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ORIGINAL ARTICLE

Evaluation of primary immunodeficiency in patients with meningitis in fever hospitals

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ABSTRACT

Background:The hallmark of primary immunodeficiency diseases is increased susceptibility to recurrent, severe and opportunistic infections. In this study we evaluate patients with meningitis for underlying primary immunodeficiencies. **Methods**: During the period from August 2016 to February 2017, thirty infant and children patients (16 males and 14 females) with age ranged from 40 days to 15 years participated in the study were admitted to Faqus and Zagazig fever hospitals with meningitis were evaluated for primary immunodeficiencies by measurement of serum immunoglobulin levels, assessment of T-Cell Receptor Excision Circles and assessment of complement system by CH50 assay. **Results**: This study showed that (50%) had deficient IgG, (20%) had deficient IgA, (30%) hyper IgE, (30%) hyper IgM and 10% deficient in all immunoglobulins. The study also showed that (43.3%) of the study group had TREC deficiency, (36.7%) were CH50 deficient and 26.7 had both TREC and CH50 deficiency. **Conclusions**: Meningitis may be the presenting manifestation of immunodeficiency diseases as there is high incidence of primary immune deficiency in patients with meningitis. TRECS and CH50 are decreased in most cases of meningitis which indicate high percentage of primary immunodeficiency diseases among those patients.

Keywords: Meningitis; Primary immunodeficiency; CH50; TREC

INTRODUCTION

Meningitis is an inflammation of the membranes that encircles the brain and spinal cord and it may be caused by infectious or non-infectious causes [1].

Primary immunodeficiencies are a heterogonous group of disorders characterized by increased susceptibility to infections [2].

In children who have a history of recurrent infections as meningitis, sepsis, or other life-threatening infections, levels of immunoglobulins should be measured. All children who have a second time recurrence of bacterial meningitis should be screened for primary immunodeficiency diseases as congenital immunoglobulin or complement deficiencies [3].

Investigation of serum CH50 level is useful for screening for the complement deficiency disorders, since a normal result indicates the classic complement pathway is functionally intact. CH50 level gives useful information about all inborn and most of acquired complement deficiencies [4].

T cell receptor excision circles level has been evaluated in children with primary immunodeficiencies in whom the decreased number and function of T and/or B cells result into significant affection of immunity. These disorders, which usually manifest during infancy and childhood and associated with increased frequency of infections caused by uncommon microorganisms, are often related to immunoregulatory defects [5].

METHODS

A cross sectional study was carried out at Faqus and Zagazig fever hospitals during

the period from August 2016 to February 2017.

Thirty infant and children patients (16 males and 14 females) with age ranged from 40 days to 15 years participated in the study were admitted to Faqus and Zagazig fever hospitals with meningitis.

Patients from 1month - 18 years from both sexes who proved clinically and laboratory to have bacterial, viral, tuberculous meningitis were included in this study.

These patients were subjected to Full history taking, Complete clinical examination, the following Investigations (Complete blood count with differential, C-Reactive Protein, Measurement of serum immunoglobulin levels (IgA, IgG, IgM, IgE), Lumber puncture, Assessment of T-Cell Receptor Excision Circles and Assessment of complement system by CH50 assay.

Written informed consent was obtained from all participants and the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis:

All data were collected, tabulated and statistically analyzed using SPSS 20.0 for windows (SPSS Inc., Chicago, IL, USA) and MedCalc 13 for windows (MedCalc Software bvba, Ostend, Belgium). Quantitative data were expressed as the mean ± SD & median (range), and qualitative data were expressed as absolute frequencies (number) & relative frequencies (percentage). Continuous data were checked for normality by using Shapiro Walk test. Mann Whitney U test was used to compare between two groups of non-normally distributed variables. Percent of categorical variables were compared using Chi-square test or Fisher's exact test when appropriate. Spearman's rank correlation coefficient was calculated to assess relationship between various study variables, (+) sign indicate direct correlation& (-) sign indicate inverse correlation, also values near to 1 indicate strong correlation& values near 0 indicate weak correlation. All tests were two sided. P-value< 0.05 was considered statistically significant (S), p-value < 0.001 was considered highly statistically significant (HS), and p-value ≥ 0.05 was considered statistically insignificant (NS).

RESULTS

Our study showed that there was statistically significant increase of TLC in CSF of deficient TREC group compared to normal group as shown in **Table (1)**.

