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IMMUNOGLOBULIN - G SUBCLASS PATTERN AMONG CHILDREN WITH DOWN`S SYNDROME

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ABSTRACT

Down syndrome is the most common and best known chromosomal disorder. The possible relation between DS predisposition to recurrent respiratory infection and IgG subclasses have been infrequently addressed in children. All previous studies showed IgG1 and IgG3 were significantly raised among children with Down's syndrome whereas IgG2 and IgG4 were deficient.

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INTRODUCTION

Down syndrome (DS) also known as trisomy 21, is a genetic disorder caused by the presence of all or part of a third copy of chromosome 21. DS is the most common and best known chromosomal disorder and is the single most common genetic cause of mental retardation. It affects over 300,000 people in USA and 30,000 in UK (Patterson, 2009). In Egypt, although governmental care of this syndrome has increased tremendously in the past few years, prenatal diagnosis is still inaccessible to most of the families and almost all cases of DS are diagnosed postnatal. In the last decades great changes have taken place in the management of children with DS. In addition to the advances in neonatal care, new surgical techniques and the development of new medical drugs, a change in attitude toward these children has taken place. The result is an increase in their life expectancy (Megarbane, 2009). Expectations for the life course of individuals with DS have changed from 12 years in 1949 to nearly 60 years of age today. Along with this longer life expectancy comes a larger population of adult with DS who display premature age-related changes in their health (including increase risk for skin and hair changes, early onset visual and hearing impairment, adult onset seizure disorder, thyroid dysfunction, diabetes, obesity and musculoskeletal problems) (Summar, 2011). The incidence of DS is estimated 1.4 per 1000 live births in the United States. El Sobky and Elsayedestimated risk of 2285 DS births among 1.6 million births annually (El-Sobky, 2004). Approximately 95% of the diagnosed DS cases have pure trisomy 21 from non dysjunction error of chromosome 21. Advanced maternal age is by far the strongest epidemiological variable associated with DS due to increased mutagenic exposures upon some older mother's reproductive cells. Maternal age affects the chances having a pregnancy with DS, at age 20 the chance 1 in 1441; at age 30 it is 1 in 959; at age 40 it is 1 in 84; and at age 50 it is 1 in 44 (Morris, 2002). Although the probability increases with maternal age, 70% of children with DS are born to women 35 years of age and younger, reflecting the fact that younger people have more children. The father's older age is also a risk factor in women older than 35 but not in women younger than 35, and may partly explain the increase in risk as women age (Mokhtar *et al*., 2003). Besides the known risk factors, consanguinity, region (rural/urban) of residence of parents, exposure of parents to chemicals, educational status of parents, smoking habits of father, prenatal scanning reproductive performance of mother are possible risk factors for DS in Egypt (Mokhtar *et al*., 2003). Children with DS have an increased risk of

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infections, especially respiratory tract infections, which can be of diverse pathogenic origin (e.g. viral, bacterial, fungal or a combination of these). This increased susceptibility to infections has been linked to abnormal parameters of the immune system, as DS is the most common recognizable genetic syndrome associated with immune defects (Cruz *et al*., 2009). Infections of the respiratory tract, particularly otitis media, have been identified as one of the most significant health problems in DS children of school age by their parents, with a higher frequency than in the general population. This increased susceptibility to infections have been linked to abnormal parameters of the immune system for more than 30 years https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3074212/#b11). Although multiple differences between the immune system of DS children and that of the general population have been described, the clinical relevance of these differences is less clear. Various medical and anatomical co-morbidities commonly associated with DS increase the susceptibility to infections and might also affect the immune responses.

