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A COMPARATIVE STUDY OF THE QUALITATIVE CHANGES IN THE LEVELS OF IL-4 , IL-6 AND IL-10 AND THEIR RELATIONSHIP TO HEMATOLOGICAL PARAMETERS IN CHILDREN WITH E. VERMICULARIS INFECTION

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Abstract: Background; Enterobiasis (pinworm infection) caused by Enterobius vermicularis is a common parasitic infection prevalent worldwide especially in children. It causes many important symptoms and can lead to digestive problems and lead to malnutrition in children. **Aims of the study**; Knowing the relationship between levels of cytokine and the severity of infection in children and the extent of the impact of the infection on the child's health in Iraq. **Methodology;** A Case-control study included 100 children suffering from infection with the worm E.vermicularis. The ages of the participants ranged from 3 to 10 years. The study included 50 healthy children matched in age and sex to the patient group. 5 ml of blood was collected from each participant at Al-Haboubi Teaching Hospital and at Nasiriyah General Hospital for the period between 3/1/2024 to 10/3/2024. CBC assay using a Sysmex device. Interleukins were examined using enzyme-linked immunosorbent assay. **Result;** The results showed that there was no statistical significance in age among the participants. While the results of WBC and CRP were significantly high in the patient group, in contrast to PCV and Hb which were significantly low. While interleukin 4 and interleukin 6 results showed a significant increase in the patient group, while interleukin 10 showed a significant decrease. **Conclusions**; High levels of biomarkers, indicate the immune response that causes by infection with the worm. Anemia due to the pathophysiology of inhibiting appetite and lack of absorption in Intestines for nutrients.

Keywords: Vermicularis, Interleukins, Hematological parameters, Pinworm infection

Introduction

E. vermicularis is the preferred helminth infection, especially among school-age children in middle and high-income countries. The species E. vermicularis demonstrates a worldwide distribution that does not appear to be influenced by socioeconomic level, ethnicity, or culture. Inadequate personal or group hygiene, together with overcrowding in childcare facilities, educational institutions, orphanages, and houses, are variables that can facilitate the spread of Enterobius infestations (Friesen et al., 2019; Burkhart, 2005). The main mode of transmission for enterobiasis is by the consumption of eggs that have been contaminated. Upon ingestion, ova undergo a metamorphosis, wherein they undergo development into larvae and adult worms. This change primarily takes place in the ascending colon, caecum, and lower ileum. At night, pregnant female worms move via the anus, moving from the colon to the skin around the prostate and pelvis, where they lay their eggs. Autoinfection occurs when finger sucking is combined with touching or scratching the perianal region. The embryos possess a substantial, external albuminous coat that attaches to fomites. The transmission of Enterobius can occur through the environment to individuals who share a common residence or attend the same kindergarten or school (Cook, 1994). Risk factors that can lead to an increase in pinworm infection include sharing a bed with children, in addition to sharing clothes between children and poor social status. In addition, the use of unsterilized water may increase the risk of infection in children (González-Moreno et al., 2011; Matthys et al., 2011). E. vermicularis distribution and incidence in Thailand have been extensively studied. Epidemiological data on E. vermicularis infections in rural areas, particularly Southern Thailand, is scarce. A 2009 national survey in Thailand reported 0.2% E. vermicularis infections in Southern Thailand. An intestinal parasite infection investigation was conducted in Nakhon Si Thammarat, Southern Thailand, in 2016. The prevalence of E. vermicularis was 0.3%. However, these recent articles accidentally discovered E. vermicularis infections using parasitological surveys that did not use Scotch tape, the most reliable method (Steinmann et al., 2010). The infection possesses the capacity to advance to superficial cellulitis of the perianal epidermis, hence potentially giving rise to problems. The presence of eosinophilic infiltration distinguishes occasional instances of abscess development resulting from colonic inflammation. The occurrence of urinary tract infections is often attributed to the auto-inoculation or abnormal migration of E. vermicularis from the rectum to the urinary system (Song et al, 2003; Ögren et al., 2015). The migration of mature E. vermicularis has been associated with various health issues. Some of the consequences that may arise include vulvovaginitis, adnexitis, uterine infection, and appendicitis. Furthermore, there have been documented cases of a link between infection with E. vermicularis and the protozoan parasite Dientamoeba fragilis (Choudhury et al., 2017). Gastric parasites significantly contribute to the development of hypersensitivity and allergic responses. The objective of this study was to investigate the potential association between parasites and allergies by the examination of intestinal protozoans and helminths in stool samples obtained from individuals exhibiting symptoms of allergies. Parasitic diseases elicit a wide range of clinical symptoms that exert control over the entirety of the human body. Initially, the host may have hypersensitivity reactions to the chemical compounds excreted by the parasites. Moreover, it is possible for allergic reactions to occur (Giacometti et al., 2003; Falcone et al., 2004). Over the past few decades, there has been a substantial rise in the prevalence of allergy illnesses. Allergenic illnesses are associated with Th2 (T helper 2) reactions. The cytokine IFN-5 is synthesised by Th2 cells and has a role in the interaction with harmful mediators generated by innate immune cells. The therapeutic targeting of Th2 cytokines is attractive due to their role in allergies, as they offer protection against gastrointestinal nematodes. The discovery of immunological therapies that effectively prevent the onset of pathology while simultaneously