Relation between T cell receptor excision circle and complete blood count of the studied group showed that in TREC deficient group there was statistically significant decrease in platelet and lymphocytes compared with normal group as shown in **Table (2)**.

There was statistically significant decrease of IgG and IgE in TREC deficient patients while IgM and IgA levels showed no significant differences compared to TREC normal patients as shown in **Table (3)**.

There was statistically significant increase of TLC in CSF of deficient CH50 groups compared with normal group as shown in **Table (4), Fig. (A,B,C).**

In CH50 deficient group there was significant decrease in platelet, lymphocytes and no significant decrease in hemoglobin, neutrophils compared with CH50 normal group as shown in **Table (5) Fig. (D,E,F).**

There was statistically significant decrease in IgG and increase in IgE in CH50 deficient patients while IgM and IgA levels showed no significant difference compared to CH50 normal patients as shown in **Table (6) Fig. (G,H,I).**

Table 1. Relation between T cell receptor excision circle and CSF analysis of the studied group:

Variable	Normal level (17)	Deficient (13)	Mann-whiteny test	p
Protein (mg/dL) mean ± SD Range Median	 124.5±156.8 (10-640) 100	 131.5±75.3 (20-231) 109	 0.3	 0.8
Glucose (mg/dL) mean ± SD Range Median	 35.9±21.5 (3-70) 40	 26.7±20.1 (4-60) 33	 1.2	 0.2
TLC (cells/µL) mean ± SD Range Median	 344.2±461.8 (10-1830) 220	 1327.2±1806 (100-5300) 635	 2.1	 **0.03***

Table 2. Relation between T cell receptor excision circle and complete blood count of the studied group:

Variable	Normal level (17)	Deficient (13)	Mann-whiteny test	p
HB (g/dl) mean ± SD Range Median	 11±2.5 (6.9-17) 10.6	 10.6±2.2 (6.5-15.4) 10.9	 0.9	 0.7
Platelets × 10^3/ul mean ± SD Range Median	 295.1±143.2 (110-532) 256	 234.7±179.6 (39-608) 136	 2.5	 **0.02***
TLC × 10^3/ul mean ± SD Range Median	 10.1±6.1 (3.1-23.1) 8.3	 9.9±6.6 (3.5-23.3) 7.5	 0.03	 0.9
Neutrophil × 10^3/ul mean ± SD Range Median	 8.1±8.4 (1.5-33.7) 5.5	 8.9±9.7 (2.3-39) 4.4	 0.2	 0.8
Lymphocytes × 10^3/ul mean ± SD Range Median	 5.5±8.8 (1.2-39) 5.2	 3.8±10.9 (0.5-28) 2	 3.4	 **0.002***

Table 3. Relation between T cell receptor excision circle and immunoglobulins of the studied group:

Variable	TREC Normal level (17)	TREC Deficient (13)	Mann-whiteny test	p
IgG (g/l) mean ± SD Range Median	 49.9±181.5 (0.13-754) 5.2	 4.5±3.6 (0.5-12.2) 3	 8.9	 **0.001****
IgM (g/l) mean ± SD Range Median	 13.1±29.1 (0.3-93.8) 0.9	 9.1±18.9 (0.3-64) 0.8	 0.4	 0.6
IgA (mg/dl) mean ± SD Range Median	 69.2±76.1 (2.2-256) 45	 45.5±48.2 (0.6-193) 50	 0.9	 0.3
IgE (IU/ml) mean ± SD Range Median	 198.2±467.8 (0.18-1458) 11.2	 46.4±91.2 (0.1-312) 1.7	 4.6	 **0.01***

Table 4. Relation between CH50and CSF analysis of the studied group:

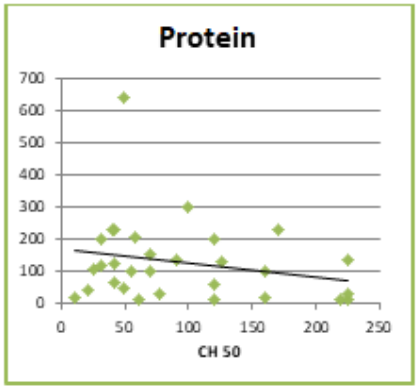
Variable	Normal level (19)	Deficient (11)	Mann-whiteny test	p
Protein (mg/dL) mean ± SD Range Median	 105.2±86.4 (10-300) 100	 166.2±173.7 (20-640) 117	 1.2	 0.2
Glucose (mg/dL) mean ± SD Range Median	 36.9±21.5 (4-70) 40	 23.4±17.8 (3-60) 16	 0.3	 0.8
TLC (cells/µL) mean ± SD Range Median	 629.8±123.8 (10-5300) 200	 1012.5±145.6 (10-5000) 420	 3.1	 **0.02***

