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Measuring IgM, IgG, and C4 levels in children with recurrent bacterial infections

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ABSTRACT

Several children have recurring bacterial illnesses that can last for long periods and have little prospect of recovery. A compromised immune system may be the cause on occasion, but other factors may include the environment they live in or a lack of care. The study's purpose was to determine how age affected children's immune blood factor levels. This study involved 45 children with recurrent bacterial infections and aimed to assess levels of specific immune components. These were IgM, IgG, and C4. In addition, both sexes had a complete blood count (CBC) at ages 1-7 years. The concentration of these components in the agar was determined by immunodiffusion, and the results were compared with those of negative control samples. Patients and controls had similar rates for the other immunological variables. When the entire blood count was compared to control samples, the white blood cell count (granulocytes, lymphocytes, and WBC) decreased. Still, the other immunological parameters remained unchanged between patients and controls. In contrast, when compared to control samples, the patients' IgM and C4 levels were much lower. Females showed lower WBC and granulocyte counts than males, and their IgM rates were lower. Compared with older ages and control samples, the first age group (ages 1-3) showed a noticeable decline in blood parameters, except for IgM.

Keywords: IgM, IgG, CBC, C4, immunodiffusion technique

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قياس مستوى IgM و IgG و C4 عند الأطفال الذين يعانون من الالتهابات البكتيرية المتكررة

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الملخص

يعاني العديد من الأطفال إصابات بكتيرية متكررة قد تستمر لفترات طويلة مع احتمالية ضعيفة للشفاء ,قد يعود ذلك الى طبيعة البيئة التي يعيشون فيها او الى قلة رعايتهم ,لكن قد يعود السبب أحيانا الى وجود ضعف في جهازهم المناعي ,اهتم هذا البحث في قياس مستوى بعض العوامل المناعية للأطفال الذين يعانون من إصابات جرثومية متكررة شملت هذه العوامل كل من IgM,C4,IgG و كذلك تم تحديد صورة كاملة للدم (CBC)وباعمار تراوحت 1−7 سنة ولكلا الجنسين, تم استخدام تقنية الانتشار المناعي في الاكار لغرض تحديد تركيز تلك العوامل ومقارنتها مع حالات السيطرة السلبية كعينات سيطرة.

أظهرت صورة الدم الكاملة انخفاض في معدل تعداد كريات الدم البيضاء (Granulocytes, lymphocyte and WBC) مقارنة مع عينات السيطرة، في حين كان معدل باقي العوامل المناعية مقارب بين المرضى والسيطرة. في حين كان انخفاض الIgM و c4 واضحا للمرضى مقارنة مع عينات السيطرة.

وظهر معدل WBC والGranulocytes انخفاضا لدى الاناث أكثر من الذكور. كما ظهر معدل الIgM بانخفاض اعلى لدى الاناث عنها لدى الذكور. تهدف الدراسة الحالية لتحديد تأثير العمر على مستويات العوامل الدموية المناعية لدى الأطفال قيد الدراسة، بشكل عام ظهرت العوامل الدموية انخفاضا واضحا لدى الفئة العمرية الأولى (1−3) سنة مقارنة مع الاعمار الأكبر ومع عينات السيطرة، في حين اظهر ال IgM فقط انخفاضا لدى الاعمار 1−3 سنوات مقارنة مع الاعمار الأكبر وعينات السيطرة.

INTRODUCTION

Three weeks after pregnancy, the immune system begins to develop and continues to grow throughout infancy and youth. [1]. Throughout development, the fetus is exposed to both maternal and external antigens. Prenatal exposure may occur through the ingestion of amniotic fluid by the fetus or through the placental barrier. [2]. Notably, fetal immune cells can be primed by the transplacental transfer of maternal Ig-antigen complexes. [3]. The fetus can mount an immune response. Research has shown that it can respond to external antigens, such as those in vaccines or in illnesses. [4, 5]. After birth, the newborn's immune system must shift from a largely tolerogenic response to an antimicrobial response that protects the child from the new, microbe-rich environment. [6].

