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Association Between Seropositivity of *Helicobacter pylori* Infection and Anaemia Amongst Children Aged 5-15 Years in Western Highlands of Kenya

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Abstract
Anaemia is a global health problem, whose development is influenced by several factors. *Helicobacter pylori* infection is among the factors associated with anaemia. Long term interruption of malaria transmission in the highland area of Kipsamoite led to an increase of haemoglobin levels in some few individuals. However, there are still reported cases of low Hb levels associated with anaemia. In studies that have been done on the role of *H. pylori* infections on anaemia, researchers hold varied views on whether or not *H. pylori* infections play a role in iron deficiency anaemia. This study investigated the association between *H. pylori* infections and anaemia in children aged 5-15 years in Western highland region of Kenya. The study adopted a case-control design and purposive sampling technique was used in selection of subjects. Haemoglobin levels and *H. pylori* occurrence were measured and entered into Microsoft excel. These data was summarized into descriptive statistics. Chi-square was used in hypotheses testing. A total of 105 participants were enrolled, 35 were cases and 70 were the controls. The mean haemoglobin level was found to be statistically significantly (p<0.00), haemoglobin of cases was lower (11.05 ± 1.726) than that of controls (13.01 ± 1.897). The proportion of anaemic children among the cases was 77.1% (27) while the non-anaemic were 22.9% (8). The Chi-square showed positive statistical significant difference (p<0.05) between cases and controls. The study concluded that there was a great association between *H. pylori* infection and occurrence of anaemia in Western region of Kenya.

Keywords: Anaemia, Case, Controls, *Helicobacter pylori*

1. Introduction

Anaemia is still a public health problem globally. According to Benoist, Mclean, Egii, Cogswell (2008), about 293.1 million children under five years are suffering from anaemia with 29 percent being from sub-Sahara Africa. In tropical and developing countries, aneamia is particularly more than 50% prevalent among pre-school

children and pregnant women who are either moderately or severely anaemic. Furthermore the main causes of anaemia in tropical countries include: malnutrition, parasitic, bacterial infections, viral infections, inherited haemoglobinopathies, glucose 6 phosphate deficiency and obstetrical complications that result in blood loss (Monica, 2000)In addition, anaemia can be categorized as either, iron deficiency anaemia, megaloblastic anaemia, haemolytic anaemia, anaemia of chronic diseases or a plastic anaemia. According to WHO (2011), iron deficiency anaemia is the most prevalent type of anaemia globally.

Moreover, gastrointestinal bleeding and malabsorption are also factors considered to be contributing to iron deficiency anaemia. Bacteria *Helicobacter pylori,*is an important microorganism which has been associated with gastrointestinal bleeding and malabsorption and hence considered an important bacterium in iron deficiency anaemia.

H. pylori is a spiral shaped bacterium propelled by flagella, lives in the stomach and small intestines of the host (Monica,2000).Most physicians often overlook these bacteria, even when patients complain of symptoms that are classic for *H. pylori* infection, which include stomach pain, nausea, acid reflux, intestinal discomfort and halitosis (IDI, 2002).*H. pylori* needs iron to survive and has been characterized has one of the microorganisms capable of getting heme in hemoglobin and from iron bound to lactoferrin normally found in human secretions such as saliva, tears and gastrointestinal fluids. With an adequate supply of iron, *H. pylori* can thrive and proliferate to the extent of causing stomach cancer (IDI, 2002). *H. pylori* utilizes iron for its survival and that is why most studies done, associate this bacterium with iron deficiency.

It has been speculated that *H. pylori* contribute to iron deficiency anaemia by competing with the host for iron. In addition, Kearney, (2005), points out that colonization of *H. pylori* in the gastrointestinal tract impairs the absorption of iron and hence affects the ferritin stores causing iron deficiency anaemia without necessarily destroying the gastrointestinal mucosa. The epidemiological studies which have been done have shown that *H. pylori* is highly prevalent in developing countries than in developed countries.

2. MATERIALS AND METHODS

The study was carried out in Nandi County, Mosop Sub-County, Sangalo location specifically Kipsamoite sub-location. This highland area has an altitude of 2319M above the sea level, located at latitude of 0.33265N and longitude of 34.99659E. This area experiences low and seasonal malaria transmission within the year, with peaks of malaria outbreaks between the months of May and August. This is influenced by the general climate which comprises of fluctuation in the amount of rainfall between the years and the change in temperature patterns. The area receives high rainfall between the months of March and November with the highest rainfall recorded in the month of August. In different months the changes in minimum and maximum temperature is observed with the highest temperature being noted in the months of January and February. Soil is fertile and supports production of various crops such as maize, potatoes, beans, millet and horticultural crops with tea being the main cash crop. Livestock farming is also practiced for both beef and dairy.