preserving protective responses is a feasible endeavour (Black, 2001; Finkelman & Urban, 2001). A robust Th2 cytokine response has been observed, particularly in cases of prolonged worm infections. Individuals afflicted with helminth infections exhibit an increased propensity for experiencing allergy reactions triggered by the Th2 immune response. Certain individuals may experience hypersensitive reactions to the chemicals emitted by helminths. Long-lived parasites, such as helminths, are of particular interest due to their ability to modulate the immune system of their hosts, thereby evading elimination and mitigating the risk of severe illness in the hosts (Cribier & Noacco, 2003; Maizels & Yazdanbakhsh, 2003). Moreover, protozoan infections might give rise to allergic reactions. Obligational bias, giardiasis, and Blastocystis have been described in many papers as potential causal agents of allergies in both animal and human models (Barahona et al., 2003). The induction of eosinophilia is ascribed to the production of interleukin-5 (IL-5) by Th2 cells. Interleukin-5 (IL-5) serves as a "eosinophil activator" and is considered the primary cytokine involved in the maturation and differentiation of eosinophils. The presence of parasitic infections significantly contributes to the elevation of eosinophil levels in the bloodstream. The increase in eosinophil counts is attributed to the toxicity-allergic impacts of some parasites on the host organism. In the defence of parasite prey, eosinophils serve as effectors. Both groups of illnesses are associated with a polarised Th2-type immune response, which is distinguished by the presence of reactive cell types such as eosinophils and mast cells (Yazdanbakhsh et al., 2001; Capron & Dombrowicz, 2002; Lawrence, 2003). Recent studies have revealed a robust correlation between intestinal infection and inflammation, which is closely associated with the onset of inflammatory bowel illness (IBS). Mast cells and the inflammatory substances they secrete have been associated with several gastrointestinal disorders, including unexplained inflammatory bowel disease (IBD). Parasites induce the degranulation of mast cells, hence facilitating the release of histamine into the body (Behm & Ovington, 2000; Klion & Nutman, 2004). Healthy individuals do not produce IL-5, however individuals with an inflammatory bowel illness may exhibit a significant production of IL-5 from their mast cells. Parasites can induce the production of IL-5, which may contribute to the development of IBD (He & Xie, 2004; He, 2004).

