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Association between C1q Rs631090gene Polymorphism and Juvenile Systemic Lupus Erythematosus in Egyptian Children, A Single Centre Study

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ABSTRACT

Background: Systemic lupus erythematosus is a condition characterized by the immune system destroying multiple organs in the body.

Aim: To assess and characterize C1q rs 631090 polymorphism in a group of Egyptian children with juvenile systemic lupus erythematosus (jSLE) and to investigate the relationship between this polymorphism, phenotypes, presenting manifestations, activity, and damage indices. This mutation was previously studied in adult systemic lupus erythematosus (SLE) patients in Egypt but not in pediatrics, also C1q deficiency was the diagnosis of one of our SLE patients who presented with severe skin manifestations and recurrent infections.

Patients and Methods: 114 children were recruited in this study, 67 Egyptian juvenile SLE patients and 47 healthy age matched children as control group. Whole blood (EDTA) samples were collected from studied population then DNA was genotyped for rs631090(c.187+267T>C).

Results: Out of our study population, 24 patients (35.8%) had gene mutation either homozygous or heterozygous (C/C and C/T); homozygous mutation C/C in (13.4%), which was significantly greater than the control group. Lupus nephritis incidence significantly varied among patients with homozygous and heterozygous mutations, with the homozygous group showing lower incidence (p value 0.002). Vasculitis was highest in homozygous C/C in (33.3%) compared to (11.6%) in non-mutant group T/T and none (0%) of the heterozygous group C/T.

Conclusion: Our study suggests that a homozygous mutation in the gene C1q rs631090 may be a beneficial prognostic factor for juvenile SLE patients with milder disease complications.

Keywords: Juvenile SLE, Complement deficiencies, Gene C1q rs631090, Homozygous mutation C/C, Lupus nephritis.

INTRODUCTION

Systemic lupus erythematosus is a systemic autoimmune disorder with multi-organ involvement. Juvenile systemic lupus erythematosus (jSLE) manifests before the 18th birthday with peak age of onset approximately 12.6 years **(1)**, yet early onset lupus has been increasingly recognized in Egypt-mandating the search for the underlying genetic factors. The complement system is a vital component of the innate immune system, comprising many proteins found in the plasma and on cells. It functions as a cascade reaction, began in response to pathogens, leading to the opsonization and lysis of these pathogens. Additionally, it helps in recruiting immune cells to the site of inflammation. Activation of the complement system can occur through three distinct pathways: the classical pathway (CP), the lectin pathway (LP), and the alternate pathway (AP). Each of these pathways is activated by a particular ligand **(2)**.

Inflammatory damage is a result of complement activation. A genetic deficit of C1q, C1r, C1s, C4, or C2 in the classical complement pathway impairs the removal of immune complexes and waste from dying cells, greatly increasing the risk of developing systemic lupus erythematosus (SLE) **(3)**.

The excessive production of end complement products resulting from complement activation at the site of immune complex deposition paradoxically leads to inflammation and damage to tissues.

The first single-gene flaws to cause lupus-like disease have been discovered as complement deficits, particularly C1q. SLE is developed by approximately ninety percent of persons with homozygous C1q deficiency. Additionally, there are data indicating that a partial lack of C1q also heightens the susceptibility to cutaneous lupus erythematosus and systemic lupus erythematosus **(4)**.

The purpose of the present investigation was to assess and characterize C1q rs631090 polymorphism in a group of Egyptian kids with jSLE and to examine the relationship between this polymorphism, phenotype, presenting manifestations, activity, and damage indices.

PATIENTS AND METHODS

This is a retrospective investigation caaried out at Cairo University Pediatric Hospital. It was performed on 67 juvenile systemic lupus erythematosus cases diagnosed regarding the Systemic Lupus International Collaborating Clinics (SLICC) criteria **(5)** followed up in pediatric rheumatology clinic during time interval of the study and 47 apparently healthy children (as control group). Study duration was from 6\2019 till 7\2021.

The inclusion criteria for cases were as follows: the onset of illness occurring between six months and eighteen years of age, and disease period not less than 6 months. Exclusion criteria involved age of illness onset

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more than 18 years and children with history of any other associated autoimmune disease.

All kids enrolled in the study have been exposed to full history taking involving general charactarstics and illness manifestations, together with full physical investigation.

At the time of study enrollment, disease activity was assessed for all patients using SLEDAI-2k severity score [6] with a score of zero indicating no activity,1 to 5 indicating mild activity,6 to 10 indicating moderate activity, 11 to 19 indicating severe activity and a score of 20 or more indicating a very high activity [7].

