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Study of Serum Immunoglobulins G and M Levels in Children with Down Syndrome and Their Relation with Recurrent Lower Respiratory Tract Infection

Manar Emad Aldeen Ghazy[1*], Heba Said El Mahdy[1], Maaly Mohamed Mabrouk[2]and Mohamed Shawky Al-Farargy[1]

Department of Pediatric Medicine[1]and Department of Clinical Pathology [2],
Faculty of Medicine, Tanta University, Egypt

***Corresponding author:** Manar Emad Aldeen Ghazy**, Mobile:** 01020299644; **Email:** maysaakubasi@yahoo.com

ABSTRACT

Background: Children with Down syndrome appear to be more likely susceptible to respiratory tract infections and it is an important cause of morbidity and mortality among them. **Aim of the study:** It was to investigate the relationship between levels of IgG and IgM in Down syndrome and recurrent lower respiratory tract infections. **Subjects and Methods:** This study was conducted on 40 children who were categorized into 2 groups: patient group, which includes children with Down syndrome patients presented with LRTIs, their karyotyping revealed trisomy 21 in all cases and their age range from 1 to 13 years. Control group, which includes 20 healthy children matched for sex and age with patient group. They were subjected to full history taking & thorough clinical examination, and they investigated for complete blood picture, C-reactive protein and serum immunoglobulins (IgG & IgM) using ELISA technique. **Results:** Plasma levels of immunoglobulin G (IgG) were elevated in Down syndrome with significant increase the frequency of lower respiratory tract infections and hospital admission. Plasma levels of immunoglobulin M (IgM) were decrease in down patients with significant increase in the frequency of lower respiratory tract infections and hospital admission. **Conclusion:** These findings suggest the importance of estimation and follow up of serum levels of IgG &Ig M in cases of Ds with recurrent respiratory tract infections.

Keywords: Immunoglobulins, Down syndrome, Recurrent Lower Respiratory Tract Infection.

INTRODUCTION

Down syndrome (DS) is one of the most common chromosomal anomalies in humans [(1)], it`s caused by having three copies of chromosome 21 instead of two [(2)]. It is approximately 1 in 800 births in the general population, but figures in Egypt vary between 1 in 555 to 1 in 770 [(3)].

Ultrasonographic examination of the fetus in the second and third trimesters of pregnancy allows for the assessment of several facial measurements that are significantly different in fetuses with trisomy 21 from in those that are chromosomally normal. Amniocentesis and chorionic villus sampling (CVS) are the invasive diagnosis of Down's syndrome before birth, but carry a risk of miscarriage in 1% of those tests [(4)].

Lower respiratory tract infections (LRTIs) are generally more serious than upper respiratory infections and it is the leading cause of death among all infectious diseases [(5)]. In addition, up to 29% of deaths in DS are associated with pneumonia, influenza and aspiration [(6)].

The increased incidence of respiratory tract infections in children with DS is likely to be multifactorial. Structural abnormalities in the airways such as macroglossia, narrow nasopharynx, adeno-tonsillar hypertrophy, laryngomalacia and tracheomalacia are likely to play a role [(7)]. They also have mucus secretions and reduced ciliary beat frequency when compared with controls without DS [(8)].

Aim of the study:

It is to investigate the relationship between levels of IgG and IgM in Down syndrome and recurrent lower respiratory tract infections.

PATIENTS AND METHODS

This case control study was conducted at Genetic Unit of Pediatric Department, Tanta University Hospital, during the period from December 2016 to February 2018. **The study was approved by the Ethics Board of Tanta University.**

A total of 40 children with Down syndrome were included in this study and were categorized into 3 groups: **Down syndrome group: 20 children [13 males and 7 females]** with Down syndrome aged from 1-13 years old, was included in the study as patient group. **Control group: 20 healthy children** [**12 males and 8 females**] matched with the patient group and aged from 1-13 years old. Children with Down syndrome free now from infection confirmed by karyotyping and their ages ranged between 1-15 years were included in the current study. Also children with chronic infection or with evident malnutrition were

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excluded.

Written Informed consent was obtained from the parents or guardians of the child. The study was approved by the Ethical Committee of Faculty of Medicine, Tanta University.