Because their adaptive immune systems are still developing at birth, newborns need to improve their memory. The phenotype and activity of newborn immune cells differ from those of adult immune cells [7]. During differentiation, the newborn's lymphocytes show a preference for the Th2 response [8]. This makes the neonates more vulnerable to several diseases, particularly in preterm infants[9, 10]. Although both innate and adaptive immune responses can be elicited in full-term neonates [11], the quality and quantity of these responses differ from those in adults [12]. Numerous maternal factors that affect the early immune response, colonization, and maturation of breastfed children are presented to them[13]. In addition to neonatal Treg cells, breast milk IgA also helps block the differentiation of T helper lymphocytes at the intestinal mucosa [14]. The infant intestinal mucosa can support host/microbiota interactions by promoting a pro-tolerogenic milieu through this process, which continues until weaning. Umbilical cord blood, which appears to be an inaccurate

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indicator of postnatal immune cell development, has been used in most studies[15]. Furthermore, many microorganisms are present in the breast milk microbiome.

Substances that could trigger the baby's immune system. Furthermore, because of its low resistance to bacterial colonization, breast milk protects the infant's digestive mucosa against infection. [16]. It is well known that both preterm and typical newborns have unique immune systems. Children's innate and adaptive immune systems evolve with age. Many parts of the human immune system differ in healthy children because they are designed to help them transition from the womb to the outside world.[17]. Identifying and treating primary immunodeficiency diseases (PIDs) in neonates can be challenging, even though many PIDs occur during this time. The complexity is primarily due to the immaturity of the neonatal immune system, which can mask immunological abnormalities, and/or the challenge of interpreting laboratory test results and clinical data. Before the onset of adverse infections and subsequent tissue damage, early diagnosis of PIDs is crucial for optimal treatment and improved outcomes.[18].

Premature newborns' immunological deficits correspond to their degree of immaturity. Preterm infants also have sensitive skin, mild to severe hypogammaglobulinemia, and lower levels of antimicrobial peptides, plasma complement, and lymphocytes. [19]. Neonatal innate immune system components include natural killer (NK) cells, complement, and antigen-presenting cells such as macrophages, granulocytes (mostly neutrophils), and NK cells. [20]. However, most newborns survive this time without any damage due to intact innate immunity, various adaptive immunological defense mechanisms, and passive protection from maternally transmitted immunoglobulin (IgG) [18]. IgM production begins at the onset of infection and continues to increase for a few weeks before decreasing as IgG production begins. [21]. One way to improve the immune system is by frequent exercise and sports, which encourage the release of inflammation-reducing cytokines. [22]. Because they are associated with the immune response to infection, an increased lymphocyte count may reflect immune system activity, and the outcome may result from bone marrow production failure. [23]. The goal of the study was to ascertain how age affected the children's immunological blood factor levels.

MATERIALS AND METHODS

Sample Collection

Sixty blood samples were taken from children aged one to seven years old, both male and female (23 samples male and 22 samples female). 45 of them exhibited a variety of clinical signs that the trained doctor determined were indicative of immunological impairment; 15 of these samples were collected from healthy children as controls. The samples were collected between April 15, 2023, and August 15, 2023, at the Ibn Sina Teaching Hospital, Al Salam Teaching Hospital, and Ibn Ether Hospital in the Nineveh Governorate, Iraq.

The study involved withdrawing 5 milliliters of blood from both patients and healthy participants. The blood was then distributed by placing two milliliters in an EDTA tube and three milliliters in a gel tube. The blood was then allowed to clot at room temperature for ten to fifteen minutes. Pending immunological testing, the serum was separated by centrifugation at 3000 cycles per minute for 10 minutes. It was then transferred to Eppendorf test tubes containing 500 microliters each and stored at -20 °C. The tests listed below were carried out:

1-Determination of the IgG protein by radial immunodiffusion plate.

2-Determination of the IgM protein, by radial immunodiffusion plate.

3- Determination of the C4 protein using a radial immunodiffusion plate.

4-Complete blood count (C.B.C).

Statistical analysis

A completely Randomized Design was used to examine the data in accordance with the simple experiment. Using Duncan's multiple-range test

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(SPSS), at the 1% significance level, the various important factors were indicated with alphabetic letters. Health and patients were also compared using a t-test.

