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Antithrombin-III in Pediatric Systemic Lupus Erythematosus

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Pediatric patients with Systemic Lupus Erythematosus (SLE) and antiphospholipids antibodies (APL) are at high risk of developing thromboembolic events. The mechanism involved in the pathogenesis of the prothrombotic state remains obscure. It has been suggested that a reduced fibrinolytic capacity in SLE may probably caused by endothelial cell alteration through immune complex vasculitis. Antithrombin-III (AT-III) is the most potent physiological inactivator of thrombin and other serine proteases in the blood clotting mechanism. This study aimed to investigate natural anticoagulant AT-III and vWF serum levels in childhood-onset SLE. Also, correlate their levels with anticardiolipin antibodies (ACL Ab) to detect whether endothelial cell activation is associated with thrombotic events in those children. In addition, attempt to establish the presence of risk factors for the development of thrombosis in those patients. The population study included two groups: Group I: thirty seven children and adolescents (9 males and 28 females) with SLE disease. Their mean ages at the time of diagnosis were 9.8±2.52 years. The mean duration of the disease was 3.7±1.75 years. All patients were fulfilled the revised classification criteria for SLE. The SLE disease activity was determined using a detailed, well-established protocol for systemic lupus erythematosus disease activity index. GroupII: control healthy subjects. They were twenty five children (10 males and 15 females) with mean age 10.8±3.23 years. All patients and controls were subjected to: Full medical history, Thorough clinical examination and laboratory tests which included Antithrombin III (AT-III), Von Willebrand factor antigen (v WF) Ag, Antinuclear antibodies (ANA) and Anticardiolipin antibodies (ACL antibodies). Also in this study, follow up of SLE patients during the period from year 2000-2005 were done to evaluate the clinical outcomes of those patients. The present study revealed a significant lower concentrations of antithrombin-III (AT-III) (108.1±34.92 mg L^{-1}) in SLE cases than controls (207.6±116.20 mg L^{-1}) ($p = 0.002$). No correlation was obtained between lower AT-III concentrations in the studied SLE children and disease activity nor the duration of the disease. Positive ACL antibodies were detected in 85.5% of the studied SLE children. There were significant elevation of either IgM or IgG ACL antibodies (4.7±1.89 MPLU) and (14.1±7.96 GPLU) in SLE patients than controls (2.4±1.91 MPL U) and (6.1±3.94 GPLU) respectively ($p = 0.000$). A negative correlation was found between the elevated levels of Ig G ACL antibodies and the decreased concentrations of AT-III in studied SLE patients ($R^2 = -0.4$, $p<0.05$). No significant difference of v WF: Ag concentrations between the studied SLE children and the controls was detected. The clinical outcome of SLE children from start of the study (year 2000) till year 2005 (end of the study) was as follow, 19 patients had lupus nephritis (LN), 15 patients had neuropsychiatric features, 12 patients had serositis and 5 patients manifested thromboembolic features. DVT was diagnosed in 3 of them. Lower levels of AT-III in SLE children who developed DVT (91.35±62.21 mg L^{-1}) or neuropsychiatric complications (96.2±29.57 mg L^{-1}) than that detected in SLE cases who did not manifest such sequela (112±36.43 and 116.1±36.64 mg L^{-1}, respectively) but these results were not statistically significant. No significant differences of AT-III concentrations were found in SLE cases who developed progressive staging of LN (126.6±36.8 mg L^{-1}) compared to their corresponding levels in SLE children who had stationary course of LN or did not manifests LN at all during the study (105.2±34.3 mg L^{-1}).

Key words: Systemic Lupus Erythematosus (SLE), antithrombin-III (AT-III), von Willebrand Antigen (v WF: Ag), anticardiolipin antibodies (ACL Ab), thromboembolic manifestation, Lupus Nephritis (LN)

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INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a systemic autoimmune disorder with overwhelming thrombotic states. Thromboembolic events in adult SLE are described in literature (Levy *et al*., 2003). However, there is a paucity of data regarding the rate of thrombosis in pediatric SLE. Few studies reporting lower rate of thrombosis compared to adult (Ravelli and Martini, 1997; Pocurull *et al*., 2002).