Methods

A case-control study included 100 children suffering from infection with the worm Anthropus vermicularis, who were diagnosed by stool analysis and concentration analysis. The ages of the participants ranged from 3 to 10 years and they suffered from clear symptoms. All signs and symptoms were recorded. The study included 50 healthy children matched in age and sex to the sick group. Verbal consent was taken from the parents of the participating children to draw blood, and 5 ml of blood was collected from each participant at Al-Haboubi Teaching Hospital and at Nasiriyah General Hospital for the period between 3/1/2024 to 10/3/2024. 3 ml of blood was placed in a tube. The gel tube was left at room temperature for 15 minutes and then separated using a centrifuge. 2 ml of blood was placed in EDTA tube to conduct a CBC using a German-made Sysmex device. Interleukins were examined using enzyme-linked immunosorbent assay.

Results and Discussion

Results

Socio- demographic characteristics of the patient group and the control group in the study

In this research, two groups were compared, the control group, which included 50 individuals, and the case group, which included 100 individuals. When analyzing age, the mean ages in the control group were 6.34 with a standard deviation of 2.04, while the case group was found to have a mean

age of 6.27 with a standard deviation of 2.10. There was no statistically significant difference in age between the two groups, as indicated by the P value of 0.84. Regarding weight, the control group had an average weight of 17.54 with a standard deviation of 1.24, while the case group had an average weight of 15.88 with a standard deviation of 1.63. This difference in means was statistically significant, as indicated by the statistical P value of less than 0.05. Looking at anorexia, it was found that only 2.0% of the control group answered that they had this condition, compared to 91.0% in the case group, a statistically significant difference with a P value of less than 0.01. On the other hand, 98.0% of participants in the control group did not suffer from anorexia compared to 9.0% in the case group. As for complaints of abdominal pain, it was noted that there were no confirmed cases (0.0%) in the control group compared to 87.0% in the case group, which is a clearly statistically significant difference as the P value was less than 0.001. In contrast, 100.0% of participants in the control group were free of abdominal pain, while only 13.0% of the control group were free of it.

Table (1): Socio- demographic characteristics among to the study group

Parameters	Control group (n=50) Mean±SD		Case group (n=100) Mean±SD		P. value
Age	6.34 ± 2.04		6.27 ± 2.10		0.84
weight	17.54 ± 1.24		15.88 ± 1.63		<0.05
Loss of apettite	Yes	2.0%	Yes	91.0%	<0.01
	No	98.0%	No	9.0%	
Abdominal pain	Yes	0.0%	Yes	87.0%	<0.001
	No	100.0%	No	13.0%	

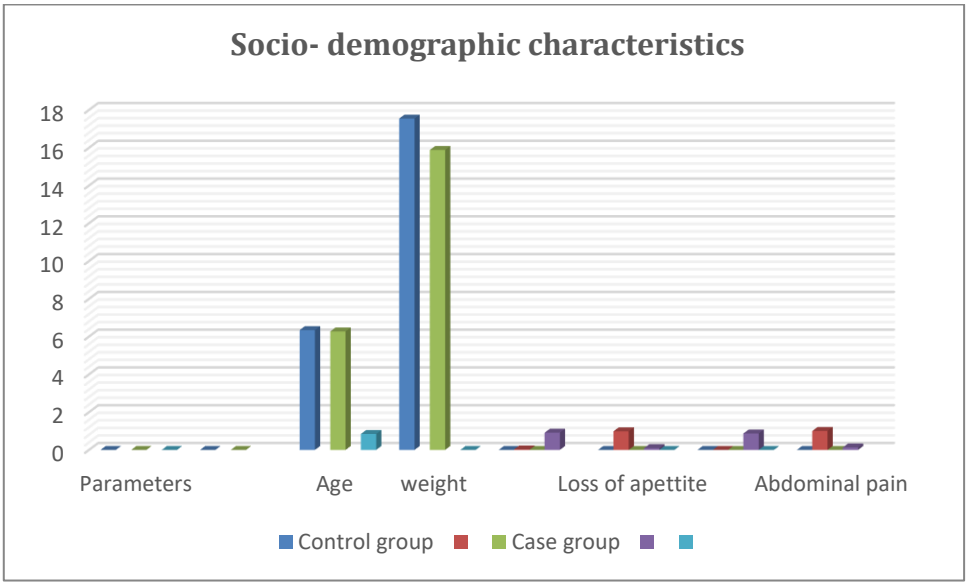

Figure 1: Socio- demographic characteristics among to the study group

Difference between immune and blood indicators between patients and the control group

