

ROLE OF FREE RADICALS IN CHILDREN WITH MALNUTRITION

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ABSTRACT

Protein Energy Malnutrition (PEM) in children, is still an important issue throughout the world especially in developing countries, because it is the largest contributor to the increased morbidity and mortality in children under age five years (WHO, 1999; Black 2003). Limited knowledge about the pathogenesis of kwashiorkor, have consequences slow progress in the development of treatment or prevention strategies during the last decade. The objective was to study the role of free radicals in children with malnutrition. All patients with children (ages 1 month - 14 years) that MRS in Child Inpatient at Dr. Soetomo and willing to participate in this study, was examined for anthropometry, clinical examination and laboratory. Investigation aims to determine the value of the anthropometry z-scores of weight / age, height for age, weight / height, BMI and percentage of ideal body weight, so that nutritional status can be determined. This study revealed that concentrations of NO in children with malnutrition are 1.5 times higher than control group (children with good nutrition). Concentration of NO at higher kwashiorkor when compared with the control group (children with good nutrition), but did not differ significantly when compared with marasmic. Besides, there were no significant correlation between high levels of NO in children with kwashiorkor degree of edema. There were no significant correlation between high levels of child malnutrition NO with duration of treatment in hospital. Also, there was a decrease in NO concentration when there is clinical improvement, but this decrease was not significant.

Keywords: Protein Energy Malnutrition, free radical, nitric oxide

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INTRODUCTION

Protein Energy Malnutrition (PEM) in children, is still an important issue throughout the world especially in developing countries, because it is the largest contributor to the increased morbidity and mortality in children under age five years (WHO, 1999; Black 2003). PEM ranked second in the list of most common causes of death among children under five in developing countries (WHO, 1994). Müller, 2005 stating that the PEM is the direct cause of 300,000 deaths per year worldwide, and is an indirect cause of 53% of child mortality worldwide. Degree of severity of PEM directly related to the high mortality (Rice, 2000; Müller, 2005).

PEM in children is defined as a situation in which the body weight compared with height less than -2 SD from the reference standard WHO / NCHS (National Center for Health Statistics, USA). If there is severe wasting (<70% or <-3 SD weight for height compared to the reference standard WHO / NCHS) and / or accompanied

by the edema in both legs known as PEM weight (WHO, 1999; WHO 2005). In Indonesia, the incidence of severe PEM ranges 6-8% in 1989 until 2003. From the National Health Survey data shows that cases of severe PEM is still as much as one-half million children under five (Susanto, 2005). KEP weight, is clinically divided into three syndromes: marasmic, kwashiorkor and marasmic-kwashiorkor (WHO, 1999; Heird, 2004). Malnutrition and mortality rates in developing countries reached 20% - 30% (Schofield, 1996). While kwashiorkor mortality ranges from 10% - 50% (Golden, 1994). The mortality rate of this magnitude has not reduced significantly in the 4-5 last decade (Schofield, 1996; Golden, 1994). Fuchs, 2005 confirms that more deadly kwashiorkor compared with marasmic. Pathogenesis of kwashiorkor to date remains unclear (Monte, 2000; Krawinkel, 2003). The old theory about protein deficiency is opposed by many scientists, so there is some new theory. Golden, 1994 stating that the deficiency of proteins in kwashiorkor theory is wrong, and put forward a new theory which states there is an

imbalance between free radicals and antioxidants, as the basis for the pathogenesis of kwashiorkor.

Limited knowledge about the pathogenesis of kwashiorkor, have consequences slow progress in the development of treatment or prevention strategies during the last decade.

MATERIALS AND METHODS

All patients with children (ages 1 month - 14 years) that MRS in Child Inpatient Dr. Soetomo and willing to participate in this study, was examined for anthropometry, clinical examination and laboratory. Investigation aims to determine the value of the anthropometry z-scores of weight / age, height for age, weight / height, BMI and percentage of ideal body weight, so that nutritional status can be determined.

Besides the clinical and laboratory examination to detect symptoms and signs of malnutrition, such as edema, dermatosis, hepatomegaly, hair changes and mental changes. To determine the existence of anemia and hypoalbuminemia, was examined for hemoglobin and albumin. If edema was found, it was determined the degree of edema: mild, moderate or severe.

From the results of anthropometry, clinical examination and laboratory examination, we can determine the classification of malnutrition: marasmic, kwashiorkor or marasmic-kwashiorkor. Furthermore done taking venous blood specimens to be examined initial NO concentration. Patients followed by the investigators, until there is clinical improvement, which will be done taking specimens for examination of NO concentration.