Results And Discussion

The blood parameter rates for the study patients are compared with those of the control samples in Table 1. Blood cell rates were generally lower than those of the control samples, particularly the WBC and granulocyte counts. In contrast, the RBC and PLT counts were similar between patients and controls, whereas WBC and lymphocyte counts showed notable variation.

Table 1: Complete blood count for children under study.

Std. Deviation	Sig	t-value	Mean	number		Immunological test
1.73308	0.014	2.546	5.8280	45	patient	WBC
3.74278			8.3856	15	control	(4-11) 10^9/L
0.60195	0.010	2.660	1.6553	45	patient	Lym
1.59281			2.7802	15	control	(0.8-4) 10^9/L
1.14524	0.229	1.215	3.4300	45	patient	Gran
6.15951			5.3838	15	control	(2-7.8) 10^9/L
0.43441	0.673	0.426	4.4353	45	patient	RBC
0.32742			4.4807	15	control	(3.50-5.50) 10^12/L
1.28564	0.212	1.267	11.1178	45	patient	HGB
0.76594			11.4667	15	control	(11-16) g/dL
73.03893	0.224	1.230	270.40	45	patient	PLT
77.66847			298.49	15	control	(150-450) 10^9/L

WBCs largely provide the child's innate immunity and are essential for defending the body against infections from the outside world. As their numbers decline, the body becomes vulnerable to recurrent infections. A malfunction in the generation, division, and differentiation of these cells may compromise the body's immune system and immune response. [(24)].

The concentrations of a few other immunological markers were determined for each patient.

Table 2 presents the IgG, IgM, and C4 concentrations in the study subjects. In contrast to the control samples, the patients' IgM and C4 levels decreased, whereas the two groups' IgG levels were nearly equal. In the early stages, the complement factor C4 and the IgM antibody are crucial immunological components that help regulate the immune response, prevent infection, or lessen its appearance or recurrence. When the body's rate of these components decreases, it suggests an immunological problem, as patients, particularly children, continue to experience recurrent infections. [(25)]. This decrease is due to immune System Dysregulation: immune homeostasis can be upset by bacterial infections, which impair antibody synthesis. Defects in T-cell function, which are essential for class-switching from IgM to IgG production, may be involved. Increased Consumption: Immunoglobulins and complement proteins, such as C4, are actively used to fight off bacterial infections. Lower serum levels may result from this increased consumption. Complement Activation, during bacterial infections, the classical complement pathway, of which C4 is a component, becomes extremely active. Circulating C4 levels may be depleted by excessive activation.[(26)].

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Table 2: Immune marker concentration of studied patients

Std. Deviation	Sig	t-value	Mean	Number		
266.97608	0.912	0.110	679.80	45	patient	IgG
313.81448			689.78	15	control	
67.19841	0.584	0.550	130.94	45	patient	IgM
3288.43075			600.72	15	control	
10.97809	0.464	0.737	22.1467	45	patient	C4
23.73565			26.8422	15	control	

*Normal value IgG (800-1800) mg/dl, IgM (60-280) mg/dl, C4 (20-50) mg/dl.

Table 3: Blood parameters rate in infected females with control samples

Std. Deviation	Sig	t-value	Mean	number	female	
1.05068	0.126	1.584	5.3880	22	Patient	WBC
3.78683			8.1314	15	Control	
.33948	0.123	1.596	1.2300	22	Patient	Lym.
1.87808			2.5955	15	Control	
.84320	0.458	0.754	3.4360	22	Patient	Gran.
3.61697			4.6800	15	Control	
.13936	0.733	0.344	4.4120	22	Patient	RBC
.36871			4.4705	15	Control	
.95862	0.389	0.918	11.2091	22	Patient	HGB
.77910			11.5800	15	Control	
40.07743	0.151	1.483	240.20	22	Patient	PLT
92.73268			303.73	15	Control	

*Normal value WBC (4-11) $10^{\wedge 9}$/L, Lym (0.8-4) $10^{\wedge 9}$/L, Gran (2-7.8) $10^{\wedge 9}$/L, RBC (3.50-5.50) $10^{\wedge 12}$/L, HGB (11-16) g/dL, PLT (150-450) $10^{\wedge 9}$/L.