In a comparative study between two groups of individuals; The control group numbered 50

individuals and the case group numbered 100 individuals. Several health indicators were measured along with their standard deviation values. The results showed a higher average white blood cell (WBC) count in the case group (10.16 ± 1.91) compared to the control group (5.89 ± 0.63), and the differences were statistically significant (P < 0.001). A clear increase in the average level of active C-reactive protein (CRP) was also recorded in the case group (10.62 ± 0.54) compared to the control group (5.19 ± 0.84), which is also statistically significant (P < 0.001). For hemoglobin (HB) level, there was a statistical decrease in the mean in the case group (11.32 ± 1.65) versus the control group (12.67 ± 2.77) with a P value equal to 0.03. Finally, the data revealed a significant difference in the mean corpuscular volume (PCV), as the control group showed a higher mean (40.0 ± 1.44) compared to the case group (35.0 ± 1.28), and the statistical significance of this difference was less than 0.01. All of these results indicate that there are important differences between the two groups regarding the blood indicators studied.

Table(2): The immune and blood indicators between patients and the control group

Parameters	Control group (n=50) Mean±SD	Case group (n=100) Mean±SD	P. value
WBC	5.89 ± 0.63	10.16 ± 1.91	<0.001
CRP	5.19 ± 0.84	10.62 ± 0.54	<0.001
HB	12.67 ± 2.77	11.32 ± 1.65	0.03
PCV	40.0 ± 1.44	35.0 ± 1.28	<0.01

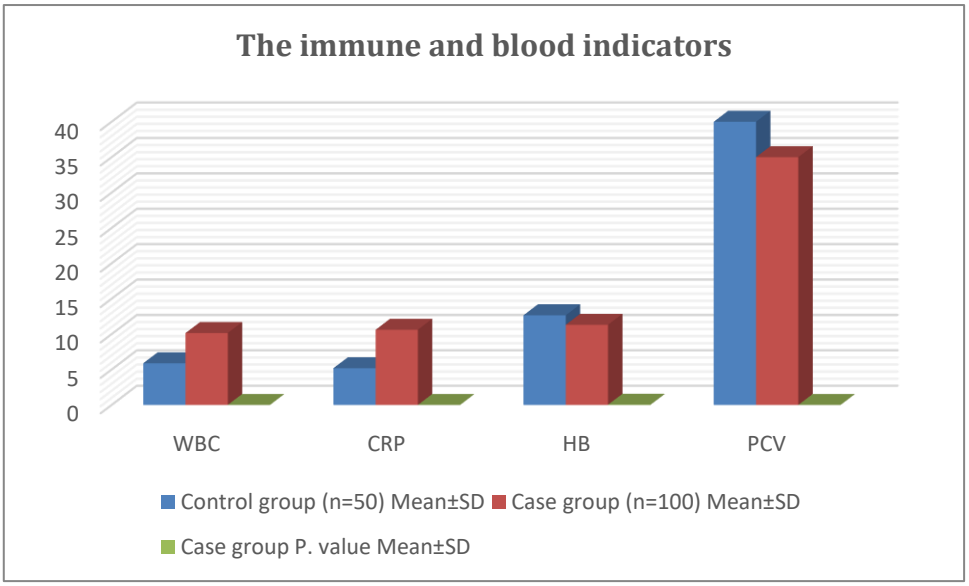

Figure 2: Immune and blood indicators between patients and the control group

Difference between interleukins between patients and control groups

In the research that compared a control group of 50 individuals with a case group of 100 individuals, the study looked at concentrations of some interleukins in the blood. The results show that the average level of interleukin-4 (IL-4) in the control group reached 1.39 with a standard deviation of ±0.41, while in the case group a slightly higher value of 1.53 with a standard deviation