The precise pathogenetic mechanisms underlying prothrombotic state in SLE is not fully understood (Levy *et al*., 2003).

Antiphospholipid antibodies (APL), especially lupus anticoagulant (LA), put SLE patients at increased risk for arterial and venous thromboembolic complication. The interaction between the antiphospholipid antibodies and the antigen targets on the coagulation components have been incriminated to play fundamental role (Kiraz *et al*., 1999). It had been reported that purified human antiphospholipid antibodies cause endothelial cell activation with subsequent activation of coagulation *in vitro* (Frijns *et al*., 2001). Shibata *et al*. (1994) advocated that autoimmunity to vascular heparin sulfate proteoglycan (vHSPG), which is an important component of the microvasculature, resulted in endothelial alteration. Reduced fibrinolytic capacity in SLE may probably caused by alteration of the endothelial cells through immune complex vasculitis (Ihle and Ziemer, 1986).

Jarret *et al*. (1983) suggested that increased frequency of thromboembolic events in SLE patients had been attributed to reduced or dysfunctional antithrombin III (AT-III). Antithrombin III (AT-III) is the most potent inhibitor of the coagulation cascade. It is a non-vitamin K-dependent protease. It inhibits the action of thrombin as well as other precoagulant factors (e.g., factor Xa). Antithrombin III activity is markedly potentiated by heparin. The potentiation of its activity is the principle mechanism by which heparin and low-molecular- weight heparins cause anticoagulation (Andrews *et al*., 2000; Harper *et al*., 2004). Acquired deficiencies of AT-III are commonly due to increased coagulation secondary to endothelial injury, or the presence of antiphospholipid antibodies. Excessive activation of the coagulation pathway in both situations result in increased rates of AT-III consumption (Ota *et al*., 2003).

The measurement of fibrinolytic activity and von Willibrand factor (v WF) levels reflect the evaluation of endothelial cell damage in SLE (Doria *et al*., 1995). Endothelial perturbation is defined by elevated plasma levels of both tissue type- plasminogen activator (TPA) and von Willebrand factor (Ferro *et al*., 1997).

The aim of this study is to investigate natural anticoagulant AT-III and vWF serum levels in childhood - onset SLE. Also, correlate their levels with anticardiolipin antibodies (ACL Ab) to detect whether endothelial cell activation is associated with thrombotic events in those children. In addition, attempt to establish the presence of risk factors for the development of thrombosis in those patients.

MATERIALS AND METHODS

The population study consists of two groups: Group 1 included thirty seven children and adolescents (9 males and 28 females) with SLE disease. They were recruited from pediatric rheumatotology unit, Abu EL-Ryish Pediatric Hospital and pediatric clinic, National Research Centre (NRC) in Cairo, EGYPT during year 2000. Their mean ages at the time of diagnosis were 9.8±2.52 years with range from 4 to 15 years while their mean ages at the start of study were 13.2±3.53 years. The mean duration of the disease was 3.7±1.75 years with range from 1 to 8 years. All patients were fulfilled the revised classification criteria for SLE.

The SLE disease activity was determined by using a detailed, well-established protocol for systemic lupus erythrematosus disease activity index (SLE-DAI), (Dafna *et al*., 2000).

Group 2 included control healthy subjects. They were twenty five children (10 males and 15 females) with mean age 10.8±3.23 years.

At the time of recruitment, all patients and controls were assessed for the following parameters:

- Full medical history, considering history of drug intake and previous thromboembolic manifestations.
- Thorough clinical examination, global disease activity was calculated for each assessment in which a mild, moderate and severe grades are given by scores = 32, = 46 and = 76, respectively.
- laboratory tests.

Venous blood samples were withdrawn from each one. each sample was divided into two, first one for measuring the anticardiolipin antibodies (ACA) and antinuclear antibodies (ANA). The second one was put on sodium citrate for estimation of AT-III and vWF.