Table 5. Relation between CH50 and complete blood count of the studied group:

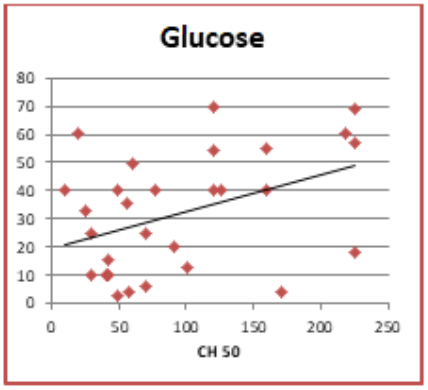
Variable	Normal level (19)	Deficient (11)	Mann-whiteny test	p
HB(g/dl)				
mean ± SD	11.4±2.2	9.9±2.5		
Range	(8.5-17)	(6.5-15)	T=1.7	0.09
Median	10.9	9.6		
Platelets× 10^3/ul				
mean ± SD	268.3±157.2	200±172.3		
Range	(53-608)	(39-532)	3.5	**0.03***
Median	224	159		
TLC× 10^3/ul				
mean ± SD	9.7±6.4	10.5±6.2		
Range	(3.1-23.3)	(3.5-23.1)	0.3	0.7
Median	8.2	12		
Neutrophil× 10^3/ul				
mean ± SD	9.2±10.4	7.1±5.6		
Range	(1.5-39)	(2.2-20.9)	0.6	0.5
Median	5.5	5.4		
Lymphocytes× 10^3/ul				
mean ± SD	6.1±10.6	4.2±11.1		
Range	(0.5-48)	(1.3-32)	4.5	**0.01***
Median	2.8	1.9		

Table 6. Relation between CH50 and immunoglobulins of the studied group:

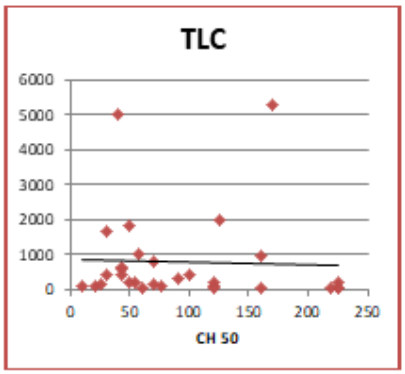
Variable	CH50 Normal level (19)	CH50 Deficient (11)	Mann-whiteny test	p
IgG(g/l)				
mean ± SD	44.9±171.8	5±5.1		
Range	(0.13-754)	(0.5-16.4)	7.9	**0.001****
Median	5.2	3		
IgM(g/l)				
mean ± SD	9.9±22.9	13.7±29.1		
Range	(0.3-93.8)	(0.3-80)	0.4	0.6
Median	0.9	0.9		
IgA(mg/dl)				
mean ± SD	53.1±57.2	69.1±80.2		
Range	(0.6-242)	(2.6-256)	0.6	0.5
Median	40	50		
IgE(IU/ml)				
mean ± SD	103.4±331.3	182.7±418.5		
Range	(0.1-1458)	(0.1-1412)	3.6	**0.02***
Median	3.3	11.2		


Protein
700
600
500
400
300
200
100
0
0
50
100
150
200
250
CH 50

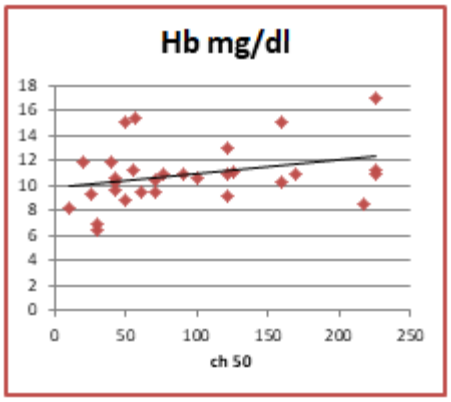
(A)


