Thyroid Dysfunctions in a Sample of Egyptian Children and Adolescents with Systemic Lupus Erythematosus: Relation to Disease Activity and Duration

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Systemic lupus erythematosus (SLE) is a chronic, autoimmune, inflammatory disease affects any organ of the body, including the thyroid gland. Both hypothyroidism and hyperthyroidism have been found in SLE patients more frequently than general population. The aim of this study was to evaluate the frequency of autoimmune thyroid dysfunctions in juvenile SLE and its relation to disease activity and duration. A prospective case-control study was carried on 40 children with juvenile SLE and 30 healthy as controls, all were subjected to measurement of serum TSH, Free T3, Free T4 and anti-TG by ELISA. The SLEDAI scoring system was used to evaluate the disease activity. Fourteen patients (35%) demonstrated thyroid dysfunctions, in the form of; euthyroid sick syndrome in 6 (15%), overt hypothyroidism in 4 (10%), hyperthyroidism in 2 (5%) and subclinical hyperthyroidism in 2 cases (5%). Positive anti-TG was detected in 8 cases (20%) with a significant (P<0.05) increase in mean levels of serum anti-thyroglobulin antibodies in patients (38.25±15.224 Iu/ml) as compared to controls (22.79±3.71 Iu/ml). There was a significant positive correlation between SLEDAI and anti-TG and a significant negative correlation between disease duration and anti-TG, TSH In conclusion; thyroid dysfunctions increase in children with SLE patients and correlate with severity of the disease.

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by autoantibodies directed against self-antigens resulting in tissue inflammatory damage (Klein & Miller, 2015). Thyroid autoimmune diseases have been associated with variety of rheumatological diseases including SLE, caused by an immune response, both humoral and cell mediated, resulting in tissue damage localized in the thyroid. The presence of thyroid autoantibodies contributes to the pathogenesis of a number of thyroid disorders, such as Hashimoto thyroiditis, primary myxedema and Graves' disease (Scherbaum, 1987), both hypothyroidism and hyperthyroidism is seen in association with SLE (Viggiano *et al.,* 2004) (Innocencio *et al.,* 2008). Autoimmune diseases associated with many factors such as genetic, hormonal and environmental factors (Kakehasi *et al.,* 2006). One important feature of autoimmune diseases is tendency for overlap such that an individual with specific syndrome is more likely to develop a second one (Haghighi, 2009). The association between SLE and thyroid abnormalities was first described in 1961 by White & Williams who showed that, the presence of thyroid disturbance appeared to be more frequent in SLE patients than in the general population (Byron, 1987). Furthermore, anti-peroxidase and anti-thyroglobulin antibodies (anti-TG) have been frequently found in SLE patients (Weetman & Walport, 2004). The possibility of coexistence of thyroid disorder in SLE should be carefully considered through the course of patients follow up, especially in those with long disease duration (Shan & Taichung, 1993). Many studies evaluated the thyroid dysfunctions and its pathogenesis in adult lupus patients with few studies on children, so the main purpose of this study to evaluate occurrence of immunological thyroid dysfunctions using (anti-TG) in Egyptian

children with SLE and its relation to the disease activity and duration.

Material and Methods

A prospective case-control study, was conducted at Pediatric Department, Faculty of Medicine, Tanta University Hospital, and was carried on 40 children and adolescents prior to 18 years old with juvenile systemic lupus erythematous diagnosed according to the revised American Rheumatology College (ACR) criteria for diagnosis of SLE (Hochberg, 1997) and 30 healthy children with matched sex and age as a control group between January 2014 and January 2016.

All children were subjected to the following:

- Throughout history taking, disease duration and clinical examination.
- Demographic features and anthropometric measurements.
- Systemic lupus erythematosus disease activity index (SLEDAI) (Bertsias *et al.,* 2010) is a validated disease activity measure for childhood-onset SLE with a total score of 0 - 105. The tool consists of 24 weighted items grouped into the following nine domains: central nervous system (CNS), vascular, renal, musculoskeletal, serosal, dermal, immunological, constitutional and hematological diseases.

Routine laboratory investigations:

- BUN, serum creatinine, CBC and ESR.
- 24 hr. urinary proteins.
- Serum complements (C3, C4) .
- Anti-nuclear antibodies (ANA), anti-double strand DNA (anti- dsDNA).