Immunoglobulin G (**IgG**) is a type of antibody., IgG is the most common type of antibody found in the circulation (Luiz Carlos UchoaJunqueira, 2005). IgG is the main type of antibody found in blood and extracellular fluid allowing it to control infection of body tissues. By binding many kinds of pathogens such as viruses, bacteria, and fungi. IgG can be further divided in four subclasses, named, in order of decreasing abundance IgG1, IgG2, IgG3, and IgG4.https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4202688/#B1. The importance of IgG-subclass deficiency is reflected in the isotypes of IgG antibodies produced against microbial antigens. Antibodies against pneumococcal polysaccharide antigens are predominantly IgG2 and, to a lesser degree, IgG4. In contrast, antibodies against protein antigens, such as tetanus, are predominantly IgG1 and, to a lesser degree, IgG3. Finally, antibodies against large extracellular parasites, such as *Schistosoma* and *Filaria* organisms, exclusively belong to IgG4 subclass (Anantaphruti *et al*., 2005).

Aims and Objectives of the Study

The study aimed at

- Estimation the level of IgG subclasses level in children with Down syndrome.
- Find out the relation –if any- between the estimated levels and recurrence of upper respiratory tract infection (URTI)

MATERIALS AND METHODS

Study settings

- Study was conducted in the genetic clinic of Alexandria University children`s Hospital.

Target Population

- **Group1:** 30 children with Down syndrome.
- **Group2:**30 apparently healthy, age and sex matched children taken as control group.

Inclusion criteria: Age range: 4-18 years, confirmation of diagnosis of Down syndrome was done byKaryotyping (Speicher, 2005).

Exclusion criteria: Children with:

- Immunocompromised status secondary to other disease as:HBV-HCV-HIV positive.
- Patient on long term steroid therapy.
- Associated complications such as Diabetes Mellitus, leukemia, malignancy, hypothyroidism, and systemic lupus erythematosus.

Methods

Study Design: Case control study comparing the IgG subclasses values in both Down and Control groups. Informed consent was taken from parents of all subjects included in this study. An ethical approval was obtained from the Research and Ethics committee of Alexandria Faculty of Medicine.

Collected Data: History-Age-Sex-Maternal Age-history of repeated upper respiratory tract infection -family history of DM – CBC-ELISA for estimation of the levels of IgG subtypes: gG1,IgG2,IgG3,IgG4

RESULTS

The study was conducted on 30 children diagnosed with Down syndrome, coming for follow up at the genetics clinic of Alexandria University children`s Hospital. Total 30 apparently healthy, age and sex matched children were taken as control group. The comparison between the two studied groups regarding age, the mean age in DScases (group I) was 11.56±3.83, while the in control group was 11.47±3.28, on comparing thetwo groups regarding age it was found that there was no significant difference between the two groups regarding age ($p > 0.05$). The comparison between the two studied groups regarding sex, the male represent 53.3% in DS cases(group I)and56.7% in control, there was no significant difference between the two groups regarding sex. The comparison between the two studied groups regarding maternal age at delivery, the mean age of maternal in control group was 32.94±4.86, and in cases the maternal age was 35.28±5.60, there was a significant increase in maternal age in cases more than control ($p < 0.05$). The comparison between the two studied groups regarding mode of delivery, there was no significant difference between the two groups regarding the mode of delivery ($p > 0.05$). The comparison between the two studied groups regarding history of more than 4 repeated upper respiratory tract infections per year, it was found that there was a significant increase in history of repeated upper respiratory tract infection in cases (76.7%) more than the control group (6.7%) ($p< 0.05$).

The comparison between the two studied groups regarding Hb, the mean Hb levelin DScases was 11.02±0.89 While in control groupwas 11.03±1.08, there was no significant difference between the two groups regarding Hb level ($p > 0.05$). The comparison between the two studied groups regarding IgG1, the level of IgG1 in DS cases the mean level was 13.03±3.25, While incontrol groups was 11.28±3.35,there was a significant increase in IgG1 in DS cases than the control ($p < 0.05$). The comparison between the two studied groups regarding IgG2, the mean IgG2 in DS cases group was 1.66±1.40, While in (control) was 4.28±1.40,there was a significant decreasein IgG2 in DS cases (group I)than the control group ($p <0.01$). The comparison between the two studied groups regarding IgG3, the level of IgG3 in DS cases (group I) was 1.21±0.45, While in control groupwas 0.97±0.45,there was a significant increase in IgG3 in DS cases(group I) than control ($p <0.05$).