- Antithrombin III (AT-III) levels was determined by radial immunodiffusion kit supplied by (The Binding Site LTD) (Rose *et al*., 1983).
- Von Willebrand factor antigen (v WF) Ag assessment by immunoelectrophoresis using kit supplied by (Helena Bioscience) (Sadler *et al*., 2000).

- Antinuclear antibodies (ANA) and Anti-Smooth Muscle (ASMA) were detected by means of indirect immunoflourscence using air-dried cryostat sections from mouse kidney stomach and liver (IMMCO Diagnostics, Inc) as substrates. The test for these antibodies was considered positive when the titre equal or higher than 1/20.
- Anticardiolipin antibodies (ACL antibodies) of class G and M were detected by using a quantitative solid phase enzyme linked immunosorbent assay (REAADSR) that uses cardiolipin-coated micro wells and incorporates horseradish peroxidase (HRP) labeled antihuman IgG and IgM anticardiolipin concentration (Wilson *et al*., 1999; Chi, 2002). Samples below or equal 10 GPL or MPLunits (measuring ACL IgG and IgM autoantibodies respectively) were regarded as negative and above 10 units were regarded as positive (elevated).

Also in this study, follow up of SLE patients during the period from year 2000-2005 to evaluate the clinical outcomes of these patients were done.

Statistical analysis: Data entry and analysis was done using SPSS for windows version 13. Descriptive analysis as mean, standard deviation and percentage was done. For comparing between two means, t test was used. When the data was not normally distributed non-parametric test (Mann-Whitney test) was used. To find the relation between two continuous variables, Pearson correlation test was used. $p<0.05$ was taken as a significant level.

RESULTS

Table 1 shows descriptive clinical data of the studied SLE patients. All studied cases had diffuse generalized lymphadenopathy and musculoskeletal complaints in the form of either arthralgia and/or arthritis. hypertension was found in 67.6% (25/37) during the follow up period. 48.6% (18/37) of our cases proved to have Lupus Nephritis (LN) with various grades by renal biopsy. 43.2% (16/37) of the SLE cases manifested mucocutaneous features in the form of malar rash, photosensitivity, discoid and alopecia. The malar rash and photosensitivity were the most common presentation.

Neuropsychiatric manifestations were found in 40.5% (15/37) of cases. Psychosis (11cases) and/or seizures (8 cases) were the commonest presentation. 32.4% (12/37) manifested serositis in the form of either pleural effusion and/or pericardial effusion at the of start of study, 3 cases of them had exacerbation and remission course during the follow up period. Thromboembolic manifestations occurred in 13.5% (5/37) of them all over the study in the form of DVT, hemipelgia and stroke. Deep venous thrombosis (DVT) diagnosed by Doppler in 3 cases of them during the fellow up period (from year 2000 to year 2005). Carditis was diagnosed in 10.8% (4/37) of cases. 5.4% (4/37) of the studied SLE cases showed cutaneous vasculitis.

Table 2 demonstrates statistical analysis of the studied laboratory tests among SLE patients versus the controls. There were significant elevation of either IgM or IgG ACL antibodies (4.7±1.89 MPLU) and (14.1±7.96 GPLU) among SLE patients than controls (2.4±1.91 1MPLU) and (6.1±3.94 GPLU), respectively ($p = 0.000$). Significant lower levels of AT-III in SLE patients (108.1±34.92 mg L^{-1}) than controls (207.6±116.20 mg L^{-1}) were found ($p = 0.002$). No significant difference of v WF: Ag concentrations was detected between 2 groups (cases and controls).

SLE patients were classified according to SLE- DAI (Dafna *et al*., 2000) into mild 56.7% (21 cases) and moderate 43.3% (16 cases).No one had severe activity index. The median disease activity index was 42. Table 3 showed no significant difference of all studied laboratory parameters (IgM or IgG ACL antibodies, v WF: Ag and AT-III concentrations) between mild and moderate SLE- DAI.