Glucose
80
70
60
50
40
30
20
10
0
0
50
100
150
200
250
CH 50

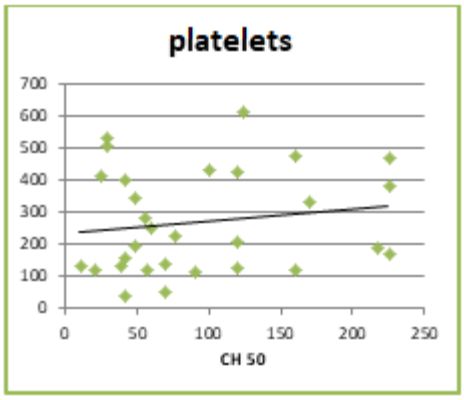
(B)


TLC
6000
5000
4000
3000
2000
1000
0
0
50
100
150
200
250
CH 50

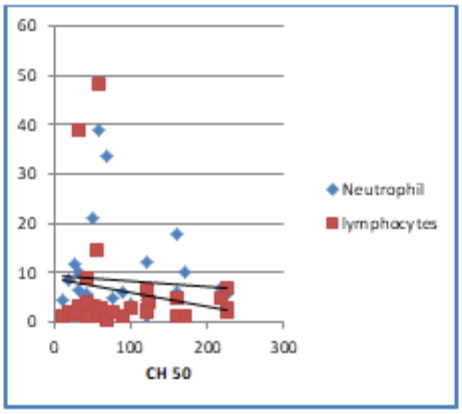
(C)


Hb mg/dl
18
16
14
12
10
8
6
4
2
0
0
50
100
150
200
250
ch 50

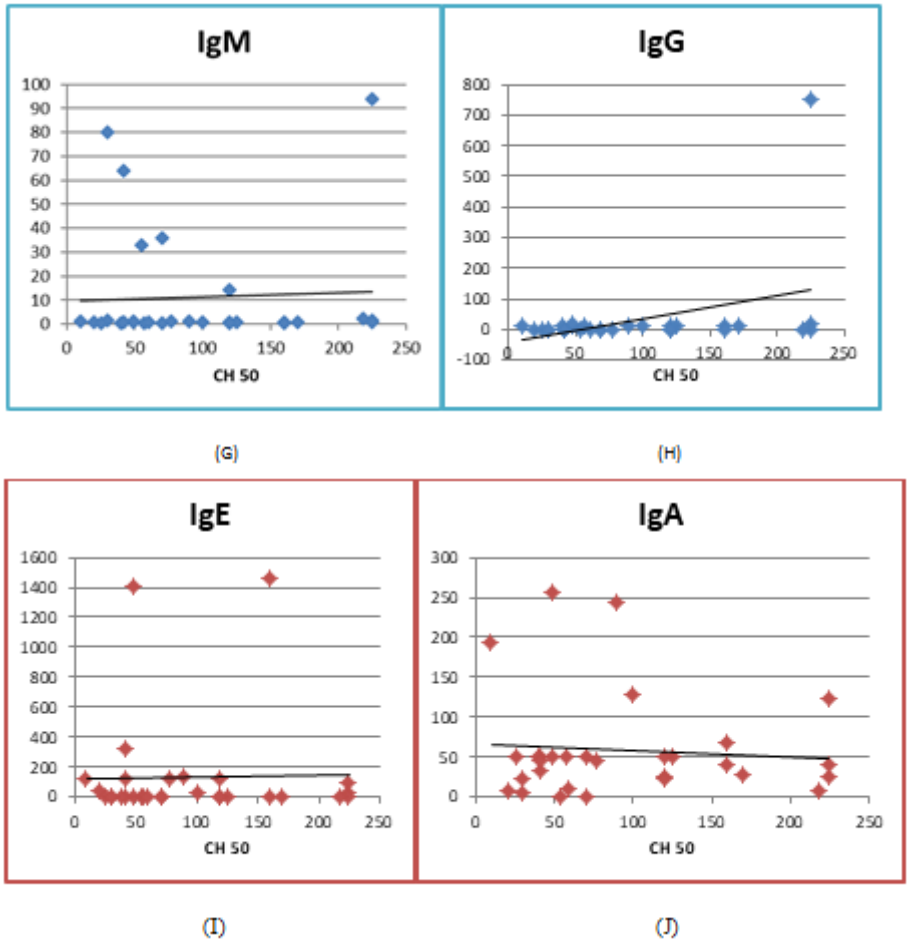
(D)


platelets
700
600
500
400
300
200
100
0
0
50
100
150
200
250
CH 50

(E)


60
50
40
30
20
10
0
0
100
200
300
CH 50
Neutrophil
lymphocytes

(F)



Scatter plot with line curves for the correlation between CH 50 and protein, glucose, TLC, HB, platelets, lymphocytes, neutrophils and immunoglubins.

