concentration is about 3 times, with maximum concentrations achieved within 1 week.[12] C-reactive protein is a protein produced by the liver, especially when there is an infection or inflammation in the body. Several studies have suggested an association between ADHD and the mechanism of inflammation due to positive results regarding genes associated with inflammation. Cytokines are reported to play an important role in the metabolism of tryptophan and the dopaminergic pathway in the brain, which is also involved in ADHD. Changes in proinflammatory and anti-inflammatory cytokines can have an effect on the pathogenesis of ADHD.[12]

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