At KRS patients, calculated the length of care in hospitals. Basic Data collected will be analyzed through descriptive with a frequency distribution table, the average value and standard deviation. Two independent samples t test was used to determine the differences in NO levels in children with malnutrition and the control group. Two independent samples t test was also used to test for differences in NO concentration in marasmic and kwashiorkor compared with the control group.

Spearman correlation test was used to prove the relationship between high levels of NO by edema of kwashiorkor. Spearman correlation test was also used to prove the relationship between high levels of NO with a longer treatment of malnutrition in hospital patients. Two sample paired t test was used to verify a decrease in NO concentration in patients with malnutrition during clinical improvement.

RESULTS

During the period from 15 February 2006 until 30 November 2006 found that child malnutrition treated in the children's ward of Dr. Soetomo and 23 of them met the criteria of inclusion and exclusion. Of the 23 patients, only 16 (69.57%) are willing to participate in the study, including 8 (50%) children with kwashiorkor and 8 (50%) children with marasmic.

Sixteenth malnutrition sufferer who met the inclusion criteria and were willing to participate in the study were carried out anamnesis, anthropometric examination, physical examination and laboratory examination, including complete blood examination, the albumin concentration and NO concentration on the first day of MRS. Samples are then followed by researchers for clinical improvement. When the patient will be discharged (KRS) conducted laboratory re-examination, including complete blood examination, the albumin concentration and NO concentration.

From the eight patients with kwashiorkor, two (8.69%) of them on their own KRS (forcibly returned) and 1 (4.34%) patients died on treatment day 10 due to sepsis. In all three samples were not examined NO concentration II, namely NO concentration during clinical improvement.

Control group that participated in this study was obtained from the installation of child outpatient visits of Dr Soetomo. There were 13 patients eligible and willing to participate in the study.

Data analyzed are as many as 16 patients with severe malnutrition (8 marasmic kwashiorkor and 8). First laboratory results of NO concentration (NO concentration during the day I MRS) than among patients with severe malnutrition with the control group, patients with marasmic and kwashiorkor dengan kwashiorkor patients with control group. Statistical tests used are two independent samples t test.

Edema that occurs in patients with edema of kwashiorkor categorized as mild, moderate and severe and associated with high levels of NO I, Spearman test was used to determine the correlation between the degree of edema and NO concentration. Malnutrition patients treatment duration (13 samples) associated with high levels of NO. Spearman test was used to determine the correlation between concentration of NO I with treatment duration.

Comparison of NO levels I and II NO from 13 samples were evaluated using two sample paired t test, to prove the existence of decreasing NO concentration when

there is clinical improvement. Significance level used in this study is 0.05. Characteristics of patients with

malnutrition sample based on age and sex shown in Table 1.

Table 1. Distribution of age and sex of patients with severe malnutrition (kwashiorkor and marasmic) are investigated

Variables	Type of malnutrition (%)		Total (%)
	Kwashiorkor	Marasmic	
Age (month) *)			
1-12	4 (50.0)	1 (12.2)	5 (31.3)
13-24	4 (50.0)	3 (37.5)	7 (43.8)
25-60	0	2 (25.0)	2 (12.5)
> 60	0	2 (25.0)	2 (12.5)
Sex **)			
Male	7 (87.5)	6 (75.0)	13 (81.3)
Female	1 (12.5)	2 (25.0)	3 (18.8)
Total	8 (100)	8 (100)	16 (100)

*) P = 0.102 (NS) two-sample t test free

**) P = 1.000 (NS) Fisher's exact test

The sample of patients with kwashiorkor this study all aged <24 months, respectively 4 (50%) patients aged 1-12 months and four (50%) patients aged 13-24 months. Marasmic patients who participated in this study mostly aged 13-24 months, ie 3 (37.5%) patients. While the control group who followed this study were 10 (76.9%) sample aged 13-24 months. The mean age of patients

with kwashiorkor, marasmic and control groups respectively were: 12.5 (6.19), 46.5 (50.94), and 18.8 (8.37) months. Two independent samples t test showed no significant differences among age groups from malnutrition and the control group, and among patients with kwashiorkor and marasmic.