All children in both groups were subjected to: (**a**) complete history taking as routine including [Personal, developmental, Nature of infection, number of hospital visits and number of hospitalization and duration of hospitalization]. (**b**) Full clinical examination [General examination, Neurological examination, cardiovascular examination, chest examination, abdominal examination and urogenital examination with special emphasis to signs and complication of Down syndrome]. (**c**) Laboratory investigations**:** [Complete blood picture, C-reactive protein and Serum immunoglobulins (IgG & IgM) using **ELISA** technique].

Blood sampling:

- About 4 ml of venous blood sample was collected from each subject by use of disposable sterilized plastic syringes. The needle of the syringes was then removed and each sample was allowed to pass along vacutainer tube labeled with the patient name. The one ml was added to a tube containing 0.2 ml EDTA for complete blood picture (CBC), the rest of the blood was centrifuged for 20 min at 2000-3000 rpm for separation of serum, the serum was divided into two aliquots: one for CRP estimation and the other w stored at -20 C till the time of analysis of IgG and IgM.

All patients and controls were subjected to the following investigations:

1- Estimation of complete blood picture by Automated ADIVA 2120i**.**

2- Estimation of C-reactive protein by Latex agglutination method **(**BioMED).

3- Estimation of Serum immunoglobulins (IgG & IgM) using ELISA technique**.**

Statistical analysis

In addition to the descriptive data, statistical analysis was done using IBM SPSS STATISTC VERSION 20 PROGRAM. Data were expressed as mean ± SD and analyzed using the Chi square (x2) test and the ANOVA Test to assess the significance of difference in the levels between different parameters. *P* <0.05 was accepted as significant. Coefficient (r) of two variables was also done by using Pearson correlation coefficient (r) with P Value Calculation.

RESULTS

Laboratory assessments of the measured parameters in the different submitted groups are presented in the following tables and figures:

Table (1) Comparison between the two studied groups according to demographic data

	Down patients (n = 20)		**Normal (n = 20)**		**Test of Sig.**	**p**
	No.	%	No.	%		
Sex						
Male	13	65.0	12	60.0	χ^2= 0.107	0.744
Female	7	35.0	8	40.0		
Age (years)						
Min. – Max.	1.0 – 9.0		1.0 – 9.0		U= 175.00	0.495
Mean ± SD.	3.35 ±2.32		3.68 ±2.28			
Median	2.25		3.0			
Maternal age						
Min. – Max.	18.0 – 47.0		19.0 – 30.0		3.551	0.002
Mean ± SD.	32.0 ±8.88		24.50 ±3.22			
Median	32.50		24.50			

χ^2, p: χ^2 and p values for **Chi square test** for comparing between the two groups. t, p: t and p values for **Student t-test** for comparing between the two groups. U, p: U and p values for **Mann Whitney test** for comparing between the two groups.

Table (1) showed that there wereno significant differences in the demographic data including age and sex between down patient and controlled group (p value not <0.05) but there was significant increase in mother age in Down patients as compared to control group.

Table (2): Distribution of the studied cases according to type of karyotyping in down patients group (n=20).

Type of karyotyping	No.	%
Non-disjunction	18	90.0
Translocation	2	10.0

Table (2) showed the type of karyotyping in Down patients which was 90% non-disjunction and 10% translocation.

Table (3) Comparison between the two studied groups according to CRP

CRP	Down patients (n = 20)		Normal (n = 20)		χ^2	p
	No.	%	No.	%		
Negative	4	20.0	11	55.0	5.227*	0.022*
Positive	16	80.0	9	45.0		
+6	7	43.8	6	66.7	1.508	^{MC}p= 0.573
+12	7	43.8	3	33.3		
+24	2	12.5	0	0.0		

χ^2, p: χ^2 and p values for **Chi square test** for comparing between the two groups. ^{MC}p: p value for Monte Carlo for Chi square test for comparing between the two groups. *: Statistically significant at $p \leq 0.05$.

Table (3) showed that there wassignificant increase in the level of CRP in Down syndrome as compared to control group. (P value is <0.05).

Table (4): Comparison between the two studied groups according to complete blood picture in both studied groups.