The assessment of disease damage has been conducted utilizing the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) [8].

The results of laboratory investigations at the time of diagnosis including renal biopsy results, have been gathered from the follow up data in cases' files.

Mutation analysis:

Whole blood (EDTA) samples were collected from our patients as well as the healthy children then DNA was genotyped for rs631090(c.187+267T>C) by TaqMan probe real time PCR technique on step-1 real time PCR. Aseptic venipuncture was used to obtain three milliliters of blood into pre-chilled violet top EDTA vacutainer tubes for genomic DNA investigation. The DNA samples were maintained at a temperature of minus eighty degree Celsius to be utilized for TaqMan real-time PCR.

The test has been done in two main steps:

1. Genomic DNA was extracted from peripheral blood leukocytes obtained from EDTA anti-coagulated blood.
2. The DNA that was taken has been amplified and the genotypes have been identified using real-time PCR.

Ethical consideratioons:

Institutional Research Ethical Committee of Faculty of Medicine, Cairo University has reviewed and approved this research protocol with code: MD-99-2019 on the 24th of August 2019. Informed consents have been taken from caregivers of all participants. The Helsinki Declaration was followed throughout the study's conduct.

Statistical Analysis

The statistical package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA) has been utilized to code and input the data. Quantitative variables have been summarized utilizing the standard deviation, mean, median, minimum, and maximum, while categorical variables were summarized utilizing relative frequencies (percentages) and frequencies (number of cases). The non-parametric Mann-Whitney test [9] has been utilized to compare quantitative variables. The Chi square (χ^2) test was implemented to compare categorical data. When the anticipated frequency is less than five [10], an exact test has been carried out. Logistic regression has been utilized to compare the genotype and allele frequencies of the disease and control groups. Odds ratio (OR) with ninety-five percent confidence intervals were computed. Spearman correlation coefficient [11] has been utilized to establish correlations among quantitative variables. Statistically significant P-values have been defined as those that were less than 0.05.

RESULTS

Demographic data, activity score, damage index and results of renal biopsy at time of study enrollment were included in table 1. The investigation involved 67 Egyptian kids with juvenile SLE with a male to female ratio 1:6.4. Their mean age at diagnosis was 8.86±2.9 years and the mean age at time of investigation was 10.94± 3.04 years. 13.5% of the patients had family history of SLE, while family history of other rheumatological disease was in 4.5%.

Based on disease activity score, only 6% of the study group were in complete remission, while the rest showed various degrees of activity. With lupus nephritis being the commonest cause of high disease activity (73.1%) followed by fever, skin, hematological manifestations, and vasculitis mainly skin and cerebral vasculitis. Disease damage was detected in 13.4% of the cases, the most common causes of which were neurological manifestations mainly seizures and cerebrovascular accidents.

Renal biopsies have been conducted in 55.2% of our cases with grade II lupus being the most common type (25.4%) followed by grade III, grade IV, grade I.

Disease manifestations at the onset of the disease were variable, and are summarized in **table 2;** with renal affection being the most common presenting manifestation in 76.1% followed by constitutional manifestations in 74.6%

Disease manifestations throughout the course of the disease are summarized in **table 3** with increase in the percentage of lupus nephritis to reach 89.6% and skin manifestations to reach 95.5%.

Results of gene mutation:

Genotype among cases and control with allelic frequency in each of them and age of onset of disease are shown in **table 4.** Within 47 control healthy children, thirteen showed gene mutation (C/C and C/T) (27.7%), 12 had heterozygous mutation C/T (25.5%) and only one showed homozygous mutation C/C (2.1%), while 34 of the control group showed no mutation T/T (72.3%). Out of our study population, 24 patients (35.8%) had gene mutation either homozygous or heterozygous (C/C and C/T); homozygous mutation C/C in (13.4%), which was statistically insignificant with control group, heterozygous mutation C/T in (22.4%) and that was close to the results of the control group with statistically insignificant variance.On the other hand, wild homozygous T/T has been detected in (64.2%) of cases being lower than in control 72.3% but

with statistically insignificant variation. The homozygous group C/C showed a younger mean age at first presentation compared to the heterozygous group C/T and the wild group T/T but with statistically insignificant distinction.