of ±0.34 was recorded, and this difference was statistically significant (P = 0.03). For interleukin-6 (IL-6), there was a significant increase in the case group (5.07 ± 0.49) compared to the control group (2.11 ± 0.45), and strong statistical significance (P < 0.001) indicates significant differences between the two groups. Interleukin-10 (IL-10) showed the opposite results; The control group (7.96 ± 0.58) and the case group (5.61 ± 0.73) exhibited a statistically significant drop in mean value. Taken together, these data reveal significant differences in the levels of interleukins studied between the two groups and may have physiological or pathological implications that deserve in-depth investigation in future studies.

Table(3): Levels of interleukins between patients and the control group

Parameters	Control group (n=50) Mean±SD	Case group (n=100) Mean±SD	P. value
IL-4	1.39 ± 0.41	1.53 ± 0.34	0.03
IL-6	2.11 ± 0.45	5.07 ± 0.49	<0.001
IL-10	7.96 ± 0.58	5.61 ± 0.73	<0.001

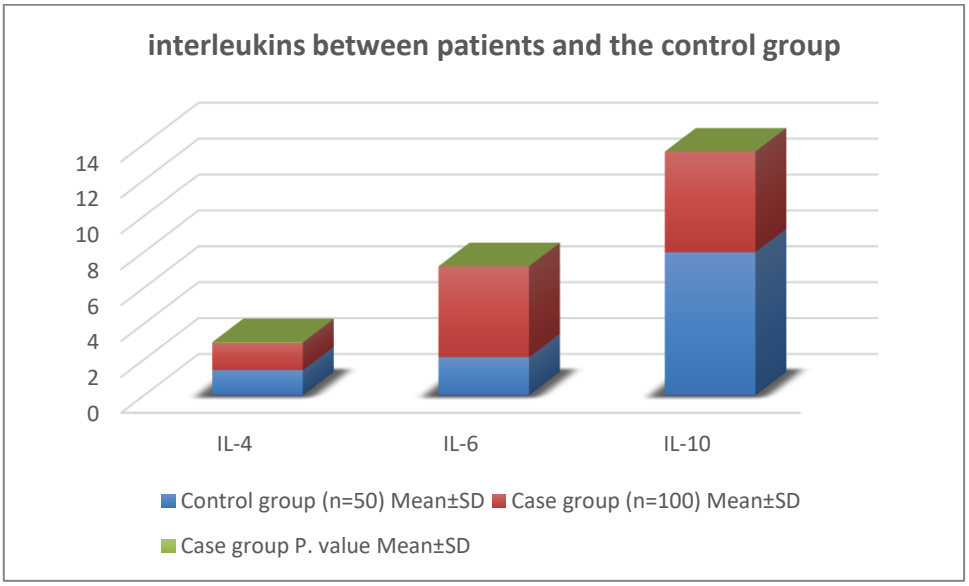

Figure 3: Interleukins between patients and the control group

Pearson Correlation of all biomarkers in the study between the patient group and the control group

Pearson Correlation was used to measure the association between the participants' age and the values of white blood cell count (WBC), C-reactive protein (CRP), and levels of interleukin 4 (IL 4), interleukin 6 (IL6), and interleukin 10 (IL 10).). According to the results of the study, no significant correlation was observed between age and WBC, as the correlation coefficient was 0.051 and the statistical significance (Sig. 2-tailed) was 0.534, indicating the absence of a statistically significant relationship. Considering the relationship between WBC and CRP, a very strong positive correlation emerged (0.896**) with high statistical significance (P < 0.001). While the relationship between CRP and IL 4 was clearly not statistically significant (correlation coefficient -0.004 and Sig. 2-tailed