CBC	Down patients (n = 20)	Normal (n = 20)	t	p
Hg				
Min. – Max.	8.50 – 13.0	10.0 – 12.50	1.884	0.067
Mean ± SD.	10.30 ±1.17	10.93 ±0.91		
Median	10.50	11.0		
PLT($\times 10^3$)				
Min. – Max.	175.0 – 445.0	185.0 – 390.0	0.712	0.481
Mean ± SD.	277.35 ±69.02	291.25 ±53.41		
Median	277.50	285.0		
WBCs($\times 10^3$)				
Min. – Max.	13.0 – 21.0	5.50 – 17.50	7.567*	<0.001*
Mean ± SD.	17.33 ±2.27	10.28 ±3.49		
Median	18.0	9.50		

t, p: t and p values for **Student t-test** for comparing between the two groups. *: Statistically significant at $p \leq 0.05$.

Table (4) showed that there wassignificant increase in the level of WBCS in Down syndrome as compared to control group (P value is significant <0.05), also there were no significant difference between Hb and PLT count level between down and control group (p value not <0.05).

Table (5) Serum levels of IgG&IgM in both studied groups.

	Down patients (n = 20)	Normal (n = 20)	Test of sig.	p
IgG				
Min. – Max.	1230.0 – 2743.0	620.0 – 1692.0	t= 7.951	<0.001*
Mean ± SD.	1919.0 ±407.5	1010.3 ±308.6		
Median	1851.0	932.0		
IgM				
Mean ± SD.	43.70 ±2.19	161.60 ±5.46		
Median	38.50	135.0		

t, p: t and p values for **Student t-test** for comparing between the two groups. U, p: U and p values for **Mann Whitney test** for comparing between the two groups*: Statistically significant at $p \leq 0.05$.

Table (5) showed that there was significant increase in the serum level of IgG in down patients as compared to controlled group (p value is <0.05), also there was significant decrease in the level of IgM in Down syndrome as compared to control group. (P value is <0.05).

Table (6): Types of congenital heart defect in the studied cases.

CHD	Down patients (n = 20)		Normal (n = 20)		χ^2	p
	No.	%	No.	%		
Negative	12	60.0	19	95.0	7.025*	FEp= 0.020*
Positive	8	40.0	1	5.0		
Small VSD	0	0.0	1	100.0	5.60	MCp= 0.219
VSD	7	87.5	0	0.0		
AV canal	1	12.5	0	0.0		

χ^2, p: χ^2 and p values for **Chi square test** for comparing between the two groups.MCp: p value for **Monte Carlo** for Chi square test for comparing between the two groups.FEp: **:**p value for **Fisher Exact** for Chi square test for comparing between the two groups*: Statistically significant at $p \leq 0.05$.

- **Table (6)** showed that there wassignificant increase in the occurrence of congenital heart diseases in down patients as compared to control group (p value is <0.05).

Table (7): Comparison between the two studied groups according to frequency of hospitalization and frequency LRTI

	Down patients (n = 20)		Normal (n = 20)		Test of Sig.	p
	No.	%	No.	%		
Hospital admission						
Negative	0	0.0	12	60.0	χ^2= 17.143*	<0.001*
Positive	20	100.0	8	40.0		
Frequency / year						
Min. – Max.	1.0 – 6.0		1.0 – 2.0			
Mean ± SD.	2.95 ±1.28		1.25 ±0.46		U= 16.00*	0.001*
Median	3.0		1.0			
Frequency LRTI / years						
Min. – Max.	5.0 – 13.0		1.0 – 6.0		U=3.50	<0.001*
Mean ± SD.	7.70 ±1.89		2.40 ±1.27			
Median	7.0		2.0			

χ^2, p: χ^2 and p values for **Chi square test** for comparing between the two groups. U, p: U and p values for **Mann Whitney test** for comparing between the two groups.*: Statistically significant at $p \leq 0.05$.

Table (7) showed that there wassignificant increase in the frequency of hospital admission among down patients as compared to control group (p value is <0.05),also there was Significant increase in the frequency of lower respiratory tract infections per year among down patients as compared to control group (p value is <0.05).