Correlations among the variable genotypes and the disease manifestations throughout the disease course are shown in **table 5**. There was a statistically significant variance in the incidence of lupus nephritis among patients having homozygous mutations and those with heterozygous mutations.Hematological manifestations were also lowest in the homozygous group C/C in 2 patients only (22.2%) being in the form of thrombocytopenia compared to C/T and T/T group being mainly anemia and leucopenia in both groups. Anemia and leucopenia did not manifest in the homozygous C/C group throughout the course of the disease, but the variation wasn't statistically significant.

Vasculitis was highest in the homozygous C/C in (33.3%) compared to (11.6%) in wild group T/T and none (0%) of the heterozygous group C/T. No statistically significant distinction in the incidence of neurological manifestations were detected between the 3 groups. Out of our study population six patients were proved to have antiphospholipid syndrome, five of which showed no mutation T/T (83.3%) and 1 patient with heterozygous mutation C/T (16.6%) and none showed homozygous mutation C/C (0%) with no statistically significant difference detected.

Cases have been classified into three groups depend on the type of gene mutations and disease activity and damage and are demonstrated in **table 6.** The main causes of disease activity in the homozygous group C/C were vasculitis and lupus nephritis in the form of proteinuria and urinary casts. In the heterozygous group C/T and in the wild group T/T, lupus nephritis was the main cause of high disease activity Damage index was lowest in the homozygous group C/C in the form of cardiomyopathy, cerebrovascular accident and peripheral neuropathy, followed by the wild group T/T then the heterozygous group C/T with statistically insignificant variance among the groups.

Out of our 67 patients, 5 patients (7.5%) were diagnosed following documented COVID 19 infection **(table 7)**; none of them was homozygous C/C for the gene rs631090, two patients (40%) were heterozygous C/T and 3 patients (60%) showed no mutation. For this particular group the main presenting manifestations at time of disease onset in (100%) was constitutional manifestations in the form of fever, generalized fatigability and weight loss and hematological manifestations in the form of hemolytic anemia in 100% as well. Compared to the rest of our study population, the incidence of hematological manifestations in the form of hemolytic anemia as well as thrombocytopenia was statistical significantly higher, but skin manifestations were significantly lower. The lupus patients with history of COVID infection just before the lupus diagnosis were diagnosed according to the SLICC criteria, and renal biopsy done revealed picture of lupus nephritis ranging from grade II (40%), grade III (20%), grade IV (40%). The percentage of hematological manifestations still were higher than the rest of our SLE patients and skin manifestations were lower.

Mortality among our study population as shown in (table 8) was 7.5% (5 out of 67 patients) during the COVID era due to pneumonia and sepsis, none of which was homozygous nor heterozygous and 100% showed no mutation (T/T). Their main presenting manifestation throughout the course of the illness in the 5 cases was lupus nephritis, skin manifestations and constitutional manifestations.

Table (1): Demographic data of JSLE patients, disease duration, and activity damage (n=67)

Causes of disease activity	**Count**	**%**
Vasculitis	9	13.4%
Hematuria	15	22.4%
Proteinuria	49	73.1%
Rash	13	19.4%
Low complement	29	43.3%
Fever	14	20.9%
Thrombocytopenia	7	10.4%
Leucopenia	11	16.4%

	Mean	**Standard Deviation**	**Median**	**Minimum**	**Maximum**
Age (years)	10.94	3.04	11.00	3.00	17.00
Age at first presentation	8.69	2.93	9.00	0.50	13.50
Age at diagnosis	8.86	2.90	9.00	0.50	14.00
Disease duration	2.25	2.27	1.00	0.50	12.00

Gender	**Male**	9	13.4%
	Female	58	86.6%
Family history of other rheumatological disease	**Positive**	3	4.5%
	Negative	64	95.5%
Family history of lupus	**Positive**	9	13.4%
	Negative	58	86.6%

		Count	Percentage
Total Activity Score	**No activity**	4	6.0%
	Mild activity	10	14.9%
	Moderate activity	19	28.4%
	High activity	21	31.3%
	Very high activity	13	19.4%
Total Damage Score	**No damage**	58	86.6%
	Damage	9	13.4%
		Count	Percentage
Renal Biopsy	**GradeIV**	9	13.4%
	GradeIII	10	14.9%
	Grade II	17	25.4%
	Grade II	1	1.5%
	Not done	30	44.8%

Table (2): Incidence of disease manifestations at time of disease onset (n=67)