Respiratory tract infections are commonly experienced in this area according to unpublished clinic records. More importantly anaemia, malaria and other bacterial infections are among the recorded and unpublished reports.

The study adopted a retrospective case-control research design involving the study of cases with *H. pylori* infection compared to controls without *H. pylori* infection. In addition a cross-sectional study was also adopted, focusing on children between the ages of 5-15 years.

The target population involved children between the age of 5-15 years which presented signs and symptoms of *H. pylori* infection. Inclusion criteria involved Children who presented with signs and symptoms of *H. pylori* infections whereas children with an obvious case of blood loss such as active or recent gastrointestinal hemorrhage, those with known chronic hematological diseases other than anaemia, children on antibiotics treatment and those who did not consent to the study were excluded. A total of 105 participants , 35 cases and 70 controls were involved in the study. Sample size was determined using the Kesley formula (Kesley, Whittemore, Evams, Thompson, 1996).

Purposive sampling technique was used to select cases-by testing for *H. pylori* infection in those individuals with signs and symptoms of *H. pylori* infections, and positive individuals were treated as cases. The controls of the study were obtained, from the participants with signs and symptoms and tested negative for *H. pylori* infection. Adapting Crimes and Schulz (2005) information, the study recruited 2 controls per case to increase the power of the study.

Collection of Blood Samples involved cleaning the finger with 70% alcohol swab and allowed to dry before being punctured using sterile lancets to enable blood specimen collection.

After collection of blood specimen, Hb level testing was done using photometry (hemocontrol machine) and the readings recorded. Hb levels values was adjusted by -0.8 g/dl for altitude as per World Health Organization recommendation (2011). In addition, the cut off for anaemia was done in relation to the age of the children and this was done as follows: age 5-11.9 years was 11.5g/dl and age 12-15 was 12g/dl. Those children who were found to be anaemic and with *H. pylori* infections were referred to the health centre clinician for further evaluation and treatment. Serum specimens were collected from the study participants and qualitative detection of IgG antibodies against *H. pylori* infections was carried out and the results recorded. Children with IgG antibodies were referred back to the clinician for further evaluation.

2.1 Data Analysis

Data was entered into Microsoft excel transferred into stata data editor. Descriptive statistics was used, summarized into frequencies (%) and mean (+SD) as appropriate. Chi square test were used in the analysis of the data. Stata (statase14) software was used.

2.2 Ethical Considerations

This study commenced after ethical approval by ethical review committee of the University of Eastern Africa Baraton (UEAB/12/9/2017). In addition, permission to conduct the study was obtained from the health centre administration. Further, written informed consent was obtained from the guardian or the parent of each participant and the results were kept confidential. Any result that was necessary for the child was communicated to the physicians for appropriate management.

3. RESULTS

3.1 Demographic characteristics of cases and control groups

Table 1. The characteristics of the study population

Variables	Case (n=35)	Control (n=70)	p-value
Number of male (M)	14 (40%)	37 (52.86%)	0.00018
Number of female (F)	21 (40%)	33(52.86%)	0.0002
Number of 5-11.9 years	16 (45.71%)	30 (42.86%)	0.00012
Number of 12-15 years	19 (54.29%)	40 (57.14%)	0.0002
Age mean $\pm$ sd	11.59$\pm$3.66	11.41$\pm$3.39	0.8126
Age median	13	12	
Age inter-quartile	7	4	

In this study there were 105 study participants (35 were cases while 70 were the controls). Among 35 cases 21 (60%) were female and 14 (40 %) were males. 16(45.71%) were between the ages of 5-11.9 years while 19(54.29%) were between the ages of 12-15 years (Table 1). On the control groups 37 (52.86%) were male and 33 (47.14 %) were female. 30 (42.86%) were between the ages of 5-11.9 years while 40 (57.14 %) were between the ages of 12-15 years (Table 1). The mean age of cases was 11.586 $\pm$3.7 and that of the controls were 11.41$\pm$ 3.4. The median age of case and controls were 13 and 12 respectively (Table 1).

Table 2: Comparison of the Hb levels of the cases and controls using Wilcoxon rank test

Parameter	cases n=35	controls n=70
Minimum Hb levels	6.6	8.6
25% percentile	10.20	11.45
Median	11.10	13.35
75% percentile	11.50	14.30
Maximum Hb levels	15.40	16.30
*p-value < 0.0001		