Table (8): Multivariate Linear regression for Frequency LRTI / years

	B	SE	Beta	t	P
Sex	0.672	0.787	0.174	0.854	0.408
Age (years)	-0.167	0.170	-0.205	-0.983	0.342
Maternal age	-0.081	0.046	-0.380	-1.755	0.101
IgG	0.002	0.001	0.460	2.147*	0.039*
IgM	-0.042	0.022	-0.445	-1.906*	0.047*
$R^2 = 0.502$, F =3.820*, p =0.028*					

B: Unstandardized Coefficients, SE: Estimates Standard error, Beta: Standardized Coefficients, t: t-test of significance. R^2:coefficient of regression. *: Statistically significant at $p \leq 0.05$.

Table (8) showed thelinear regression for frequency of lower respiratory tract infections per year which was positive for IgG and negative for IgM.

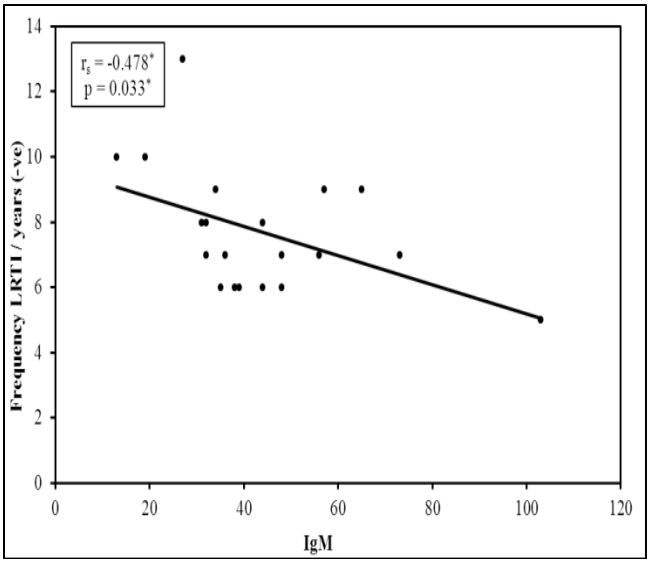

Figure (1): Correlation between IgM and Frequency LRTI / years (-ve) in down patients (n= 20).

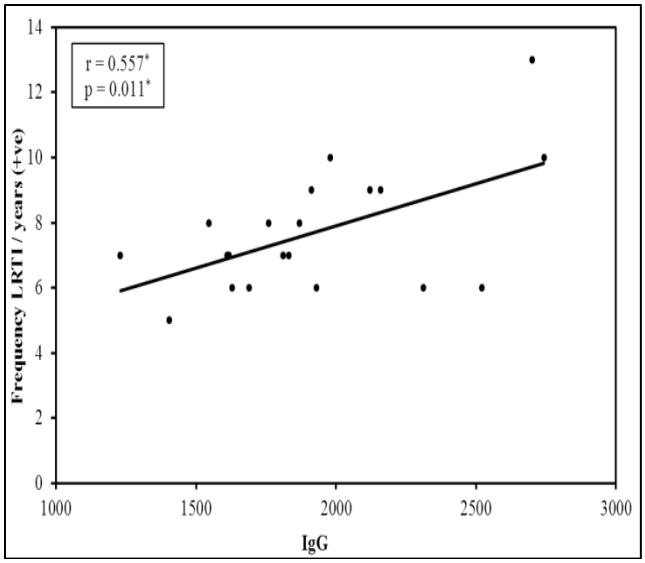

Figure (2): Correlation between IgG and Frequency LRTI / years (+ve) in down patients (n= 20).

Figure (1) showed negative correlation between IgM levels and frequency of lower respiratory tract infections per year. **Figure (2)** showed positive correlation between IgG level and frequency of lower respiratory tract infections per year (P value is <0.05).

DISCUSSION

Respiratory disease is an important cause of morbidity and mortality in Ds. It was responsible for 54% of hospital admissions of children with DS, and was also the most common reason for admission to the pediatric intensive care unit (43%) and for ventilation (50%), importantly, they have a 30% increased risk of death from sepsis [9].

The present study showed that regarding height no significant difference between the 2 groups.This is in contrast with **Asha *et al.*** [10] whose study was conducted on 50 Down syndrome patients and 50 age and sex matched controls, aged 1-18 years. Height of the subjects were referred to standard pediatric growth charts, it revealed that height in most of the DS children was under 3rd to 10th percentile and controls under 25th to 75th percentile. It is also in contrast with **Raja *et al.*** [11] study which was done on twenty children whose age ranged from 0 to 36 months with karyotype confirmed Down syndrome by Ikaros Meta system in Germany, they were 10 males and 10 females, these children were compared with the age, sex matched control, All children cases and control were screened for factors including in inclusion and exclusion criteria of the study sample, anthropometric measurements including weight, height, head circumference and chest circumference. There was significant decrease in height in the Down syndrome group.