Renal biopsy

The renal biopsy was done for all cases to determine the severity of Lupus Nephritis (LN). The pathologic changes present on kidney biopsy help guide treatment decisions and may be predictive of long-term kidney survival; the histological findings are graded using the International Society of Nephrology/Renal Pathology Society (ISN/RPS) Classification. Class I and II used for purely mesangial involvement (I, mesangial immune deposits without mesangial hypercellularity; II, mesangial immune deposits with mesangial hypercellularity), class III for focal glomerulonephritis (involving <50% of total number of glomeruli) with subdivisions for active and sclerotic lesions; class IV for diffuse glomerulonephritis (involving > or = 50% of total number of glomeruli) either with segmental (class IV-S) or global (class IV-G) involvement, and also with subdivisions for active and sclerotic lesions; class V for membranous lupus nephritis; and class VI for advanced sclerosing lesions, (Weening *et al.,* 2004).

Serum TSH, Free T3, Free T4 and anti-TG

Blood samples (5cm) were collected in plain sterile tubes and maintained at room temperature for few minutes then centrifuged at 3000 rpm, serum was separated and stored at temperature between (-10 to -30°C) till the time of performing the assay to evaluate FT3, FT4, TSH and anti-TG levels using an indirect solid phase enzyme immunometric assay (ELISA) kit from Monobind corporation, Lake forest, CA, USA (Nunez & Pommier, 1982). In principle; continue please15 µL of sample is incubated with antibody labeled with a ruthenium complex. Continue please. After addition of biotinylated and streptavidin-coated micro-particles, the still-free binding sites of the labeled antibody become occupied, with formation of an antibody-hapten complex. The entire complex becomes bound to the solid phase via interaction of biotin and streptavidin. The reaction mixture is aspirated into the measuring cell where the micro-particles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with procell. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by photomultiplier. Results are determined via a calibration curve which is instrument-specifically generated by 2-point calibration and a master curve provided via the reagent barcode.

•Statistical Analysis

Patient's data were tabulated and processed using SPSS V16. The difference between parametric data of the patients and controls was analyzed via student t-test. Chi-square test (X2) was used for comparison of frequencies and non-parametric data of the two groups. Pearson's correlation coefficient (r) was used to assess the degree of association between 2 continuous variables of patients. A value of (P<0.05) considered significant.

Results

The demographical and laboratory data of the studied groups were summarized in (Table1). The total number of the SLE patients were forty, 35 females (87.50%) and 5 males. F: M

ratio (7:1). Their ages ranged from 9 to 17 years, with a mean of 13.4±2.54 years. Thirty apparently healthy subjects were carefully chosen, matched for age and sex with the SLE patients. They were 26 females (86.66%) and 4 males, F: M ratio (6.5:1). Their age ranged from 8 to 17 years, with a mean of 13.2±2.04 years, with no significant differences between the patients and controls.

Table 1. Demographic and laboratory data of SLE children patients and controls.

Parameters	Patients (N=40)	Controls (N=30)	*P value
Female /male ratio	7/1	6.5/1	NS
Age (years)	13.4±2.54	13.2±2.04	NS
Disease duration (months)	12.65±10.39	-	-
Body Mass Index (BMI) (KG/M ^{2})	22.20±3.94	22±1.33	NS
Weight (kg)	47.667±20.8	45.3±14.019	NS
Height (cm)	146.5±13..97	148.85±11.9	NS
SLEDAI	27.050 ±13.902	-	-
BUN (mg/dl)	31.82±26.23	13.25±2.712	0.003
Serum creatinine (mg/dl)	0.98±0.55	0.61±0.20	0.001
Hb (g/dl)	9.11±1.65	11.90±1.46	0.001
TLC (x10^3/mm^3)	2.86±1.14	8.51±2.73	0.001
Platelets (x10^3/mm^3)	186.25±97.92	255.500±101.186	0.034
ESR 1st hour (mm)	74.10±31.13	13.60±8.10	0.001
ESR 2nd hour (mm)	105.25±32.90	18.25±14.30	0.001
24h urinary proteins (mg/day)	981.00± 862.25	45.78±24.22	0.001
Serum C3 (mg/dl)	52.19±25.79	135.8±9.568	0.001
Serum C4 (mg/dl)	8.09±6.98	25.15±3.099	0.001
ANA (u/ml)	101.23±83.27	12.46±20.33	0.001
Anti-dsDNA (u/ml)	227.93±165.46	10.83±4.35	0.001

*P>0.05 is not significant (NS)

Renal biopsies at initial diagnosis evaluated according to the International Society of Nephrology (ISN) lupus nephritis grading system (Weening *et al.,* 2004), as shown in table (2), ISN Classes I (50%) and III (30%) were the commonest findings.