0.966). A slight positive correlation was observed between IL 4 and WBC with statistical significance (0.199, Sig. 0.014), as well as a moderate correlation between IL 4 and CRP (correlation coefficient 0.164, Sig. 0.045). Regarding interleukin 6 (IL6), a very strong correlation was found with WBC (0.871) and CRP (0.917), with very significant statistical significance (P < 0.001), in addition to a moderate correlation with IL 4 (0.206*, Sig. 0.011). On the other hand, there was a strong negative correlation between IL 10 and both WBC (-0.807) and CRP (-0.825), with significant statistical significance (P < 0.001).

Table(4): The pearson Correlation among all biomarkers included in the study

Parameters		Age	WBC	CRP	IL 4	IL6
WBC	Pearson Correlation	.051				
	Sig. (2-tailed)	.534				
CRP	Pearson Correlation	-.004	.896**			
	Sig. (2-tailed)	.966	.000			
IL 4	Pearson Correlation	.100	.199*	.164*		
	Sig. (2-tailed)	.224	.014	.045		
IL6	Pearson Correlation	-.013	.871**	.917**	.206*	
	Sig. (2-tailed)	.879	.000	.000	.011	
IL 10	Pearson Correlation	.010	-.807**	-.825**	-.144	-.811**
	Sig. (2-tailed)	.899	.000	.000	.079	.000

Double stars (**) or single stars (*) represent high and moderate statistical significance

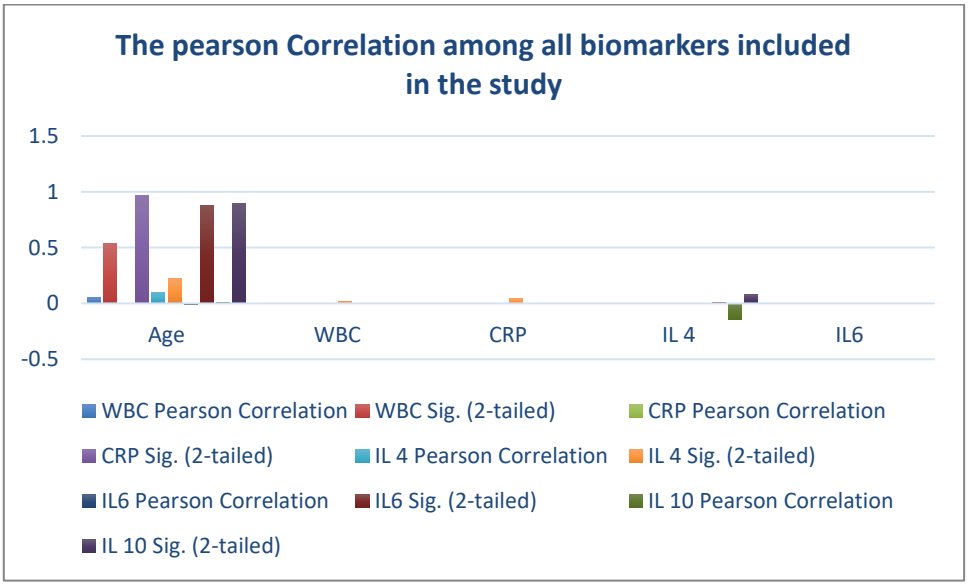

Figure 4: The pearson Correlation among all biomarkers included in the study

Discussion

Recent studies show that there is a significant relationship between infection with the worm