The present study showed that regarding body weight no significant difference between the 2 groups. This is in contrast with Raja ***et al.*** [11] study who found that there was significant decrease in weight between two groups. Also it is in contrast with **Basil *et al.*** [12] that did retrospective study on 303 children aged 2 to 18 years with diagnosis of Down syndrome from January 2008 to December 2013. All children were patients at Cincinnati Children `s Hospital Medical Centre with multiple height and weight measurements and he found that 47.8% of them were obese (body mass index >95th percentile for age and sex). This was significantly higher than the general pediatric population, which had 1 12.1% obesity rate (P<.0001) in US.

The present study showed regarding head circumference, there is no significant difference between two groups. This is in contrast with **Asha *et al.*** [10] who stated that the mean value of index of size of the head in Ds patients was decreased than control group. Also it isin contrast with **Raja *et al.*** [11] who found that there was significant decrease in head circumference between two groups.

The present study showed that regarding age and sex no significant difference between the 2 groups. This come in agreement with ***Joshi et al.*** [13] who did a prospective study on 24 subjects (12 Ds, 12 without Ds) who were living in Olmsted country during the period from November 2009 to 2010 with their age from 2 to 18 years and found no significant difference in age and sex between cases and control groups.

The present study showed as regard maternal age of Ds, there was significant increase in mother`s age in Ds group in comparison with control group. This in agreement with **Crane and Morris** [14] who studied the percentage of all births in England and Wales to mothers aged 35 and over increased from 9% in 1989 to 19% in 2003. A 51% increase in the numbers of pregnancies with Down syndrome has been observed over the same time period (from 954 to 1440). Also it is in agreement with **Delport *et al.*** [15] whose study report incidence of 1.33 live births of Ds cases In Pretoria Urban academic hospital where 52% of mothers were 35 years or older.

The present study showed as regard to hemoglobin concentration, there was no significant difference between Ds and control group. This came in agreement with **Joshi *et al.*** [13] who found that there was no significant difference in Hb level between cases and control groups. The result of the current study come in contrast with **Tenenbaum *et al.*** [16] who did cross sectional study on children attending a multidisciplinary Down syndrome medical center, 149 children with Ds aged 0-20 years, information obtained included a medical history, physical, developmental examination, nutritional assessment and the results of blood test, the result revealed 8.1% were found to have anemia. Among the 38 children who had iron studies, 50% had iron deficiency. It can be explained by Arab ethnicity, low weight for age, the presence of eating disorder and congenital heart disease were risk factors for anemia.

The present study showed as regard to platelets count, there is no significant difference between two studied groups. This is came in agreement with **Joshi *et al.*** [13] who found that there was no significant difference in the platelet count between cases and control groups. It is also in contrast with Martinez ***et al.*** [17] who did a prospective study of 135 infants confirmed Ds and 226 infants without birth defects all born during the period 2009-2015, they evaluated hematological finding in the CBC during the first 7 days of life, infants with Ds had distinctive hematological findings including a lower frequency of thrombocytopenia, it can be explained by ethnic, socioeconomic and nutritional differences.

The present study showed as regard WBCs count**,** there is significant increase in the WBCs count in the Ds group in comparison with control group. This is come in agreement with ***Martinez et al.*** [17] who found increased WBCs count ($>30x10^3$/ml) in Ds group. It is in contrast with **Joshi *et al.*** [13] who found that there was no significant difference in WBCs count between two groups.

The present study showed that regarding congenital heart diseases in Down syndrome, there`s significant increase in the rate of CHD in Ds group in comparison with control group. This result come in agreement with **El-Gilany *et al.*** [18] who perform a retrospective study in 1720 Ds children in Egypt, Mansura during a period of 14 years from 2003 p to 2016. Their study showed prevalence of overall, isolated and multiple result of CHD was 36.9%, 29% and 8% respectively.