Manifestation at disease onset	**Percentage in jSLE cases**
constitutional manifestations	74.6%
Renal manifestations	76.1%
Skin manifestations	70.1%
Musculoskeletal manifestations • **Arithritis**	47.8% • 25.4%
Serositis	47.8%
Neurological manifestations	9.0%
Hematological manifestations • **Leucopenia** • **Thrombocytopenia** • **Anaemia**	43.3% • 19.4% • 17.9% • 23.9%
Oral ulcers	9.0%
Alopecia	6.0%
Vasculitis	4.5%

jSLE: Juvenile Systemic Lupus Erythematosus

Table (3): Incidence of disease manifestation throughout the course of the disease (n=67)

Manifestation throughout disease course	Percentage in jSLE cases
Constitutional manifestations	95.5%
Lupus nephritis	89.6%
Skin manifestations	86.6%
Musculoskeletal manifestations • **Arithritis**	44.8% • 26.9%
Serositis	47.8%
Cardiovascular manifestations	4.5%
Neurological manifestations	23.9%
Hematological manifestations • **leucopenia** • **thrombocytopenia** • **anaemia**	50.7% • 29.9% • 20.9% • 25.4%
Oral ulcers	19.4%
Alopecia	9.0%
Vasculitis	11.9%

jSLE: Juvenile Systemic Lupus Erythematosus

Table (4): Genotype among cases and control with allelic frequency in each of them

		Cases n=67		Controls n=47		P value	OR	95% CI	
		Count	%	Count	%			Lower	Upper
rs 631090 gene	**C/T**	15	22.4%	12	25.5%	0.979	0.988	0.409	2.388
	C/C	9	13.4%	1	2.1%	**0.069**	7.116	0.859	58.955
	C/T+CC	24	35.8%	13	27.7%	0.361	1.460	0.649	3.285
	T/T	43	64.2%	34	72.3%	Reference			
	allele C	33	24.6%	14	14.9%	**0.076**	1.867	0.936	3.724
	alleles T	101	75.4%	80	85.1%	Reference			

	C/T		C/C		T/T		P value
	mean	SD	mean	SD	mean	SD	
Age	11.97	2.12	9.44	2.9	10.90	3.24	0.173
Age at first presentation	9.90	1.84	7.72	3.64	8.48	3	0.230

Table (5): Manifestations throughout the disease course in relation to the various genotypes (n=67)

	rs 631090 gene						
	C/T		C/C		T/T		P value
	Count	%	Count	%	Count	%	
Constitutional manifestations	15	100.0%	6	66.7%	43	100.0%	0.002
Lupus nephritis	13	86.7%	5	55.6%	42	97.7%	0.002
Skin manifestations	13	86.7%	7	77.8%	38	88.4%	0.671
Musculoskeletal manifestations	6	40.0%	2	22.2%	22	51.2%	0.281
Serositis	6	40.0%	3	33.3%	23	53.5%	0.518
Cardiovascular manifestations	1	6.7%	1	11.1%	1	2.3%	0.290
Neurological manifestations	3	20.0%	2	22.2%	11	25.6%	1
Hematological manifestations	8	53.3%	2	22.2%	24	55.8%	0.202
Leucopenia	5	33.3%	0	0.0%	15	34.9%	0.111
Thrombocytopenia	3	20.0%	2	22.2%	9	20.9%	1
Anaemia	5	33.3%	0	0.0%	12	27.9%	0.155
Arithritis	5	33.3%	2	22.2%	11	25.6%	0.849
Oral ulcers	3	20.0%	1	11.1%	9	20.9%	0.906
Alopecia	1	6.7%	1	11.1%	4	9.3%	1
Vasculitis	0	0.0%	3	33.3%	5	11.6%	0.045
Antiphosholipid syndrome	1	6.7%	0	0.0%	5	11.6%	0.833

Table (6): Main causes of disease activity in various genotypes and total damage index n=67:

	rs 631090 gene						
	C/T		C/C		T/T		P value
	Count	%	Count	%	Count	%	
Vasculitis	0	0.0%	4	44.4%	5	11.6%	0.013
Arithritis	0	0.0%	1	11.1%	5	11.6%	0.442
Urinary Cast	8	53.3%	4	44.4%	24	55.8%	0.879
Hematuria	5	33.3%	2	22.2%	8	18.6%	0.471
Proteinuria	11	73.3%	4	44.4%	34	79.1%	0.121
Rash	1	6.7%	3	33.3%	9	20.9%	0.258
Low Complement	7	46.7%	1	11.1%	21	48.8%	0.135
Fever	2	13.3%	2	22.2%	10	23.3%	0.825
Thrombocytopenia	2	13.3%	2	22.2%	3	7.0%	0.233
Leucopenia	1	6.7%	1	11.1%	9	20.9%	0.557
total Damage score	3	20.0%	1	11.1%	5	11.6%	0.764