Table 1: Descriptive clinical data of the studied SLE patients (n = 37)

Data	Mean±SD
Age at diagnosis (years)	9.8±2.52
Age at the start of study (years)	13.2±3.53
Disease duration (years)	3.7±1.75
Sex Ratio (male/female)	9/28
Clinical manifestations	No. (%)
Mucocutaneous manifestations (malar rash photosensitivity, discoid and alopecia)	16 (43.2)
Cutaneous vasculitis	4 (5.4)
Musculoskeletal manifestations (arthralgia, arthritis)	37 (100)
Renal manifestations (lups nephritis)	18(48.6)
Neuropsychiatric manifestations (seizure, psychosis)	15 (40.5)
Thromboembolic manifestations (DVT, hemipelgia and stroke)	5 (13.5)
Visceral manifestations-Serositis	12 (32.4)
Diffuse lymphadenopathy	37 (100%)
Raynaud phenomonon	3 (4.1)
Carditis	4 (10.8)
Hypertension	25 (67.6)

Table 2: Laboratory characteristics of SLE cases versus controls

Laboratory test	SLE cases (n = 37)	Controls (n = 25)	p-value
Anticardiolipin antibodies ACL-IgM (MPLU)	4.7±1.89	2.4±1.91	0.000
Anticardiolipin antibodies ACL-IgM (MPLU)	14.1±7.96	6.1±3.94	0.000
von Willebrand factor: antigen v wf: Ag (%)	76.4±22.51	87.8±28.33	0.2
Antithrombin III AT-III (mg L^{-1})	108.1±34.92	207.6±116.20	0.002

Table 3: Differences in studied laboratory parameters in SLE cases according to systemic lupus erythematosus disease activity index (SLE -DAI) classification (Dafna *et al*., 2000)

Diseases activity index (DAI)	Mild (n = 21) ≥32 Mean±SD	Moderate (n = 16) ≥46 Mean±SD	p-value
Anticardiolipin antibodies ACL-IgM (MPLU)	4.6±1.73	4.8±2.14	0.69 NS
Anticardiolipin antibodies ACL-IgM (MPLU)	12.8±9.24	15.7±5.83	0.28 NS
vonWillebrand factor: antigen v wf:Ag (%)	72.8±22.24	80.9±22.74	0.616 NS
Antithrombin III AT-III (mg L^{-1})	112.6±38.40	102.1±29.91	0.616 NS

ACL antibodies were positive in 85.5% (32/37) of studied SLE patients. Positive correlation between increased levels of IgM ACL antibodies and increased concentrations of IgG ACL antibodies in SLE patients was found (R^2 = 0.39, p< 0.05). There was a negative correlation between AT-III levels and IgG ACL antibodies concentrations in SLE patients, as decrease of AT-III levels, there is increase of IgG ACL antibodies (R^2 = -0.40, p<0.01), (Fig. 1).

No significant correlation between reduced AT-III levels and v WF: ag concentrations or the disease activity index (R^2 = 0.15, p = 0.38) or duration of the disease (R^2 = 0.18, p = 0.29).

All studied laboratory tests did not differ significantly between SLE children who had positive ANA (31 cases) and those who had not (6 cases).

Table 4 shows studied laboratory parameters in SLE patients who developed clinical outcomes versus cases who did not manifest the same sequela during the follow up period from year 2000 to year 2005. Lower levels of AT-III in SLE children who developed DVT (91.35±62.21 mg L^{-1}) or neuropsychiatric complications (96.2±29.57 mg L^{-1}) than that detected in SLE cases who did not manifest these sequela (112.3±36.43 and 116.1±36.64 mg L^{-1} respectively) were observed during the fellow up period, but these results were not statistically significant. Higher concentrations of ACL IgG antibodies were observed in patients with deep venous thrombosis (DVT) (18.5±2.61 GPLU), neuropsychiatric complications (15±6.34 GPLU) and Lupus Nephritis (LN) (14.4±6.54 GPLU) than that detected in cases without such sequela (12.5±6.32, 13.4±8.98 and 13.7±9.27 GPLU, respectively) during the follow up, but this was not statistically significant.

Figure 2 illustrates flow chart of the studied SLE cases during the follow up period from year 2000 to year 2005. Three cases of the initially studied SLE children proved to develop DVT by Doppler.