The present study showed significant increase in C-reactive protein (CRP) on Ds group in compared with control group. This is come in agreement with **Manti *et al.*** [19] who performed a cohort study on 46 members of individuals from the University Hospital Of Messina, Sicily, Italy. All were born in the island of Sicily and of Caucasian ethnic background. Karyotyping showed full trisomy in all participants with Ds. Although all patients with Ds were screened during the study, only 24 of them consented to give blood for this research. They showed significant increase in CRP level in Down syndrome group. It is agreed also with **Koster *et al.*** [20] who performed a cross sectional study on 678 children presenting with suspected pneumonia to show association between CRP level and pneumonia during the period between January 2007 to January 2012. The result showed that of 678 presenting children, 286 underwent both CRP measurement and chest radiography, 148 had pneumonia (52%). The proportion of pneumonia increased with CRP level.

The present study showed significant increase level of IgG in Down syndrome patient in comparison with control group. ***The*** result came in agreement with Martinez ***et al.*** [21]who did a retrospective study on 52 children with Ds (24 females, 28 males) and 51 control group (24 females, 27 males), information about congenital heart defects, infection related hospitalizations and autoimmune diseases were obtained, he found that there was higher levels of IgG in the Down syndrome group. But this result came in contrast with **Deepa *et al.*** [22] whose study performed on 30 children with Ds (13 males, 17 females). Their age ranged from 1.5 to 9 years. The result showed that IgG level decrease with increasing grades of malnutrition, it can be explained by impaired production of B cells in malnutrition.

The present study showed that significant decrease in the level of IgM in Down syndrome in comparison with control group. This also was in agreement with **Joshi *et al.*** [13]who found that there was an increased serum IgG in Down syndrome group. It also came in agreement with **Martinez *et al.*** [21] who found that there was a decreased level of IgM in the

Down syndrome group. But this result came in contrast with **Deepa *et al.*** [22] who showed that IgM level increase with increasing grades of malnutrition.

The present study showed significant correlation between increased level of IgG and frequency of LRTIs and hospital admission. This was in agreement with ***Deepa et al.*** [22] who correlated immunoglobulin levels with infection prevalence and showed increased level of IgG with increasing episodes of recurrent LRTI.

The present study showed significantincrease in the episodes of recurrent lower respiratory tract infections in Ds cases in compared with control group. This came in agreement with ***Deepa et al.*** [22] who showed that the episodes of lower respiratory tract infections were more common among cases (*56.6% had 4-5 episodes of lower respiratory tract infections than control*). This also came in agreement with **Broers *et al.*** [23] who studied 22 children with Ds and 22 of their healthy, age-rang matched siblings. Data were collected were rate of infections and hospitalization because of LRTIs. Immunoglobulin and IgG subclass levels in blood were determined. They found that children with Ds had a significantly higher frequency of LRTIs.

The present study showed significant increase in the episodes of hospital admission of Ds cases than control group. It is agreed with **Deepa *et al.*** [22] who found that children with Ds were hospitalized for LRTIs whereas none of the controls were hospitalized for the same. Among cases 18 (60%) were hospitalizes more than 3 times and 12 (40%) children were hospitalized less than 3 times. It is also in agreement with **Broers *et al.*** [23] who found that children with Ds had a significantly higher frequency of LRTIs and related hospitalization than their siblings. This is also agreed with **Hilton *et al.*** [24]who did comprehensive review on 232 hospital admissions among Ds children over a 6 year period and found that LRTIs was the most common cause for acute hospital admission. This was in contrast with non-Ds children who were most commonly admitted for asthma, chemotherapy administration, fractures, gastroenteritis, bronchiolitis and adeno-tonsillectomy.

Conclusion: Plasma levels of immuno-globulin G (IgG) were elevated in Down syndrome with significant increase in the frequency of lower respiratory tract infections and hospital admission. Also plasma levels of immunoglobulin M (IgM) were decrease in down patients with significant increase in the frequency of lower respiratory tract infections and hospital admission. Estimation and follow up of serum levels of IgG & IgM in cases of Ds with recurrent respiratory tract infections should be done. Also trails to increase level of immunity in patients with Down syndrome as vaccinations either routine or additional ones, improve the quality of life and medical service among them to decrease their susceptibility to respiratory infections are recommended.

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