Table (7): Characteristics of post covid SLE patients n=5

	onset following documented covid 19 infection							
	Yes			No				P value
	Mean			Mean				
Total activity score	3.60			13.35				0.013
Total damage score	0.00			0.56				0.602
	C/T			C/C		T/T		P value
Onset following documented covid 19 infection	Yes	2	13.3%	0	0.0%	3	7.0%	0.636
	No	13	86.7%	9	100.0%	40	93.0%	

		Post covid SLE patients n=5		Non-post covid n=62		P value
Manifestations at disease onset		**Count**	**%**	**Count**	**%**	
Constitutional manifestations	**present**	5	100.0%	45	72.6%	0.319
Skin manifestations	**present**	1	20.0%	46	74.2%	0.025
Hematological manifestations	**present**	5	100.0%	24	38.7%	0.012
Leucopenia	**present**	1	20.0%	12	19.4%	1
Thrombocytopenia	**present**	3	60.0%	9	14.5%	0.037
Anaemia	**present**	5	100.0%	11	17.7%	< 0.001
Manifestations throughout disease course						
Constitutional manifestations	**present**	5	100.0%	59	95.2%	1
Lupus nephritis	**present**	5	100.0%	55	88.7%	1
Skin manifestations	**present**	1	20.0%	57	91.9%	0.001
Hematological manifestations	**present**	5	100.0%	29	46.8%	0.053
Leucopenia	**present**	1	20.0%	19	30.6%	1
Thrombocytopenia	**present**	3	60.0%	11	17.7%	0.058
Anaemia	**present**	5	100.0%	12	19.4%	0.001

jSLE: Juvenile Systemic Lupus Erythematosus

Table (8): Mortality among the study population during the study.

	Patients who passed away n=5	
	Count	%
Constitutional manifestations	5	100.0%
Lupus nephritis	5	100.0%
Skin manifestations	5	100.0%
Hematological manifestations	2	40.0%

C/T		C/C		T/T	
Count	**%**	**Count**	**%**	**Count**	**%**
0	0.0%	0	0.0%	5	100%

DISCUSSION

The purpose of this investigation was to evaluate and characterize C1q rs631090 polymorphism in a group of Egyptian kids with jSLE and to investigate the relationship between this polymorphism, phenotypes, and damage index. The DNA from our study subjects was genotyped for rs631090 (c.187+267T>C). Few studies included analysis of the same single nucleotide polymorphism (SNP), and none studied the characteristics of different genotypes of the gene C1q rs631090. Among these studies are the work of **Wang *et al.*** [12], showing that C1q rs631090 was associated with systemic lupus erythematosus only in the homozygous and recessive model.

The overall presence of gene mutation C/C or C/T was more frequent among patients than control, although not statistically significant; possibly related to the small sample size, but the homogenous gene mutation C/C was higher in juvenile lupus patients than in control group as well as the C allelic frequency. This came in agreement to what was stated by **Yu *et al.*** [13] where gene polymorphisms of the C1q gene (rs292001, rs631090, rs294223 loci) were analyzed in adult SLE patients from Chinese population. The frequency of the T allele at the rs631090 locus in the investigation group was lower than that in the controls. These findings indicate that the C allele at the rs631090 locus of C1q is susceptibility variants associated with SLE.

The homozygous group C/C showed a younger mean age at first presentation of 7.72±3.64 years compared to the heterozygous group C/T and the non-mutant group. The finding was in agreement with the results of **Al-Mayouf *et al.*** [14] investigating juvenile Saudi Arabian SLE patients with C1q deficiency

No difference in gender predominance was detected between different genotypes which is in concordance with the results of the investigation of **Al-Mayouf *et al.*** [14].

Patients in the homozygous group C/C had lower incidence of lupus nephritis than the other groups (55.6%) –although not statistically significant- the relatively less frequent lupus nephritis in patients with homozygous mutation may be explained by the C1q deficiency, which together with C3 and C4 are important for lupus nephritis. Our results were in concordance with the results of the investigation of **Radanova *et al.*** [5] studying Bulgarian patients with lupus nephritis for five C1q SNPs including rs631090, with lower incidence of lupus nephritis in patients having C/C genotype compared to C/T and T/T, and a T allele being more related to lupus nephritis than C allele.