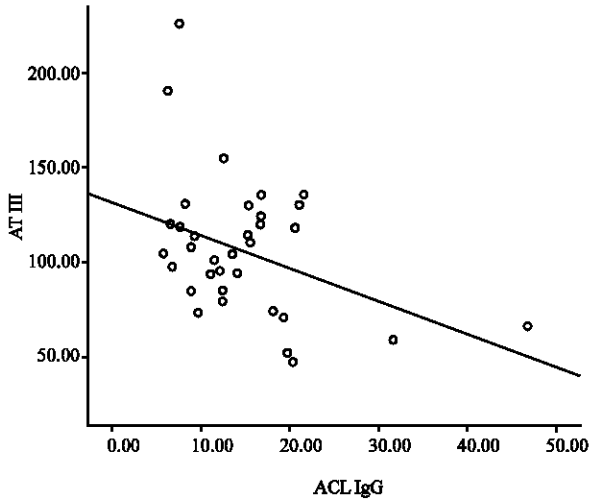

Fig. 1: Negative correlation between ACL IgG and AT III (R^2 = -0.4 and p<0.05)

Neuropsychiatric manifestations presented by psychosis (7 cases), convulsions (4 cases) and both (4 cases) were found at the start of study (year 2000). All had exacerbation and remission course. the rest of SLE cases were free of these symptoms till the end of the study.

It was found that 48.6% (18/37) of the studied SLE children had Lupus Nephritis (LN) at the start of the study while 51.4% (19/37) of them had no nephritic manifestation. One case 5.3% (1/19) from those who did not initially manifest LN, developed grade (V) LN at the end of follow up period. Progressive staging of lups nephritis were detected in 4 cases 22.2% (4/18) of those who had initially LN at the start of the study (one case from grade II to III), 2 cases (from grade II to IV) and one case (from grade IV to V). While 14 cases 77.8% (14/18) had stationary pathological grades of LN (6 cases with grade II, 5 cases with grade III, one case IV and 2 cases with grade V).

No significant difference of AT-III concentrations or other studied laboratory tests were found in SLE cases who developed progressive staging of lups nephritis (n = 5) (126.6±36.8 mg L^{-1}) when compared to their corresponding levels in SLE children who had stationary course of LN (n = 14) or did not manifests nephritic element during the study (n = 18) (105.2±34.3 mg L^{-1}).

All over the study, 12 cases developed serositis, only three of them had exacerbation and remission course from the start of the study. However, no significant difference of the studied laboratory tests were found between SLE cases who developed serositis and those who had not, apart from IgM ACL antibodies which was significantly elevated in patients with serositis (5.7±1.99 MPLU) than those without (4.2±1.68 MPLU) (p< 0.05).

Table 4: Studied Laboratory parameters of SLE cases who developed clinical outcomes versus the SLE cases who did not manifest the same sequela during the fellow up period from year 2000-2005

	Neuropsychiatric		Deep venous thrombosis (DVT		Lupus nephritis (LN)	
Laboratory test	With	Without	With	Without	With	Without
Anticardiolipin antibodies	4.5±1.74	4.8±2.02	4.5±0.35	4.6±6.15	5.1±2.09	4.2±1.61
ACL-IgM (MPLU)	p = 0.68 NS		p = 0.43 NS		p = 0.42 NS	
Anticardiolipin antibodies	15±6.34	13.4±8.98	18.5±2.61	12.5±6.32	14.4±6.54	13.7±9.27
ACL-IgM (MPLU)	p = 0.18 NS		p = 0.46 NS		p = 0.48 NS	
vonWillebrand factor:	75.5±21.20	77.2±23.71	77.7±7.11	79.3±23.72	78.5±22.82	74.6±22.61
Antigen v ef:ag (%)	p = 0.82 NS		p = 0.72 NS		p = 0.48 NS	
Antithrombin III AT-III	96.2±29.57	116.1±36.64	91.35±62.21	112.3±36.43	108.7±25.20	107±42.94
(mg L^{-})	p = 0.07 NS		p = 0.06 NS		p = 0.22 NS	