Table 4: Immune marker concentration rate in females

Std. Deviation	Sig	t-value	Mean	Number		Female
197.67641	0.952	0.060	728.32	22	Patient	IgG (800-1800) mg/dl
342.05560			737.96	15	Control	
65.23245	0.652	0.456	112.11	22	Patient	IgM (60-280) mg/dl
4701.07742			147.78	15	Control	
5.45967	0.449	0.769	20.6600	22	Patient	C4 (20-50) mg/dl
31.59227			31.7227	15	Control	

The study's goal was to determine the association between a patient's gender and immunological and blood variable deficiencies by assessing the levels of these variables in male and female patients and comparing them with those of healthy individuals. When comparing female patients to healthy individuals, the rates of these variables are displayed in Tables 3 and 4. Both platelet and immune cell rates were declining, with notable variations in WBC and lymphocyte counts. IgM and C4 rates decreased, but there were no significant differences between the female research participants and the control group.

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Table 5: Blood picture of males under study compared to control

Std. Deviation	Sig	t-value	Mean	Number	Male	
2.00506	0.051	2.032	6.0480	23	patient	WBC
3.76858			8.6287	15	control	(4-11) 10^9/L
.60138	0.016	2.552	1.8680	23	patient	Lym
1.28079			2.9570	15	control	(0.8-4) 10^9/L
1.31309	0.308	1.037	3.4270	23	patient	Gran
7.90078			6.0570	15	control	(2-7.8) 10^9/L
0.49523	0.491	0.701	4.4017	23	patient	RBC (3.50-
0.39269			4.5150	15	control	5.50) 10^12/L
1.55313	0.362	0.926	11.0304	23	patient	HGB
0.79505			11.4100	15	control	(11-16) g/dL
82.61053	0.760	0.308	285.50	23	patient	PLT (150-450)
61.66542			293.48	15	control	10^9/L

Table 6: The rate of concentration of immune indicators in male children compared to the control

Std. Deviation	Sig	t-value	Mean	Number	Male	
284.13762	0.917	0.105	643.70	23	patient	IgG (800-1800)
302.56439			655.54	15	control	mg/dl
46.16338	0.433	0.811	102.96	23	patient	IgM (60-280)
69.97682			122.52	15	control	mg/dl
11.28959	0.883	0.150	22.1739	23	patient	C4(20-50) mg/dl
13.12948			22.8900	15	control	

Tables 5 and 6 compare the rates of the factors under study for males and females. The rate of granulocyte count decreased more in males than in females, whereas the rates of these blood and immune factors, particularly IgM, C4, and WBC, decreased more in females than in males compared with the control. The non-significance can be attributed to certain facts. Variability in Biology: Immune response disparities between sexes are controlled by both genetic and hormonal factors. Whereas females frequently show higher CD4/CD8 ratios and enhanced antibody responses, males typically exhibit higher CD8+ T cell percentages and stronger monocyte-derived cytokine responses. These alterations might affect granulocyte dynamics without producing statistically significant differences. Granulocyte Function: Granulocytes are important in bacterial infections, but other immune components, such as cytokines and regulatory T cells, can affect their numbers and function. Additionally, granulocytes differ in sex. According to studies, women often have a greater immune response than men, making the female immune system more effective than the male immune system. This, however, does not apply to children, since before puberty their hormone levels are less effective than those of adults. [27]. Sex hormones, such as testosterone in males, can modulate immune responses, altering granulocyte dynamics. Research suggests that testosterone may suppress certain immune functions, including granulocyte survival and proliferation. [28].

According to our findings, females are more effective than males of the same age at lowering the levels of some immunological components. particularly considering that, as Tables 7 and 8 demonstrate, the majority of the ill children in the research were younger than three years old.