Table 2. Distribution of age and sex of patients with malnutrition and the control group

Variables	Samples (%)		Total (%)
	Malnutrition	Control	
Age (mo) *)			
1-12	5 (31.3)	1 (7.7)	6 (20.7)
13-24	7 (43.8)	10 (76.9)	17 (58.6)
25-60	2 (12.5)	2 (15.4)	4 (13.8)
> 60	2 (12.5)	0	2 (6.9)
Sex **)			
Male	13 (81.3)	11 (84.6)	24 (82.8)
Female	3 (18.8)	2 (15.4)	5 (17.2)
Total	16 (100)	13 (100)	29 (100)

*) P = 0.819 (NS) two-sample t test free

**) P = 1.000 (NS) Fisher's Exact Test

Most sufferers of malnutrition were male, which is 81.3% or a total of 13 samples. Similarly, the control group, a total of 11 (84.6%) the sample was male. Kwashiorkor patients who participated in this study, 87.5% male sex and marasmic 75%. By using fisher's exact test, the result shows that there was no significant difference between the sexes sample of malnutrition and the control group, or among a group of kwashiorkor and marasmic.

Based on the percentage of ideal body weight, the result shows that the majority (62.5%) patients achieved 70-90% kwashiorkor and marasmic all patients achieving <70%. While all of the control group (100%) reached

90-120%. By using two independent samples t test showed that there were significant differences between kwashiorkor and marasmic, in terms of achieving your ideal weight.

Calculating z-score of weight / height showed that four patients with kwashiorkor reached -3 to -2 SD and four samples reach -2 to 2 SD. While the majority of patients with marasmic (seven samples) to reach the z-score weight / height <-3 SD. Two independent samples t test showed that there was significant differences in achievement z-score of weight / height between patients with kwashiorkor and marasmic.

Table 3. Distribution of sample according to% ideal weight and value of the z-score weight / height in patients with malnutrition and the control group

Variables	Samples (%)			Total (%)
	Kwashiorkor	Marasmic	Control	
% Ideal BW*)				
< 70	1 (12,5)	8 (100)	0	9 (31,0)
70.01-90.00	5 (62,5)	0	0	6 (20,7)
90.01-120.00	2 (25,0)	0	13 (100)	14 (48,3)
Z score BW/H**)				
< -3.00 SD	0	7 (87,5)	0	7 (24,1)
-3.00 - -2.00 SD	4 (50,0)	1 (12,5)	0	5 (17,2)
-2.00 – 2.00 SD	4 (50,0)	0	13 (100)	17 (58,6)
Total	8 (100)	8 (100)	13 (100)	29 (100)

*) P = 0.001 two independent samples t test for groups of kwashiorkor and marasmic

**) P = 0.000 two independent samples t test for groups of kwashiorkor, and marasmic

Levels of NO in patients with malnutrition

The mean levels of Nitric Oxide in 16 patients with severe malnutrition are 173.10 (52.99) μ M and in control group (n = 13) are to 118.51 (50.61) μ M. By using two independent samples t test, the result shows that there were significant differences between the levels of NO in patients with malnutrition and the control groups.

The mean levels of Nitric Oxide in kwashiorkor (n = 8) are 175.27 (55.94) μ M and in marasmic (n = 8) are 170.94 (53.66) μ M. Two independent samples t test indicate that no significant differences in NO levels between patients with kwashiorkor and marasmic.

The mean NO concentration is higher in patients with kwashiorkor when compared with the average of NO in the control group. This difference was statistically significant, using two independent samples t test.

From the eight patients with kwashiorkor who participated in this study, four (50%) of whom experienced mild edema, 3 (37.5%) were edema and one (12.5%) severe edema. By using Spearman correlation test, the result shows that there is no significant correlation between NO concentration to the degree of edema.

The mean treatment duration of malnutrition patients (n = 13) The sample of this study was 21.92 (13.93) days

with a range of 8-55 days. Pearson correlation test was used to determine the correlation between NO concentration and duration of treatment, and the result is that there is no significant correlation between NO concentration with duration of treatment of malnutrition in hospital.

Table 4. Mean NO concentration in patients with kwashiorkor associated with the degree of edema

Degree of edema	N	Mean NO levels (μM)
Mild	4	200.26
Moderate	3	158.12
Severe	1	126.78

$p = 0.212$ (NS) Spearman correlation test

Table 5. Mean NO levels in people with malnutrition associated with treatment duration (days) in hospital

Duration of treatment (days)	N	Mean NO levels (μM)
< 14	4	155.25
15 - 21	4	168.18
22 - 28	2	228.30
29 - 35	1	123.44
> 35	2	113.40

$p = 0.275$ (NS) Pearson correlation test

In this study, conducted twice examination of the concentration of NO in patients with severe malnutrition (8 marasmic and kwashiorkor 5). Blood samples for examination were taken on the day I NO I MRS, while blood samples for examination of NO II taken when patients KRS. Average concentrations of NO I are 161.58 (48.28) μM and NO II are 145.84 (53.81) μM . By using two sample paired t test (paired t test) showed that there was no significant difference between levels of MRS with higher levels of NO when NO when KRS.