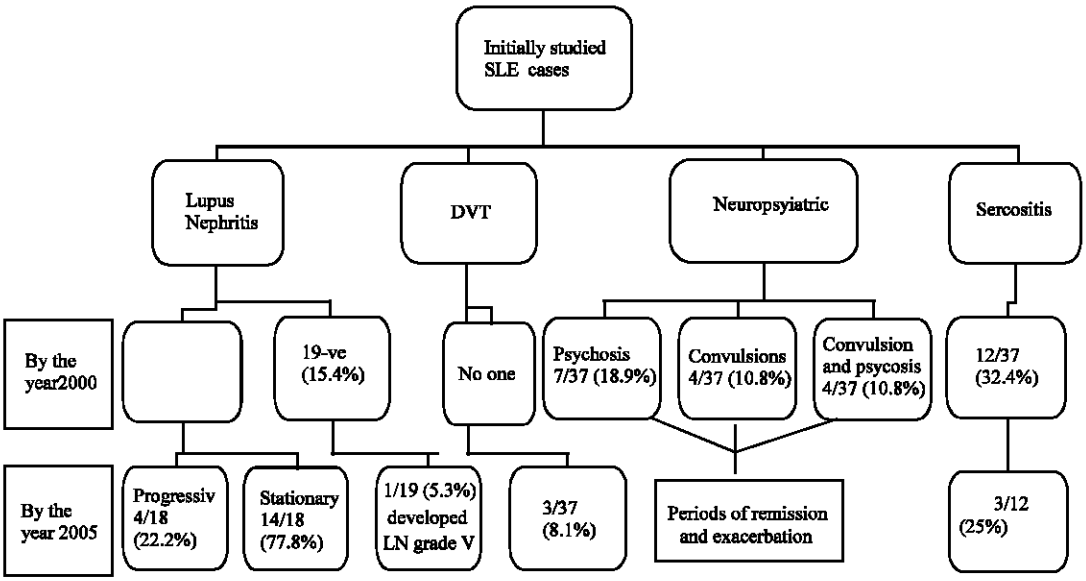

Fig. 2: Flow chart of the studied SLE cases during (2000-2005)

DISCUSSION

Pediatric patients with Systemic lupus erythematosus (SLE) and antiphospholipid antibodies (APL) are at high risk of developing thromboembolic events (Levy *et al*., 2003). It has been suggested a reduced fibrinolytic capacity in SLE may probably caused by endothelial cell alteration through immune complex vasculitis (Ihle and Ziemer, 1986). Antithrombin-III(AT-III) is the most potent physiological inactivator of thrombin and other serine proteases in the blood clotting mechanism (Rose *et al*., 1983).

The present study revealed a significant lower concentrations of antithrombin-III (AT-III) (108.1±34.92 mg L^{-1}) in SLE cases than that detected in controls (207.6±116.20 mg L^{-1}) (p = 0.002) (Table 2). This result goes in parallel with that published by Gladman *et al*. (1983), Boey *et al*. (1984) and Liu *et al*. (1990). This finding confirms that acquired AT-III deficiency in SLE patients may be considered in thrombophilic mechanism (Ihle and Ziemer, 1986). But other studies failed to show a significant decrease of AT-III levels in SLE patients (Jarrett *et al*., 1983; Tomas *et al*., 1998). No correlation was obtained between lower AT-III concentrations in the studied SLE children and disease activity nor the duration of the disease which was matched with Gladman *et al*. (1983) study.

Positive ACL antibodies were detected in 85.5% of the studied SLE children. These data are supported by that of Vogel *et al*. (1991) who found positive ACL antibodies in 50.8% of studied SLE cases. Significant higher concentrations of either IgM (4.7±1.89 MPLU) or IgG (14.1±7.96 GPLU) were found in SLE children compared to that detected in controls (2.4±1.91 MPLU) and (6.1±3.94 GPLU) respectively (p = 0.000) (Table 2).