E. vermicularis, commonly known as the pinworm, and interleukin 4 (IL-4) levels in children. Interleukin 4 is a cytokine secreted by Th2 lymphocytes that promotes an allergic-type immune system response known as the Th2 response. Infection with parasites such as Enterobius vermicularis is known to stimulate the immune system to enhanced production of IL-4, which reflects the body's attempt to enhance the production of IgE antibodies and activate basophils and mast cells in order to dislodge the parasites (AL-Bairmani et al., 2023). Studies show that kids with this worm infection have a lot of Th 2 lymphocytes causing an increase, in interleukin 4 levels. This rise signals the bodys system working to fight off the infection naturally. It's an reaction, against parasites (Patsantara et al., 2016; Hamid et al., 2019). It's important to mention that higher levels of IL 4 can lead to side effects, like heightened reactions and potential interference with other infections. This emphasizes the significance of maintaining an response towards pathogens and its implications on a childs overall health (Elsawey et al., 2022). The Th2 response plays a crucial role in eliminating parasites and providing protection against them. The Th2 response was mostly triggered by helminths, particularly in certain tropical regions (Turner et al., 2003). The study conducted by (Pit et al., 2000) revealed that intestinal helminths possess the ability to induce levels of IL-5. Th2 lymphocyte responses may have a role in regulating protective immune responses against intestinal worms. Notable aspects of gastrointestinal nematode infections include the presence of a Th2 cell cytokine that stimulates the generation of eosinophils, as well as an elevated quantity of eosinophils in the gastrointestinal mucosa. (Herrstom et al., 2001) reported a higher prevalence of E. vermicularis in children diagnosed with allergic illness, as determined by the presence of allergic symptoms. (Sorci et al., 2003) established a correlation between pinworms (specifically oxyuridae and nematoda) and the quantity of eosinophils.

According to (Varga et al., 2001) individuals who contracted A. lumbricoides exhibited more severe allergic reactions, whereas those infected with G. intestinalis also experienced allergic reactions. Previous research has demonstrated that the synthesis of IgG1, IgG3, IgM, and IgA plays a crucial role in safeguarding against diseases caused by intestinal protozoa such as E. vermicularis. The presence of anti-parasitic antibodies in the bloodstream was observed exclusively upon the production of cytokines such as IL-4, which is synthesised by Th2 cells. Elevated concentrations of antibodies induced by IL-4 were detected in the bloodstream. Individuals with a protozoon infection had elevated levels of IL-5 derived from the same cellular source, surpassing those obtained from supernatants (Soliman et al., 1998). One of the crucial roles of the immune system is the development and differentiation of diverse subsets of T-cells. Our observations suggest that the absence of IL-6 can result in the development of more robust Ag-specific Th2 responses, which in turn leads to improved immunity and resistance against parasites. The absence of IL-6 in mice did not result in a reduced number of Th17 cells in the MLN. Instead, these mice produced Th17 cells that were comparable to those of wild-type mice after infection. Furthermore, the administration of a neutralising anti-IL-17 antibody to wild-type (WT) rodents did not provide any significant impact on the egg burden or worm burden. After being infected with H. polygyrus, rodents lacking IL-6 displayed a modified regulatory T cell (Treg) phenotype. These rodents displayed decreased levels of Foxp3, Helios, and GATA-3 at a steady state, while simultaneously producing elevated amounts of IL-2 and IL-17. The complete reversal of the resistant phenotype in the IL-6-deficient mice, resulting in the rescue of the Treg-cell phenotype, inhibition of Ag-specific Th2 responses, and restoration of susceptibility to chronic helminth infection, was achieved through the administration of an anti-IL-2:IL-2 combination (Bettelli et al., 2006; Hou et al., 2007; Korn et al., 2008). Understanding the modulation of Th2 immunity is of utmost importance in the context of several illnesses, with helminth