DISCUSSION

Primary immunodeficiency diseases are a multifarious group of inherited disorders, which mainly characterized by increase susceptibility to severe infections, autoimmunity and lymphoproliferation. Despite impressive progress in identification of PID, there is a lack of knowledge, attitude and behavior among physicians in identification of patients with primary immunodeficiency [6].

A recent analysis of data and surveys estimated that more than six million people worldwide are affected with PID, with most of them undiagnosed [7].

Early detection and diagnosis of patients with PID is important for prognosis and quality of their life [8].

However, late detection of PID is generally occur after a patient suffered from repeated infections. Currently, the time between onset of symptoms and treatment may be as long as 12 years [9].

Patients with PID often present with increased occurrence conditions which are associated with suppressed or inadequate immune function as severe, persistent, and recurrent infections, autoimmunity, inflammation, allergy, and malignancies [7].

All patients suffering from severe or recurrent infections or infection by opportunistic or unusual pathogen must be investigated for primary immunodeficiency diseases [10].

Bacterial meningitis remains a dangerous, life threatening infection with high rates of morbidity and mortality even with the availability of potent antimicrobial drugs. In many studies, infectious meningitis is reported in patients with immunoglobulin and

complement deficiencies. Many primary immunodeficiency diseases as certain congenital complement deficiencies, defects of antibody production, or asplenia may be first recognized by the occurrence of bacterial meningitis, especially in infants or young children. We should suspect primary or acquired immunodeficiency in any patient with bacterial meningitis on the basis of the etiology, clinical epidemiology, and presence of other risk factors. Although, bacterial meningitis may be the first and only presentation for some infections in unknown patients with immunodeficiency diseases [3].

In our work we evaluated the PID among patients with meningitis in Faqus and Zagazig fever hospitals.

This study carried out on 30 patients with a mean age 4.7±4.3 years and (53.3%) of them were males who proved clinically and laboratory to have meningitis .

Gaschignard et al 2014 reported that the proportion of patients with meningitis seems to be higher in younger children aged <2 years (n = 98/109, 90%) than in older children (n = 44/54, 81%; P= .21) [.11].

This study showed that (66.7%) of the study group had bacterial meningitis while 33.3% had viral meningitis.

Husain et al 2006 reported in their study which done on 970 children presenting with meningitis that (11%) of them had bacterial meningitis. The most common isolated organisms were: Streptococcus pneumoniae (54%), group B streptococci (13%), and Neisseria meningitidis (11%). The mean age was 2.2 +/- 3.5 yr.[12].

In 2001, Davison and Ramsay reported that among1216 clinically diagnosed cases of meningitis in children in England, Meningococcal meningitis was the most common reported cause (48%), with other bacteria (12%), viruses (19%), the rest accounting for others and unknown causes [13].

Our study showed that (90%) of the study group were still alive, This data is in agreement with Hénaff et al 2017 who found that Among the 316 patients with pneumococcal meningitis, the mortality rate was as high as 9.5%, But disagree with Biaukula et al 2012 who found that more than one third of children with bacterial meningitis died during the episode, which is similar to findings from Africa [14 -17].

Immunodeficiency should be suspected in any children with a history of recurrent infections, as meningitis, sepsis, or recurrent upper and lower respiratory tract infections, so immunoglobulin levels should be measured before an episode of bacterial meningitis. If a second episode of bacterial meningitis occurred, all children should be screened for congenital immunoglobulin or complement deficiencies. It is recommended that if single episode of meningitis occurs at an age earlier or later than that characteristic for the causative meningeal pathogen, immune evaluation should be done. Quantitative assessment of B cells should be performed if total levels of IgM and/or IgG are low. Early complement deficiencies, specially C2 or C3 deficiencies, may predispose children to pneumococcal or Haemophilus infections, and screening can be accomplished by an assessment of total complement function (CH50) [3].

This study showed that (50%) had deficient IgG, (20%) had deficient IgA, (30%) hyper IgE, (30%) hyper IgM and 10% Deficient in all Immunoglobulins.