DISCUSSION

This research is a case control study design with a comparative study to compare the NO levels of malnutrition in patients with the control group (children with good nutrition), comparing between the NO concentration with marasmic kwashiorkor, and to assess the correlation between NO concentration to the degree

of edema. Followed by a prospective study to assess the correlation between high levels of NO with the length of treatment of malnutrition in hospital patients and to assess the decrease in NO concentration when there is clinical improvement.

Patients with severe malnutrition in this study largely on the age group of 13-24 months with a mean of 29.5 (39.2) months. While the kwashiorkor group all aged <24 months with a mean of 12.5 (6.19) months. Marasmic patients who become more varied sample of this study age, from age 6 months to 140 months with a mean of 46.5 (50.94) months. This shows that malnutrition is more common in the age of approximately 29.5 (39.2) months. While kwashiorkor is most common in the age of 12.5 (6.19) months. Williams (1935) reported that kwashiorkor usually occurs in children aged 6 months to 2 years. Kwashiorkor is the youngest patient aged nine weeks and the oldest 5 years old. and closely related to the provision of basic ingredients of traditional foods of corn (maize diet) as a substitute for breastmilk. Monte (2000) states that the peak prevalence of PEM was 24 months. This is closely related to inadequate nutritional intake (both quantitatively and qualitatively), and the high incidence of diarrhea. In this period the need for energy and protein increased, particularly to support the process of growth and development.

Soetjiningsih (2002) states that the period of the first three years of life is the peak incidence of PEM because children begin weaning, while the additional food provided is often less nutritious. Also during this period is often difficult to feed children, because children already know the taste / have their own taste to certain foods, often tired of the food provided, many children play, or due to psychological factors, such as eating too forced, maternal deprivation, or the existence of newborn brother. The causes of malnutrition during the weaning period, where the diet changed from babies only breast milk to adult food direction, namely (1) lack of knowledge of family / mother of the baby's needs and nutritious food supplements; (2) ignorance family / mother about the provision of additional food from local ingredients are nutritious; (3) poverty, making it less able to provide nutritious food.

In this study, eight patients with kwashiorkor become research subjects. Found that mean age of 12.5 (6.19) months, with the youngest aged six months and the oldest aged 19 months. From the eight patients with kwashiorkor, it all got a history of inadequate nutrient intake, which is given sugar water or water and soup with a duration of 4-6 months in advance. Reasons given sugar water / water is the low level of economic starch families (average family income of Rp. 483 750,

with a range of Rp. 150000-1070000 per month), lack of knowledge of mothers about the importance of giving nutritious food supplements for toddlers and an easy supply of sugar water / water soup. Malnutrition is more common in boys than girls, with a ratio of 4:1.

Levels of NO in patients with malnutrition

Twenty years ago, Golden and Ramdath for the first time revealed the occurrence of oxidative stress as a basis for the pathogenesis of kwashiorkor. Oxidative stress is a condition caused by imbalance of free radicals with the body's defense system. Oxidative stress occurs when the amount of antioxidants decreased or increased free radical formation, or both. Inside the human body there are two main free radicals, namely superoxide (O_2^-) and nitric oxide (no.) (Fang 2002). In this study, average concentrations of NO in children with severe malnutrition is higher than the control group. This difference was statistically significant. Similarly, NO levels in kwashiorkor. When compared with the control group, the levels of NO pada kwashiorkor 1.5 times higher. These results are consistent with previous research, ie research that dilakukan by Golden (1998) and Fechner et al (2002). Golden, in 1998 conducted a study on child malnutrition by comparing the levels of NO between patients with kwashiorkor, marasmic and marasmic-kwashiorkor. NO concentration was measured as urinary nitrate, after patients are given nitrate-free diet. Preparation of urine taken in the first 24 hours after MRS. This study showed that nitric oxide levels in patients with higher kwashiorkor than in marasmic and marasmic-kwashiorkor.