The median of the Hb of the controls was 13.35g/dl while that of the cases was 11.1g/dl (Table 2). The lowest Hb levels between cases and controls were 6.6g/dl and 8.6g/dl respectively (Table 2).
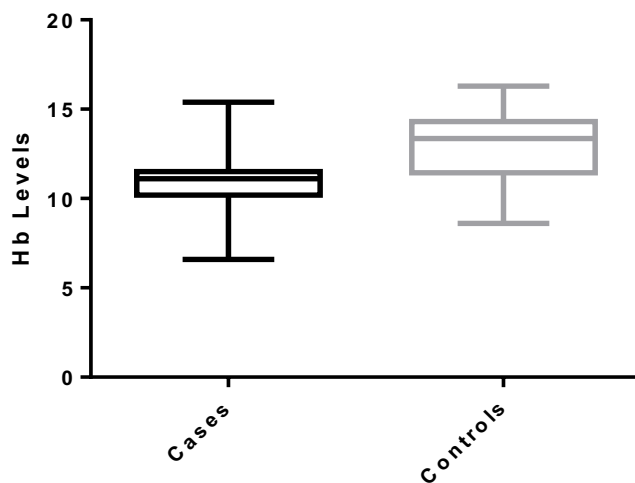

Figure1: Box plot of the comparison of the Hb levels of the cases and controls

The data values range from 6 g/dl to 16g/dl for both cases and controls (Fig 1). The data of both cases and controls were symmetric. The inter-quartile range of the controls was 3 while the inter-quartile range of the cases was 2 (Fig 1)

3.2 Association between *H. pylori* infection and occurrence of anemia in areas of low malaria transmission.

Table 2. The association between anaemia and *H.pylori* infection.

Aneamia	controls	cases	total
No	51	8	59
Yes	19	27	46
Total	70	35	105

Pearson chi-square 23.6966, p-value 0.00

In 70 controls, 51 had no anaemia while 19 were aneamic, while in 35 cases 8 were non-anaemic and 27 were anaemic (Table 2). Using pearson chi-square a significance difference was noticed (23.6966, p-value=0.00)

4. Discussion

Anaemia is one of the public health problems among the children globally. Understanding various factors contributing to development of aneamia helps the clinicians and policy developers to put in place measures on how to deal with anaemia. This study was carried out in area of low malaria transmission with prolonged interruption of malaria transmission in 2008, significant number of cases of anaemia with unknown cause was

still being reported even with unreported cases of malaria. The results of this study showed that those children with *H. pylori* infections had lower Hb levels compared to those children with IgG negative for *H. pylori* infection. The low Hb levels observed in this study could be due to coupled rapid growth of children and the *H. pylori* infection. The rapid growth of children requires high amount of iron to sustain their growth (Choe, Kim, Hong, 2000). The development of Hb molecule requires iron and hence any interference of iron affects the Hb levels. Choe *et al.,* (2000) proposed that *H. pylori* infection affects the iron metabolism and iron absorption and exacerbate the iron deficient. Different researchers have demonstrated various mechanisms which *H. pylori* could be using to interfere with iron metabolism and iron absorption causing anaemia. The current study postulated that hemorrhagic gastritis associated with *H. pylori* infection could be a possible mechanisms causing gastrointestinal bleeding causing excess iron loss. Yip, Limburg, Ahlquist *(*1998) reported that hemorrhagic gastritis associated with *H. pylori* infection as a possible cause of occult bleeding and therefore iron loss experience in Alaska population.

Secondly, the malabsorption of non-haeminic iron reduces the amount of iron in the circulation affecting the haemopoesis process and hence affecting the level of Hb concentration. Perri *et al.,* (1997) and Windle, Kelleher,Crabtree,(2007) showed that hypochloryhydria in which *H. pylori* infection is associated with iron deficiency and anaemia, decreases the absorption of non-haeminic iron absorption.

Thirdly, Yokota *et al.,* (2008) reported that *H. pylori* strains in iron deficiency anaemia patients showed ferric ion uptake and a fast-iron dependent growth when compared with strains from patients without iron deficiency. The current study therefore hypothesized that the mechanisms revealed by Yokota *et al.,* (2008) could be another possible mechanism used by *H. pylori* infection in this population to cause anaemia. In the *H. pylori* positive children in this, 77.1% had anaemia while 22.9% of the infected children did not have anaemia. This shows that certain strains of *H. pylori* are iron dependent while other strains are non-iron dependent. That could be the main reason why 77.1% had anaemia while 22.9% did not experience the development of anemia. Interference of iron metabolism and iron absorption, affects the haemopoesis process and hence interferes with Hb levels. Iron is an important complement in the development of Hb. This study noted that the *H. pylori* infection may have contributed to the low Hb levels in children in this population by interfering with iron absorption and iron metabolism.