Table 1. Comparison between the two studied groups regarding demographic data

	Group I (DS Cases) (n= 30)		Group II (n= 30)		Test of sig.	p
	No.	%	No.	%		
Sex						
Male	16	53.3	17	56.7	χ^2=	0.797
Female	14	46.7	13	43.3	0.071	
Age						
Range	5.0 – 16.0		4.0 – 18.0		t=	0.4569
Mean ± SD.	11.56 ± 3.83		11.47 ± 3.28		0.326	
Maternal age at delivery						
Range	27.0 – 43.0		24.0 – 40.0		t=	0.0319*
Mean ± SD.	35.28 ± 5.6		32.94 ± 4.86		2.11*	
Mode of delivery						
Normal vaginal	20	66.7	14	46.7	χ^2=	0.0610
CS	10	33.3	16	53.3	2.44	
History of repeated upper respiratory tract infection >4times/year						
No	7	23.3	28	93.3	χ^2=	0.0001*
Yes	23	76.7	2	6.7	19.23*	

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
*: Statistically significant at $p \leq 0.05$

Tables 3. Distribution of study patients with DS according to their karyotyping (n= 30)

	No	%
Karyotype		
Non dysjunction	28	93.3
Translocation	1	3.3
Mosaicim	1	3.3

Table 4. Comparison between the two studied groups regarding HB

	Group I (DS Cases) (n= 30)	Group II (n= 30)	t	p
Hb (gm/dl)				
Range	9.5 – 12.5	9.5 – 12.7	0.988	0.4793
Mean ± SD.	11.02 ± 0.89	11.03 ± 1.08		

Table 5. Comparison between the two studied groups regarding IgG

	Group I (DS Cases) (n= 30)	Group II (n= 30)	t	p
IgG1 (gm/l)				
Range	7.0 – 18.0	7.0 -17.4	2.04*	0.022*
Mean ± SD.	13.03 ± 3.35	11.28 ± 3.35		
IgG2 (gm/l)				
Range	0.7 – 6.75	0.7 – 7.6	6.22*	0.0001*
Mean ± SD.	1.66 ± 1.40	4.28 ± 1.40		
IgG3 (gm/l)				
Range	0.1 – 1.92	0.1 – 2.2	2.14*	0.012*
Mean ± SD.	1.2 ± 0.45	0.97 ± 0.45		
IgG4 (gm/l)				
Range	0.005 – 0.55	0.005 – 3.5	3.98*	0.001*
Mean ± SD.	0.13 ± 0.11	1.22 ± 0.11		

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

Table 8. Comparison between the two studied groups regarding repeated upper respiratory infection

	Group I (DS Cases) (n= 30)		Group II (n= 30)		χ^2	p
	No.	%	No.	%		
Infection (URTI)						
With no infection >4 times	7	23.3	24	80.0	19.288*	<0.001*
With infection >4 times	23	76.7	6	20.0		

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

The comparison between the two studied groups regarding IgG4, the level of IgG4 in, DS cases was 0.13±0.11,While in control group was1.22±0.11, there was a significant decreasein IgG4 in DS cases than the control ($p < 0.05$). the distribution of study patients with DSaccording to their karyotyping, the majority of the patients had non dysjunction karyotype, while translocation and mosaicim was found in one patient for each.

DISCUSSION

Susceptibility to infections is a feature of Down's syndrome, and is likely to be due to abnormalities of host defence, that is, of the immune response. Reported defects include components of cell mediated and humoral immunity, the inflammatory