Ahmadinejad et al 2011 in their study which done on 19 patients with first episode of bacterial meningitis they found that six patients (31.6%) had Ig deficiency, four patients had selective IgE deficiency., while only one patient had subnormal IgA levels and one patient had subnormal IgM and IgE levels. So, in patients with bacterial meningitis even the first episode immunological evaluation should be done specially immunoglobulin levels [18].

In comparison with a study done by Loh et al, 1991 the study showed that of 44 children who recovered from an attack of bacterial meningitis, 3 (7%) were found to have IgG subclass deficiency, 5(11%) had IgA deficiency and 22 (50%) had raised IgE levels.[19].

Also Sullivan et al, 1994 reported that approximately 10%–15% of children with Bruton agammaglobulinemia experience episodes of sepsis or meningitis before they received treatment with immunoglobulin. ,

while Levy et al, 1997 reported that 7 (5%) have experienced bacterial meningitis, whereas 5 (8.9%) of 56 patients with X-linked hyper-IgM syndrome experienced meningitis or encephalitis [20,21]

In agreement with our data, the study by Lorraine et al.1981showed that 2 of 9 children had subnormal levels of IgG and IgA, while IgE levels were slightly raised in five children with pyogenic meningitis.[22]

Thus, in most antibody deficiency syndromes, CNS infection may be the presenting manifestation of primary immunodeficiencies although it is not a common occurrence.[23]

Although primary complement deficiencies are associated with increased susceptibility to pyogenic meningitis,they are much rare than Ig deficiencies [18].

As the incidence rate in some studies was as high as 39% in patients with meningococcal infections, at least, a screening test for complement function (CH50) should be performed for all those patients.[3].

Our study showed that (43.3%) of the study group had TREC deficiency, (36.7%) were CH50 deficient and 26.7 had both TREC and CH50 deficiency.

This result agrees with study done by Aoki et al, 2015 on129 patients, and found that CH50 values were below the reference levels in 48 patients (37.2%) of the study group.[24]

Gaschignard et al 2014 studied pediatric patients with invasive pneumococcal disease and found that Meningitis was the most frequent type of infection (87%) among them .Also they found that the results of immunological explorations among those patients were abnormal in 26 children (16%), and a PID was identified in 17 patients (10%), including 1 case of MyD88 deficiency, 3 of complement fraction C2 or C3 deficiencies, 1 of isolated congenital asplenia, and 2 of Bruton disease. The proportion of PIDs was much higher in children aged >2 years than in younger children (26% vs 3%; P < .001).[11]

In a study done by Ellison et al, 1983 on 20 patients presenting with a first episode of meningococcal meningitis, meningococcemia for evaluation of the complement system. Total serum complement activity were evaluated in 12 patients prospectively and retrospectively in 8. 30% of those patients had a complement deficiency.[25]

The lymphocyte subpopulations of T and B cells were within the normal range with normal or slightly increased lymphocyte mitogenic responses in the study by Lorraine et al. 1981. Also, Hassieb et al. 1990 did not detect a significant difference in T lymphocytes in patients with bacterial meningitis as compared with normal controls.Hénaff et al 2017 reported that Among the 316 patients with pneumococcal meningitis, 55 (17.9%) had immunodeficiency, primary or acquired. [14,22,26].

Our study showed that there was no statistically significant difference between normal and deficient TREC groups in age and sex.

This data is in contrast to Hazenberg et al., 2001 who stated that TRECs generally show an inverse correlation with age [27].

Our study showed that there was statistically significant difference between normal and deficient TREC groups in platelets and lymphocytes with lymphocytopenia in deficient group. But regarding other CBC variables, there was no statistically significant difference between the two groups.

This is in agreement with Reust, 2013 who stated that T-cell disorders are characterized by lymphocytopenia [28].

Also, we found statistically significant increase of TLC in CSF of deficient TREC group compared to normal group.

Although it was thought that complement deficiency is more common primary immune deficiency in patients with meningitis, we found that the most common immunodeficiency in our study was T cell deficiency disorders. Also, many studies evaluate the TREC level in sepsis, but till now there is no study found the relation between meningitis and T cell disorders and our study is the first one which investigate the TREC in children with meningitis

. CONCLUSION

Meningitis may be the presenting manifestation of immunodeficiency diseases as is high incidence of primary immune

deficiency in patients with meningitis. TRECS and CH50 are decreased in most cases of meningitis which indicate high percentage of primary immunodeficiency diseases among those patients.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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