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Table 7: Blood counts in different age groups

PLT (150-450) 10^9/L	HGB (11-16) g/dL	RBC (3.50-5.50) 10^12/L	Gran. (2- 7.8) 10^9/L	Lym. (0.8-4) 10^9/L	WBC (4-11) 10^9/L	Groups	
295.30 a	11.04 a	4.48 a	4.89 a	2.59 a	8.42 a	Mean	control
15	15	15	15	15	15	N	
75.435	1.166	.475	2.45	1.208	3.359	Std. Deviation	
270.40 a	11.47 a	4.48 a	3.43 a	1.66 b	5.83 b	Mean	patient 1-3 years
27	27	27	27	27	27	N	
73.039	.766	.327	1.145	.602	1.733	Std. Deviation	
303.28 a	11.23 a	4.36 a	6.12 a	3.07 a	8.34 a	Mean	patient 4-7 years
18	18	18	18	18	18	N	
82.884	1.475	.366	2.890	2.046	4.358	Std. Deviation	
291.47	11.21	4.45	4.90	2.50	7.75	Mean	Total
60	60	60	60	60	60	N	
76.909	1.181	0.408	3.416	1.490	3.522	Std. Deviation	

Similar letters indicate that there are no significant differences at the probability level of ($p \leq 0.05$) according to the Duncan Test.

Table 8: Immune indicators of patients according to age groups

C4(20-50) mg/dl	IgM (60-280) mg/dl	IgG (800-1800) mg/dl		
20.73 a	133.98 a	760.18 a	Mean	control
15	15	15	N	
7.600	50.0	206.534	Std. Deviation	
30.92 a	111.89 a	642.85 a	Mean	patient 1-3 years
27	27	27	N	
29.538	48.661	229.952	Std. Deviation	
22.15 a	130.94 a	679.80 a	Mean	patient 4-7 years
18	18	18	N	
10.978	67.198	266.976	Std. Deviation	
25.67	483.28	687.29	Mean	Total
60	60	60	N	
21.283	284.7	300.623	Std. Deviation	

a, b Similar letters indicate that there are no significant differences at the probability level of ($p \leq 0.05$) according to the Duncan Test.

The patients were between the ages of one and seven. The patients were divided into two age groups: 1 to 3 years and 4 to 7 years. Blood parameter levels were measured and compared between the two groups and the control group. As indicated in Table 8, patients aged 1-3 years showed a greater decline in lymphocyte and white blood cell counts than patients in the second group. In comparison, IgG levels declined similarly in both groups, whereas IgM levels declined more in the first group than in the second group or control samples.

The immune system's capacity and the development of the child's immune response are significantly influenced by age, as the infant mostly relies on passive immunity from the mother, whether through IgA in milk or IgG from the placenta. As such, it is occasionally impossible to determine whether a

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child has an immunodeficiency in the first few months or even in the second year, the frequency of bacterial infections that the child contracts during that time and the recurrence of those infections at close intervals, however, make this immune system defect more noticeable as the child gets older, especially after the age of two [29]. This is because the body depends more on treatments than on the strength of the child's immune system to clear those infections, and a healthy child with a strong immune system is seen as less susceptible to disease. If an infection does occur, it is at distant intervals, recovery is quicker, and it is occasionally self-limiting with specific treatment [29].

IgG and IgM concentrations were found to increase directly with age in a previous study that included children under 8 years old. For every one of the subjects being studied, C4 was normal. [30]. According to a study, children under five years old with hypogammaglobulinemia had deficits in IgM. The study found that a decrease in B lymphocytes enabled us to predict the development of chronic lung diseases and the persistence of specific immunodeficiency with 90.5% accuracy. Another study found that children's IgG concentrations decrease with age, especially in newborns, where a significant decline was observed. [31].

According to another study, IgG concentration increased with age, whereas IgM concentration remained constant. [32]. In a previous study, blood IgG levels peaked at age 18 after rising during the newborn period, then declined until the sixth month. IgA levels were very low throughout the newborn period and increased with age. IgM levels in the blood peaked between the ages of 16 and 18, although they were lowest during the neonatal period. [33].

CONCLUSION

Compared with control samples, the study found decreases in white blood cell (WBC) counts, lymphocytes, granulocytes, IgM, and C4 levels in patients. However, no apparent decrease in IgG rate was found. Females showed lower rates of white blood cells, granulocytes, and IgM. The study also examined how age affects children's immune factor levels, finding that IgM levels were lower in the youngest age group.

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