Table 2. Renal biopsy results in SLE children patients.

Renal biopsy classes	N	%
Lupus nephritis class I	20	50
Lupus nephritis class II	4	10
Lupus nephritis class III	12	30
Lupus nephritis class IV	2	5
Lupus nephritis class V	2	5
Total	40	100

Table (3) showed the thyroid functions of the patients and controls. There was significant (P<0.05) increase of TSH levels in patients (2.86±0.043µu/ml) compared to controls (2.11±1.32µu/ml). There was a significant decrease of FT4 in patients compared to controls (P<0.05) with no significant difference as regarding FT3 (P>0.05).

Table 3. Laboratory findings in Children with SLE and controls.

Parameters	Patients (N=40)	Controls (N=30)	*P value
TSH (µu/ml):			
Range	0.230-4.3	3.61.6 -	0.022
Mean±SD	2.86±0.043	2.11±1.32	
FT3 (Pg/ml):			
Range	1.3-4	2.81.5 -	NS
Mean±SD	2.256±0.914	1.952±0.370	
FT4 (ng/dl):			
Range	0.6-2.2	1.71.1 -	0.001
Mean±SD	1.158±0.341	1.460±0.17	
Anti-TGA (Iu/ml):			
Range	19-115	- 2915	0.001
Mean±SD	38.25±15.224	22.79±3.71	

*P> 0.5 is not significant (NS).

There was a significant increase of the serum levels of anti-TG in patients compared to controls (P<0.05) as shown in table (4), positive Anti-TGA was detected in eight patients (20%). There were fourteen patients (35%) with thyroid dysfunctions (table 4); six patients (15%) with euthyroid sick syndrome (normal TSH, low FT4, normal or low FT3), four cases (10%) with hypothyroidism (high TSH with low FT4 and normal or low T3), two cases (5%) with subclinical hyperthyroidism (low TSH with normal FT4 and FT3) and two cases (5%) with hyperthyroidism (low TSH with high FT4 and FT3) (Charles & Rosalind 2008).

Table 4. Thyroid function evaluation results in children with SLE and controls.

Thyroid functions' evaluation	SLE patients N (%)	Controls N (%)
Euthyroid	26 (65%)	30 (100%)
Euthyroid sick syndrome	6 (15%)	-
Overt hypothyroidism	4 (10%)	-
Subclinical Hyperthyroidism	2 (5%)	-
Hyperthyroidism	2 (5%)	-
Total	(100%)	30 (100%)

Table (5) shows the correlations between disease duration in months, SLEDAI, serum ANA, anti-ds-DNA, C3, C4 and FT3, FT4, TSH, anti-TG levels of patients. There was a significant negative correlation between disease duration and TSH (r= -0.423, P<0.05), with a significant negative correlation between disease duration and anti-TG (r= -0.397, P<0.05) with non-significant correlations between disease duration and FT4 and FT3. There was a significant positive correlation between SLEDAI and anti-TG (r= 0.464, P<0.05) with non-significant correlations between SLEDAI and TSH, FT4 and FT3.

Table 5. Correlation results between thyroid function and autoimmunity and clinical data in children patients with SLE.

Patients	Free T3		Free T4		TSH		Anti TG	
	r	*P*	r	*P*	r	*P*	r	*P*
Disease duration	0.176	NS	0.070	NS	-0.423	0.007	-0.397	0.011
SLEDAI	0.044	NS	-0.453	NS	-0.293	NS	0.464	0.003
ANA	-0.053	NS	-0.062	NS	-0.036	NS	-0.150	NS
Anti-ds-DNA	-0.038	NS	-0.092	NS	-0.303	NS	0.094	NS
C3	-0.230	NS	-0.304	NS	0.398	NS	-0.298	NS
C4	-0.324	NS	-0.208	NS	0.345	NS	-0.268	NS

* *P* value>0.05 is not significant (NS).