Fechner, 2001 conduct a longitudinal study of 19 children with kwashiorkor and 15 control group to prove the occurrence of oxidative stress. Periodic examination was performed on serum total antioxidant, glutathione, albumin, total protein and NO. This study showed that NO in kwashiorkor was (235 (107) μM), almost twice higher than in the control group (120 (46) μM). In this study, the mean NO concentration was not significantly different in kwashiorkor compared with marasmic. This is not in accordance with the research was performed by Golden, 1998, in which significant difference was found between urinary nitrate levels in kwashiorkor and marasmic. This is possible because of the eight patients with marasmic who joined the study, none of the patients who come to hospitals because of its marasmus. Four (50%) patients treated with tuberculosis marasmic (TB), lung, 3 (37.5%) patients treated with gastroenteritis and one (12.5%) patients hospitalized with diabetes mellitus.

Reddy et al, 2004 conducted a study on 30 patients with TB who are undergoing treatment with anti tuberculosis (OAT), 15 patients with post-treatment of TB, 55 TB patients who do not undergo treatment and 25 control group. Examination Malondialdehyde (MDA-metabolites results from lipid peroxidation), activity of Superoxide Dismutase (SOD), catalase, glutathione, and total antioxidant status. This study showed that in patients with pulmonary TB increased free radical activity and its decline in total antioxidant levels.

Forte et al, 1999 conducted a study on seven patients with gastroenteritis and 15 control group. In all groups given injections of 200 mg L-Arginine for later examination nitrate levels in the urine. This study showed that in patients with increased synthesis of nitric gastroenteritis caused by increased activity of L-Arginine path that will be converted to citrulline and NO. Droge 2002, stating that on both the type 1 diabetes mellitus or type 2, an increase in free radicals, especially reactive oxygen compounds. Formation of free radicals is suggested as a result of the auto-oxidation of glucose and is associated with the formation of glycated proteins. Increased free radicals contributes highly to the occurrence of complications of atherosclerosis and other vascular damage.

The relationship between NO concentration to the degree of edema

One sign patognomonis of the edema of kwashiorkor. Allayne and Sive et al (1997) mentions that the edema is a sine qua non for upholding diagnosis kwashiorkor. Mechanism of edema of kwashiorkor is still unclear. Some experts assume that NO plays an important role in the pathogenesis of edema. In this study, high levels of NO in patients with kwashiorkor associated with the degree of edema. It turned out that the result is no significant correlation between high levels of NO with the degree of edema.

On the condition of physiological, Enos will enable Guanylate Cyclase (GC) in vascular smooth muscle, thereby increasing levels of Cyclic Guanosine monophosphate (cGMP). cGMP will react as a second messenger that will lead to rapidly decreasing levels of intracellular free Calcium and inhibit activation of 'myosin light-chain' kinase. With this mechanism activity of vascular smooth muscle contraction would be reduced and there was vasodilatation. In certain conditions inos Enos will take over the work and cause an increase in NO concentration up to 1000-fold (Burgner, 1999). In addition, NO will collaborate with superoxide to produce a potent cytotoxic oxidant that is peroxynitrite ($ONOO^-$), which will oxidize thiol or thioether, oxidizes guanosine, and stimulate the

peroxidation of fat (Grisham 1999). This peroxidation causes cell membrane becomes relatively leaky. Sodium pump activity will increase, resulting in buildup of intracellular Na. In patients with kwashiorkor, as well as decreased levels of glutathione, which is the main antioxidant in the human body because it could deter some free radicals such as hydroxyl radical, lipid radicals peroksil, peroxyinitrit and hydrogen peroxide. This condition causes the lack of protective mechanisms against free radicals (Golden 1987).

The relationship between NO concentration with duration of treatment

In this study, high levels of NO in children with malnutrition associated with duration of treatment in hospital. This study showed that there was no significant correlation between high levels of NO with duration of treatment of malnutrition in hospital patients. These results are consistent with previous research conducted Fechner et al, 2001. This indicates that NO is not the only factor that determines the clinical course of the disease and the output from malnutrition sufferer. So far, only a proven glutathione as an antioxidant that is correlated to the clinical course of the disease and the output of kwashiorkor patients.

CONCLUSIONS

Based on the data, it can be concluded that concentrations of NO in children with malnutrition are 1.5 times higher than control group (children with good nutrition), concentration of NO at higher kwashiorkor when compared with the control group (children with good nutrition), but did not differ significantly when compared with marasmic. Besides, there were no significant correlation between high levels of NO in children with kwashiorkor degree of edema. There were no significant correlation between high levels of child malnutrition NO with duration of treatment in hospital. Also, there was a decrease in NO concentration when there is clinical improvement, but this decrease was not significant. To prove the occurrence of oxidative stress in children with severe malnutrition, especially kwashiorkor, it is necessary to conduct further research to assess the levels of NO, total antioxidant levels, glutathione levels, and superoxide levels

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