The increased IgM ACL antibodies levels were positively correlated to the elevated concentrations of Ig G ACL antibodies (R^2 = 0.39, p<0.05). This finding reflect the nature of the disease as exacerbation and remission i.e not a stationary chronic disease. A negative correlation

was obtained between the elevated levels of Ig G ACL antibodies and the decreased concentrations of AT-III in studied SLE patients (R^2 = -0.4, $p<0.05$) (Fig. 1). This result reflects the involvement of AT-III in the inflammatory process in SLE and on the other hand the activation of the intravascular coagulation, a risk factor for thrombosis (Matuszewska *et al*., 2003). This finding confirms a reduced fibrinolytic capacity in SLE patients probably caused by endothelial cells alteration through immune complex vasculitis (Ihle and Ziemer, 1986).

Concerning the study of von Willebrand factor (v WF:Ag), no significant difference of v WF: Ag concentrations between the studied SLE children and the controls was detected (Table 2). This result was contradictory to that published by Doria *et al.* (1995) and Frijns *et al.* (2001) who found significantly increased levels of v WF:Ag in SLE patients compared with values in healthy controls. v WF:Ag concentrations did not differ significantly between SLE patients with or without thromboembollic manifestations which goes in parallel with result of Frijns *et al.* (2001). This finding suggest that vWf may have no role in endothelial perpeutation in SLE.

The study reviewed the data of the initially studied children with SLE treated from year 2000 till year 2005, (Fig. 2). In all, 19 patients had Lupus Nephritis (LN), 15 patients developed neuropsychiatric features, 12 patients had serositis and 5 patients manifested thromboembolic features.

DVT was diagnosed in 3 cases of SLE cases during the follow up period. This finding was supported by that published by Clair *et al.* (1981) who described DVT and circulating anticoagulant in a male adolescent with SLE.

Neuropsychiatric manifestations most commonly presented with psychosis (8 cases), convulsions (4 cases) and both (4 cases) were detected. During follow up period these manifestations remit and exacerbate in the same patients and the rest of SLE remains free of those manifestations.

Lower levels of AT-III in SLE children who developed DVT (91.35±62.21 mg L^{-1}) or neuropsychiatric complications (96.2 ±29.57 mg L^{-1}) than that detected in SLE cases who did not manifest such sequela (112±36.43 and 116.1±36.64 mg L^{-1}, respectively) were observed during the fellow up period, but these results were not statistically significant (Table 4). These data matched with that found by Gladman *et al.* (1983) and Boey *et al.* (1984) who detected lower AT-III levels in SLE patients, but its levels did not differ significantly between SLE with vasculitis and/or phelebitis and those without. In addition, those patients who had DVT or neuropsychiatric manifestations showed elevated ACL IgG than those who had not but statistically insignificant (Table 4). This could point to the role of AT III in production of such outcome in the presence of endothelial damage produced by increased ACL antibodies. The insignificance of these observations may be due to small sample size or short follow up period. Moreover, these negative findings can be attributed to prednisone therapy that influence the concentrations of natural anticoagulant. Provided low doses of steroids seem to be effective in improving endothelial cell function in SLE patients (Doria *et al.*, 1995). This study lacks the investigation of the effect of steroid therapy and anticoagulants levels on those patients.

No significant differences of AT-III concentrations were found in SLE cases who developed progressive staging of LN (126.6±36.8 mg L^{-1}) compared to their corresponding levels in SLE children who had stationary course of LN or not manifested LN during the study (105.2±34.3 mg L^{-1}).

In conclusion, the study found reduction of AT III and increased ACL antibodies levels in SLE cases than control. Also significant negative correlation was found between AT III and ACL IgG. Lower AT III and higher ACL IgG concentrations were observed in SLE cases who had DVT or neuropsychiatric sequelae during follow up period

Recommendation: The data discussed in this study call for a re-evaluation of the current paradigms for SLE pathogenesis. Physicians should be aware that circulating anticoagulants abnormalities can be associated with childhood SLE and there may be paradoxical increased incidence of thromboembolic phenomona in patients with these abnormalities. Reduced AT III level should be anticipated when there are specific aetiological factors present such as active thrombosis or neuropsychiatric manifestations. Further studies are recommended to determine the mechanisms and the role of this acquired deficiency of AT-III in the pathogenesis of the thromboembolic manifestations in SLE patients, taking into consideration the evaluation of steroid therapy on anticoagulant concentrations.

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