infection and allergies being particularly salient. Interleukin-10 (IL-10) is an essential regulatory cytokine, and its suppressive effects in type 1 immune responses have been extensively documented (Perona et al., 2012). The specific role it plays in a type 2 immune response is yet unclear. The upregulation of IL-10 expression in both the bloodstream and lymph nodes has been observed in the context of type 2 immunological responses (Etiawan et al., 2007). However, there have been suggestions that it could simultaneously enhance and diminish Th2 immunity. This study demonstrates that the immune system exhibits two distinct responses, namely Th1 and Th2, when the intestines become infected with E. vermicularis. In the intestines, IL-10 regulates these reactions by enhancing the production of Th2 cytokines while reducing the population of local Th1 cells (Hawrylowicz & O'Garra, 2005). There are many studies proving the existence of a relationship between pinworm infection and interleukin 6 levels, as interleukin 6 plays an important role in the immune response, as high levels indicate the important immune role played by the cytokine (Korn et al., 2008). Numerous research have provided evidence indicating a high prevalence of E. vermicularis infection among children who sought medical attention at Kranj Community Health Centre. The yearly prevalence range of E. vermicularis infection in preschool and primary school children between 2017 and 2022 was 25.7% to 41.6%, based on clinical suspicion. A wide range of prevalence rates has been observed in several research, exhibiting variations based on factors such as sample type, geographical region, age cohort, duration of observation, and the presence or absence of symptoms. In economically developed nations, the occurrence of E. vermicularis decreased in the second half of the 20th century due to advancements in healthcare, improved cleanliness standards, and the greater use of antihelminthic medication (Kubiak et al., 2017). The incidence rate in this study was greater than that reported in studies from EU countries. The decreased occurrence observed in recent EU studies suggests that enterobiasis is more effectively managed. Another possible explanation is that the investigations were conducted using different methodologies or that the sample used was readily testable for other prevalent parasites other than E. vermicularis (Dudlová et al., 2018). Several studies have examined children who had symptoms commonly associated with enterobiasis, such as anal pruritus, in comparison to those who did not. Research studies that obtained a single sample from each individual may have underestimated the true prevalence of enterobiasis cases. If a single sample is obtained from each patient, there is a risk of overlooking an infected patient due to improper collection by either the parent or the patient. Repeated sticky tape tests remain the most effective method for diagnosing E. vermicularis (González-Moreno et al., 2011).

A recent investigation conducted in Berlin, Germany, revealed an increasing incidence over a period of ten years. On average, 17.4% of patients had positive outcomes, with the age range of 4 to 10 years and male patients demonstrating higher rates of positively in comparison to their female counterparts (Friesen et al., 2019). The data from Gran Canaria, Spain, revealed a minor male bias, with an overall prevalence rate of 11.4%. A Norwegian investigation examining three tape samples revealed that 18% of individuals tested positive, a figure somewhat below the incidence validated by our own analysis. The research conducted by (Bùás et al., 2012) revealed a higher prevalence of type 1 diabetes among children possessing the human Leukocyte Antigen (HLA) gene, which confers an increased susceptibility to the condition. According to the authors, it was suggested that research employing a single sample for each participant shown a reduction of approximately 40% in comparison to the actual frequency. Several studies have observed seasonal variations, although not universally (Carrillo-Quintero et al., 2016). The number of white blood cells also increases in infected people, and this is due to the body's natural immune response against parasitic infection, and it may be accompanied by a number of diseases that are somewhat severe in children, such as anal itching

or loss of appetite. Therefore, hemoglobin levels showed a significant decrease in the infected group compared to In the control group due to malnutrition caused by the parasite, which leads to a lack of absorption of nutrients, and this is consistent with a number of researchers (Hama et al., 2014; Mohmmed et al., 2016; Alomashi, & Al-Shabbani, 2019).

Conclusion

High levels of WBC and C-reactive protein, in addition to high levels of interleukin 4 and 6, indicate the immune response that causes infection with the worm, in addition to the symptoms it causes. Anemia in children is one of the common causes that occurs due to worm infection due to the pathophysiology of inhibiting appetite and lack of absorption in Intestines for nutrients.

Ethical Approval

Before the samples were taken, all of the patients who were going to be part of this study were properly informed and gave their verbal permission. The Committee on Publication Ethics at the Thi-Qar Health Directorate, Al Habbobi Teaching Hospital, gave its approval to the study.

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