Discussion

Systemic lupus erythematosus is a disease of unknown aetiology in which tissues are damaged by autoantibodies and immune complexes. Although thyroid antibodies and thyroid diseases are not included in the classification criteria for SLE, it is reasonable to explore whether patients with SLE have higher prevalence of thyroid disease than that in the normal population (Braunwald *et al.,* 2001).

Several mechanisms may contribute for coexistence of both autoimmune thyroid disease and SLE; Auto-reactive T and B cell can cause primary thyroid destruction and autoimmune thyroiditis. It is also possible that autoimmune thyroid disease is secondary to the production of thyrotropin by activated lymphocytes or auto-antibodies against the thyroid, its hormone, or receptors. Other involved factors, such as genetic and environmental factors (Chan *et al.,* 2001).

In the present study, forty patients having juvenile SLE diagnosed according to revised ACR criteria for diagnosis of SLE (Hochberg, 1997) compared to thirty healthy controls.

Regarding socio-demographic data of patients, female to male ratio was 7:1 in which ensures the importance of hormonal factors in the clinical expression of the disease. This ratio when compared to other Egyptian studies in children, was like that reported by (Abdel-Hafez & Abdel-Nabi, 2015) study (7:1), lower than that reported by (Bakr, 2005) (1:12) and higher than (Salah et al., 2009) (1:2.7). (Ali *et al.,* 1989) performed on Indian children (1:4), (Uziel *et al.,* 2007) at Israel, who found (1:5), and (Dunget *et al.,* 2012) 20 study performed on Vietnamese children (1:4). This may be attributed to the different numbers of studied cases or may be reflect differences in ethnic factors and genetic backgrounds.

SLEDAI has been validated as measures of disease activity as a predictor of damage, measuring change over time and evaluation of response to therapy in SLE (Bertsias *et al.,* 2010). In general at the time of referral, children often have more severe disease activity with higher SLEDAI scores than the adults (Brunner *et al.,* 2008). In the present study mean SLEDAI score was (27±13.9). It was nearer to (Abdel-Hafez & Abdel-Nabi, 2015) study (29.95±2.06), and (Dunget *et al.,* 2012) study (23.8±11.6).

In the present study, all patients were ANA positive (100%) and anti-dsDNA in 90%. 90% of the studied patients were with low C3 and C4.which considered a diagnostic tests of SLE, this agree with (Bader et al., 2005), found positive ANA in 97%, anti-ds-DNA in 93% and lower level of serum C3 and C4 in 78% of patients. There were non-significant correlations between these routine immunological tests of patients and anti-TG, TSH, FT4 and FT3.

Lupus nephritis class I was the most dominant feature on biopsy in 20 patients (50%), 10% with class II, 30% with class III, 5% with class IV and 5% with class V. Not as described by the others; class IV was the most dominant feature on biopsy (Pluchinotta *et al.,* 2007) (Ramirez *et al.,* 2008). Because of renal biopsies were done only in suspected severe SLE nephritis but in the present studied cases, renal biopsy done routinely for all newly diagnosed SLE patients. All cases with thyroid disturbances had lupus nephritis class III and IV; indicating that, thyroid affection common with severe systemic affection as the kidney.

In the present study, there were fourteen cases (35%) with thyroid dysfunctions. Six cases (15%) with Euthyroid sick syndrome, four cases (10%) with hypothyroidism, two cases (5%) with hyperthyroidism and two cases (5%) with sub-clinical hyperthyroidism.