response, and interferon production (Annerén, 1992). Several studies have established an association between the deficiency of certain IgG subclasses and the predisposition for recurrent infections of the respiratory airways. The antibodies for virus are specially IgG1 and IgG3 associated subclasses. The response to bacterial polysaccharide antigens is predominantly an IgG2 and IgG4 reaction (Barradas *et al*., 2002). One study published by Anneren *et al*. in 1992, stateda possible relation between predisposition to infection and the serum concentrations of the IgG subclasses.The results of the studies of serum immunoglobulin concentrations in subjects with Down's syndrome have been conflicting. In adults with Down's syndrome the serum concentrations of IgG2 and IgG4 have been found to be significantly reduced and those of IgG1, and IgG3 to be normal or raised. Based on this study,it has been claimed that about half of the children with Down's syndrome are deficient in IgG4. In 2002, Barradas, (2002) in University Clinic ofPaediatrics, Hospital of Santa Maria, Lisboa, Portugal studied serum total IgG and subclasses in three different groups of children: with Down syndrome, their siblings and general pediatric population.The results of that study pointed out that an adequate strategy to improve the immune status of Down syndrome children could have a positive manifestation in the immune profile of their brothers. In the study done by Anneren *et al*. (1992) 38 children with Down's syndrome aged 1-12 years were taken as cases. The 38 cases with chromosomally verified Down's syndrome were 16 girls and 22 boys. The children were split into three age groups: 1-2 5, 4-8, and 9-12 years. Total of 50children matched healthy children served as controls. There were no significant age differences between controls and children with Down's syndrome in the two youngest groups, but the children with Down's syndrome were slightly older than the controls in the oldest age group (p=0.04).

In the study done by Barradas *et al*. 2002 caucasian children were included, divided in three different groups. One group included children with trisomy 21, another formed by their siblings and a third with otherwise considered normal children. statistical significant differences between the three groups were found. The Trisomy 21 group was constituted by 79 individual, 39 girls and 40 boys, with an average age (SD) of 4.6 (3.0) years and a variation between 1 and 14 years. Fifty-four normal children formed a control group, 31 girls and 23 boys with an average age (SD) of 3.9 (3.5) years, variation between 1 and 12 years. In our study the mean age in control (group I) was 11.47±3.28, while the cases age was 11.56±3.83. On comparing the two groups regarding age it was found that there was no significant difference between the two groups regarding age ($p > 0.05$). The comparison between the two studied groups regarding sex, male represented 56.7% in control and 53.3% in cases, there was no significant difference between the two groups regarding sex. In the study done by Barradas *et al*. (2002) it was mentioned that Children from mothers with an age below 25 years have 1:2,000 risk of having the problem, increasing with the maternal age until an incidence of 1:50 at the 40 years. In this study it was found that, the mean age of maternal in control group was 32.94±4.86, and in cases the maternal age was 35.28±5.60, there was a significant increase in maternal age in cases more than control ($p < 0.05$). In our study, it was found that there was a statistically significant increase in history of repeated upper respiratory tract infection in DS cases(76.7%) more than the control group (6.7%). ($p< 0.05$).In the study done by Anneren *et al*. (1992) the concentrations of the subclasses of IgG were determined (ELISA). The individual values and the geometrical mean concentrations and ±1 SD of the four IgG subclasses in the controls and children with Down's syndrome showed no significant age differences between controls and children with Down's syndrome in the two youngest groups, but the children with Down's syndrome were slightly older than the controls in the oldest age group (p=0.04). The children with Down's syndrome had significantly higher concentrations of IgG1and IgG3 than the controls in all three age groups. In contrast, the serum concentrations of IgG2 were normal in the children with Down's syndrome in the two youngest age groups but significantly reduced among the oldest children with Down's syndrome. The IgG4 concentrations were significantly reduced in all three age groups of children with Down's syndrome. While IgG4 deficiency was found in Down's syndrome at all ages, IgG2 deficiency tended to develop later in life among children with Down's syndrome. The study concluded that the IgG4 deficiency is not accompanied by an IgG2 deficiency in childhood in Down's syndrome. Even though the serum concentration of IgG4 is low, it may play a part in mucosal defense because of its higher relative concentration in secretions.