Eato Brooks, Morgan, Krakowa, (1991) highlighted that urease production which helps the *H. pylori* bacteria in overcoming the acidic environment of the stomach is one of the mechanisms which affects the iron metabolism and iron absorption. In addition, the absorption of iron is also interfered with by the destruction of the stomach cell membrane by *H. pylori* infection. Asahi *et al.,* (2003), noted that the binding of VacA to specialized membrane, functional domain have an implication on cell signaling. Tegtmeyer, Zabler, Schmidt, (2009), noted that VacA inhibited the activation of epidermal growth factor receptor (EGFR) and HER2/Neu, and Erk1/2MAP kinase which play an important role for cell elongation and cell scattering. The above mechanism induced by *H. pylori* infection interferes with cell membrane structure affecting the iron absorption and hence affects the Hb levels.

Our findings agreed with several studies done elsewhere, Baggett Parkinson, Muty, Gold, Gessner, (2006), assessed an association of *H. pylori* infection and ID among children of the age of 7-11 years and found a great association after age confounding was done. A strong association in children between the age of 9 years and above was noticed. The current study differs with the above study in that after stratification of age groups this study no statistical significance among the age groups was found. In addition the changes in the gastric physiology and its histology in children caused by *H. pylori* infections were investigated by Baysoy *et al.,* (2004). This study found that the destruction of the gastric physiology and its histology by *H. pylori* infections affects the serum iron levels. On the same note, a study done in Germany which was a cross-sectional study (n=1806) noticed 17% decrease in serum ferritin concentration in *H. pylori* IgG positive individuals than in *H. pylori* IgG negative individuals (Berg Bode, Blettner, Boing, Brenner, 2001). Moreover, in Korean children a positive statistical significance of *H. pylori* infections and low mean serum ferritin levels ($p<0.001$) was noticed (Choe, Kim, Hong, 2003). Furthermore, in Australia a study involving women showed high statistical significance of *H. pylori* infected women and low serum ferritin levels compared with *H. pylori* negative women even with the same diet intake of iron (Peach, Bath, Farish, 1998). The current and the above study done in

Australia were done in children and women respectively. On the same note the current study agrees that there was an association between *H. pylori* infection and low Hb levels and the Australian study agreeing that *H. pylori* infection and low serum ferritin levels was statistically significant, meaning that the role of *H. pylori* infection on Hb levels is felt across the gender group and across all ages.

In a study done in Korean adolescents (n=937), a significant association between *H. pylori* seropositivity and anaemia was noticed. In addition in a study done by Darvishi, Katayoun, Hussein, Kamyab ,(2015) in Iran found out that the serological investigation for *H. pylori* infection revealed that 52 (81.3%) patients with IDA and 10 (14.3%) non-anaemic controls were positive for specific IgG *H. pylori* antibodies and the difference between the two groups were statistically significant (p<0.0001).

Similarly, a study done in Ethiopia by Taye *et al.,* (2015) which upto 6.5 years of *H. pylori* infected children was associated with higher prevalence of anaemia and reduction of Hb level and red cell indices.

In another study done in Iran, by Darvishi *et al.,* (2015), a case-control study in children under six years, found a strong relationship between *H. pylori* infection and iron deficiency anaemia. This study strongly agrees with our findings in that both studies uses the same diagnostic method of IgG antibodies and were on the agreement that, there is association between anaemia and seropositivity of *H. pylori* infection. However, the difference was that Darvishi *et al.,*(2015) did an investigation in children under 6 years of age while this study focused on children between the ages of 5-15 years. This study proves that the association between *H. pylori* infection and anaemia is statistically significant in both older and younger children.

However, there are still controversies among various studies regarding the association between *H. pylori* infection and anaemia. Some authors believe that variation in *H. pylori* species is one of the possible factors for disagreement with the findings in the literature.A cross-sectional study done among Israel-Arab children found a great association between low serum ferritin and CagA-positive strain (Muhsen *et al.,* 2009).In double-blind randomized trial on non iron deficient in 3-10 years old children in Elpaso Texas reported that eradication of *H. pylori* infection by CagA negative strains was associated with a larger serum ferritin increase (Cardenas *et al.,* 2011). On contrary, a German study involving a large population based study could not find any association between the low serum ferritin and the seropositivity of *H. pylori* CagA strains (Berg *et al.,* 2001). On same findings Ciacci *et al.,* (2004) reported a negative association between *H. pylori* infected adults with CagA positive strains and iron absorption impairment. However, with above controversies, the current study believes that different strains of *H. pylori* infection associate differently with anaemia. This is due to the fact that 77.1% of *H. pylori* infected children had anaemia while 22.9% did not develop anaemia, postulating that this could be due to different strains of *H. pylori* infection. The study concludes that there is astrong association between *H. pylori* infection and anaemia and recommends that children with low Hb level should be subjected to *H. pylori* diagnostic tests and treated if found positive.

5. Conclusion

In conclusion, our findings indicated that seropositivity of H.pylori infection is highly associated with the occurrence of anaemia. Children with unexplained cause of anaemia should be tested for H. pylori infection and treated if found positive.

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