Clinical thyroid disease is more frequent in SLE patients than the normal population. The results of studies differ as to whether both hypothyroidism and hyperthyroidism are common in SLE patients or whether this finding is restricted to hypothyroidism alone. SLE patients have a high frequency of biochemical abnormalities of thyroid function even when they do not have clinical disease (Weetman, 2005). There are different pathogenic mechanisms for the thyroid dysfunctions in SLE patients as; 1. Autoimmunity is one of the main pathogenic mechanisms involved in thyroid dysfunction in SLE, 2. genetic influence in which a gene of susceptibility was identified in 5q14.3-q15 (major locus of susceptibility for SLE, also found in autoimmune thyroid diseases) also the presence of HLA-B8 and DR3 is significantly greater in patients with SLE and Hashimoto's thyroiditis than in the general population, 3. other pathogenic mechanisms include; the effect of drugs, such as corticosteroids and other immunosuppressant drugs taken in lupus patients, the effect of the underlying systemic disease and its inflammatory mediators (low T3 syndrome or sick euthyroid syndrome) and lastly the iodine intake in the patients (Robazzi & Adan, 2012)

A number of studies have looked at the frequency of thyroid dysfunction in SLE patients. In a study done on forty children SLE patients by (El-Ghoneimy *et al.,* 2011), they found that 6 patients (15%) had sub-clinical hypothyroidism, while the remaining 34 patients (85%) were euthyroid. Other studies had numbers higher than the present study, (Al-Girgawy & Al-shabrawy, 2007) found that; 28.90% of juvenile SLE patients showed sub-clinical hypothyroidism, 22.66% showed sub-clinical hyperthyroidism while 47.37% showed normal results. (Mousa *et al.,* 2012) found that; 21 out of 132 adult SLE (15.9%) had thyroid dysfunction and found that the most common abnormality was clinical hypothyroidism (8.3%).

The prevalence of thyroid disorders in Korean adult SLE patients was classified by Park et al study; thyroid function and disease were evaluated in 63 SLE patients of these patients. Hashimoto's thyroiditis (9.5%) as well as euthyroid sick syndrome (14.3%) was more common than Grave's disease (4.8%). They concluded form this study that thyroid disease was common in SLE patients (Park *et al.,* 1995). (Chan *et al.,* 2001) showed that; the prevalence of SCHT (13%) was more than of clinical cases (4.3%), overt and sub-clinical hyperthyroid (2.9% for both).

Hypothyroidism was reported to vary greatly from 3.9% by (Miller *et al.,* 1993) and 24% by (Weetman & Walport, 2004). The differences may be related to patients' numbers and the sensitivity of enzyme linked immunosorbent assay (ELISA) used to detect TSH . Although, most studies have shown that the prevalence of hypothyroidism in SLE is greater than that quoted for the general population, the issue of whether hyperthyroidism is also more prevalent is still debatable. Other studies suggesting there is no increase in prevalence of hyperthyroidism (Mousa *et al.,* 2012).

Positive anti-TG was detected in 20% of the studied patients with a significant increase in patients compared to controls. Thyroid disorders may be the result of anti-thyroid activity of one of the antibodies produced in SLE (Innocencio et al., 2004). Moreover, anti-TG has been found with greater frequency in SLE than in general population, even in SLE patients who do not have clinical thyroid disease (Mousa *et al.,* 2012). Also this agree with (Assal *et al.,* 2009) study on 30 juvenile SLE patients found that anti-TG was detected in 6%, another study by (Kausman & Isenberg, 1995) reported that; (21%) of 150 adult SLE patients had positive thyroid auto-antibodies, follow-up data were available on

average of 7.9 years. 12 of 20 patients (60%) were persistently thyroid auto-antibodies positive, while 8 of patients (40%) were thyroid auto-antibodies negative. In a study done by (Weetman *et al.,* 2004), the prevalence of anti-thyroglobulin antibodies in SLE patients was 27%. High titres autoantibodies were mainly detected in Hashimoto's thyroiditis that means that anti-thyroid autoantibodies may be a good predictor for the detection of Hashimoto's thyroiditis developing in SLE (Punzi & Betterle, 2004).

There was a significant negative correlation between disease duration and serum TSH, anti-TG levels of patients, non-significant correlations between disease duration and FT4 and FT3. There was a significant positive correlation between SLEDAI and anti-TG with non-significant correlations between SLEDAI and TSH, FT4 and FT3, indicating the immunological pathogenesis of thyroid disorders as anti-TG is high in newly diagnosed cases especially with high SLEDAI scoring for disease activity, in comparison with the low TSH with the prolonged disease duration which related to the prolonged affection of the thyroid with autoantibodies, chronic inflammation in patients and effect of cytotoxic drugs as steroids and cyclophosphamide which taken for years in lupus patients.

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