Hematological manifestations: there was no not statistically significant difference in the form of thrombocytopenia. Vasculitis in patients with C/C mutations was statistically significantly higher than reported in other groups (44.4%), and was the main cause of high disease activity in these patients. This difference may be related to the presence of hypocomplementemia. Urticarial vasculitis syndrome as described in **Buck *et al.*** [15] and **Alharbi and Sanchez-Guerrero** [16] by that urticarial vasculitis is frequently idiopathic, it has been reported to be associated with connective tissue diseases such as systemic lupus erythematosus (SLE). In general, urticarial vasculitis can be divided into 2 groups, those with normal complement levels and those with hypocomplementic urticarial vasculitis (HUV). The hypocomplementemic form more often is associated with systemic symptoms and has been linked to connective-tissue disease such as SLE.

The skin manifestation were more frequent in the C/C group, although not statistically significant, which is in agreemnt with the results of **Al-Mayouf *et al.*** [14] and explained in the study of **Ekinci and Ozturk** [11] that binding of C1q to apoptotic debris accelerating the removal of auto antigens and immune complexes may be a possible cause of this finding. The primary reason for the skin symptoms in cases with C1q deficiency is the excessive death of keratinocytes due to sun exposure, along with a reduced ability to remove the resulting debris.

None of the patients with antiphospholipid syndrome showed the homozygous mutation C/C while 83.3% of which were homozygous wild T/T. This may be related to the role of complement system as a key factor in both vascular and obstetric antiphospholipid syndrome as described by **Tedesco *et al.*** [1]**.** In 2011, C1q rs631090 has been studied by **Zakharyan *et al.*** [17] to investigate any association with schizophrenia and no significant associations were found. This agreed with the study results of our work with no difference in expression of psychosis or cognitive impairment between the different genotypes neither in activity scoring nor as an item of damage assessment.

Damage index was lower in the homozygous group C/C, although not statistically significant and no mortality was reported in this group. The difference was due to a 5-year-old patient who was later proved by sequencing genome to have autosomal recessive C1q deficiency. Case reports by **Lubbers *et al.*** [6] and **Zoghi *et al.*** [18] described patients with similar presentations including recurrent infections.

The present study was conducted during COVID 19 pandemic, with a clear observation that a group of documented SLE patients clinically, laboratory and pathologically had evidence of COVID19 infection before first diagnosis of childhood lupus.

This included 5 patients (7.5%) with the picture of constitutional manifestations, mainly fever, generalized bony aches followed by hematological manifestations in the form of hemolytic anemia and thrombocytopenia then renal involvement with results of renal biopsy showing 2 patient grade II (40%),1 patient grade III (20%), 2 patients grade IV (40%). Also it was of note that the mean total activity score in this group was significantly lower than the rest of the study group. Two cases (40%) carried the heterozygous mutation C/T and 3 patients (60%) had no mutation and none carried the homozygous mutation C/C. This came in agreement with the case report described by **Zamani *et al*. [(19)]**, reporting a patient who presented 2 month following COVID 19 infection by thrombocytopenia, skin rash, complement consumption, fever, and weight loss of 15 kg and proved to have SLE .

CONCLUSION

According to the data obtained from the current study we concluded that the presence of homozygous mutation C/C of the gene C1q rs631090 might be a good prognostic factor among juvenile SLE patients with milder disease complications mainly vasculitic manifestations and lower incidence of lupus nephritis. Some factors and presentations are associated with more aggressive illness course, and higher incidence of development of lupus nephritis, necessitating a more aggressive management approach, and others may be the reverse like the presence of (C/C) genotype.

LIMITATION OF THE STUDY

It is important to acknowledge that the sample size of this investigation is relatively small, and the results that have been reported require replication in a more large cohort.

Our study was held during the COVID19 pandemic which led to limitation of the number of patients and limitation in the number of face to face follow up visits for SLE patients, together with the high cost of conducting genetic testing, both factors contributed to the small sample size. But the value of the investigation is being a pilot study for genetic susceptibility factors in pediatric patients with early onset lupus conducted in Egyptian children with high incidence and aggressive behavior of childhood lupus.

DECLARATIONS

- **Funding:** No fund
- **Availability of data and material:** Available.
- **Conflicts of interest:** No conflicts of interest.
- **Competing interests:** None.

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