Barradas *et al*. (2002) mentioned that Down syndrome children showed tendency to present higher values of total IgG, with statistical significance above four years old in relation to the other two groups ($P < 0.05$). In relation to IgG1, Down syndrome children and their siblings show statistically higher values to the normal population in all age groups. Above four years old, trisomy 21 group has a significant difference to the rest ($P < 0.01$). Down syndrome children present statistically lower values of IgG2 to the normal population below eight years old ($P < 0.05$). Down syndrome children present statistically higher values of IgG3 to the normal population above four years old ($P < 0.01$). In relation to IgG4,Down syndrome group revealed statistically lower values, compared with normal population below 8 years old ($P < 0.01$).There was a significant difference in the number of cases of Down syndrome with low levels of IgG4 compared to the other two groups ($p < 0.05$). Barradas *et al*. (2002) concluded that total IgG concentration should not be a form to identify IgG subclass deficiency, mainly because the IgG2 and IgG4 represent a small ratio of the total IgG. In children the concentrations of IgG subclasses are lower, requiring quantification with methods that are more sensible. In our study, IgG subclasses were detected using Human IgG total ELISA Sand witch technique, comparing both cases to control groups concentrations of Ig G subclasses (IgG1, IgG2, IgG3, IgG4). The study showed that in comparison between the two studied groups regarding IgG1, the level of IgG1 in control groups was 11.28±3.35, while in cases the mean level was 13.03±3.25, there was a significant increase in IgG1 in cases than the control ($p < 0.05$). on the other hand, the mean IgG2 control was 4.28±1.40, while in cases group was 1.66±1.40, there was a significant increase in IgG2 in the controls , than the cases ($p <0.01$). With comparison between the two studied groups regarding IgG3, the level of IgG3 in controls was 0.97±0.45, while in cases was 1.21±0.45, there werea significant increase in IgG3 in (cases) than control ($p <0.05$). The comparison between the two studied groups regarding IgG4, the level of IgG4 in control group was 1.22±0.11, while in cases was 0.13±0.11, there was a significant increase in IgG4 in control than the cases group ($p < 0.05$). The higher serum concentrations of IgG subclasses 1 and 3 in the children

with Down's syndrome compared with the controls may well be a consequence of polyclonal stimulation from repeated bacterial infections, which obviously does not include IgG2 and IgG4. This contrast strengthens the concept that children with Down's syndrome fail to respond properly with antibodies of the latter subclasses. The results are in accordance with recent data for adult with Down's syndrome and for children concerning IgG4 and are likely to be of pathogenetic significance for the susceptibility to infections. It is interesting to note that IgG4 deficiency is found in Down's syndrome at all ages,' but an IgG2 deficiency tends to develop later in life among children and adults with Down's syndrome.8 Thus the IgG4 deficiency is not accompanied by an IgG2 deficiency in childhood in Down's syndrome. Children with Down's syndrome are especially prone to respiratory bacterial infections.4 This may be partially explained by a deficiency in IgG2 and IgG4 antibodies, of which the former are known to be directed primarily against bacterial polysaccharide antigens of encapsulated bacteria, such as Diplococcuspneumoniae and Haemophilusinfluenzae (Anantaphruti, 2005). Even though the serum concentration of IgG4 is low, it may play a part in mucosal defence because of its higher relative concentration in secretions.' Virus specific IgG antibodies are often of subclasses 1 and 3. The mechanism underlying the abnormal serum IgG subclass pattern is probably not a gene dosage effect as none of the chromosome 21 genes are known to regulate immunoglobulin production. Secondary effects of either a factor related to immunoglobulin production or a deficiency of a trace element such as selenium'4 are proposed as alternative explanations. We have recently reported that selenium supplementation in children with Down's syndrome has a significant augmentative effect on the serum concentrations of IgG2 and IgG4, but not on those of IgG1, and IgG3.'4 Although the mechanism behind the abnormal subclass pattern in individuals with Down's syndrome is unknown, it seems relevant to assay the IgG subclass concentrations among patients with Down's syndrome who have repeated infections. If only the total serum IgG concentration is assayed a deficiency in the IgG2 and IgG4 subclasses will escape detection

Conclusion

- There is a statistically significant relation between the history of repeated upper respiratory tract infection and Down syndrome.
- There is a statistically significant tendency to have decreased levels of IgG2, IgG4 in patients with Down syndrome compared to normal.
- There is a statistically significant tendency to have increased levels of IgG1, IgG3 in patients with Down syndrome compared to normal.
- There is statistically significant relationship between decreased level of IgG2, IgG4 subtypes and repeated upper respiratory tract infection in Down children.

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