ORIGINAL ARTICLE

Altered Serum Levels of Mir-130b-3p & Mir-148a-3p in Egyptian Pediatric Patients with Juvenile Onset Systemic Lupus Erythematosus and Lupus Nephritis

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Key words:
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ABSTRACT

Background*: Juvenile onset systemic lupus erythematous (JSLE) and the accompanying lupus nephritis (LN) (affects up to 80% of JSLE) harbor more aggressive disease courses and major complications with higher morbidity and mortality risks compared to adult onset SLE. Two microRNAs (miRNAs), miR-130b-3p and miR-148a-3p, are strong candidates in the pathogenesis of both JSLE and LN.* ***Objective****: Studying serum expression of miR-130b-3p and miR-148a-3p patients with JSLE and LN to evaluate their contribution to their pathogenesis.* ***Methodology****: The study included 100 LN, 50 JSLE and 50 healthy controls (HC), reverse transcriptase real time quantitative PCR (RT-qPCR) was used for evaluation of serum levels of miR-130b-3p and miR-148a-3p.* ***Results****: miR-130b-3p showed decreased expression in JSLE and LN patients compared to HC and correlated inversely with serum creatinine within patients' groups. miR-148a-3p significantly decreased expression in JSLE patients compared to controls and LN patients. MiR-148a-3p was elevated in LN cases compared to JSLE but not HC showing inverse correlation with duration of LN and serum creatinine. Positive correlation between miR-130b-3p and miR-148a-3p was detected in diseased groups (r = 0.75, p = 0.001).* ***Conclusion:*** *Our study was the first to analyze both miR-130b-3p & miR-148a-3p expression in JSLE and LN and we concluded that both might affect the pathogenesis of JSLE and that miR-148a-3p may significantly contribute to the pathogenesis of LN among JSLE patients.*

INTRODUCTION

Juvenile onset systemic lupus erythematous (JSLE) is a chronic autoimmune inflammatory disease with multisystem affection, wide spectrum of clinical patterns and unpredictable prognosis[1]. JSLE begins before the age of 16 years and comprise 10–20% of cases. Children and adolescents generally are difficult to diagnose, present with a more severe illness than adults and acquire greater disease damage over time[2]. JSLE is characterized by autoantibody production, cytokine secretion, complement activation and immune complex deposition causing tissue and organ damage[3].

Lupus nephritis (LN) is one of the most severe clinical manifestations of JSLE, it presents more frequently, appears earlier and shows more aggressive course compared to adult onset of the disease[4]. Inefficient or delayed treatment of LN exhibits higher tendency to progress to advanced stages causing acute, chronic or eventually end stage renal disease[5].

MicroRNAs (miRNAs) are short noncoding RNAs that have been identified as a class of endogenous regulators of gene expression at the post transcriptional level. MiRNAs may play crucial roles in physiological and pathological conditions such as cytokine regulation, cell proliferation, differentiation and apoptosis, so they may mediate the pathogenesis of various diseases[6] including lupus[7] and lupus nephritis[8]. Previous studies revealed that altered expression miR-130b-3p[9] and miR-148a-3p[10] may play roles in SLE and associated LN in adult patients. However, none of these studies were carried on children known that miRNA expression is significantly influenced by age[11].

We aimed to study expression of serum miR-130b-3p and miR-148a-3p in children and adolescence with JSLE and LN to evaluate their possible contribution in pathogenesis of the diseases.

METHODOLOGY

Patients:

We enrolled the following participants in our case control pilot study:

LN group: One hundred JSLE patients having LN, diagnosed and classified according to European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) Classification Criteria for SLE with LN in addition to biopsy dating within the past 6 months[12].

JSLE group: Fifty JSLE patients fulfilling EULAR/ACR Classification Criteria for SLE with no evidence LN[12].

Healthy control (HC) group: Fifty Age and sex matched healthy volunteers.

Participants were excluded in case of presence of infection, any autoimmune family history or any acute or chronic disease.

Patients were selected during periodic follow up at Abu El-Rish Children Hospital-Pediatric Rheumatology clinic, Cairo University. HC volunteers were recruited from healthy children coming for regular checkup at the Outpatients' Clinics of the National Research Centre (NRC)- Centre of excellency and from Abu El-Rish Children Hospital. The investigations were done at the NRC.

Ethical consideration:

Declaration of Helsinki in 2015 approved World Medical Association code of ethics was the reference to this study and approval of ethical Committee of National Research Centre Cairo, Egypt (number 16288) was obtained by the researchers.

Parents of the participants signed an informed written consent prior to participation.

Clinical history and physical examination

Medical history of all participants was taken in addition to their clinical examination.

Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2k) [13] was used to assess the disease activity. LN activity was assessed using renal SLEDAI[14].

Laboratory investigations:

Sample collection:

Venous blood samples were withdrawn into plain vacutainers under complete aseptic conditions. Serum was separated and immediately 200 µl were added to 1000 µl QIAzol Lysis Reagent then stored in aliquots at -80°C until further miRNA processing and the rest of the serum was used for routine labs. Urinary samples were collected to measure albumin/creatinine ratio (ACR).

Routine laboratory assays:

Creatinine in serum and urine and urinary albumin were assayed by AU400 Beckman Chemistry analyzer (Beckman Coulter, Inc., USA). Complement C3 and C4 assays were done using MININEPH ZK023.R and ZK025.R kits, respectively (Binding Site Group Ltd., Birmingham, UK) on MininephPlus Analyzer endpoint nephelometry.

Determination of serum miR-130b-3p and miR-148a-3p expression:

We used miRNeasy Mini Kit (cat. no. 217004, Qiagen, Hilden, Germany) for miRNA extraction then checked the quantity and quality of extracted miRNA by spectrophotometer NanoDrop 2000 (Thermo Fisher Scientific, Massachusetts, USA). We used miScript II RT Kit (cat. No. 218161 Qiagen, Hilden, Germany to convert 10 ng of total miRNA to complementary DNA (cDNA) by T-100 thermal cycler (Bio-Rad, California, USA). Reverse transcrptase real time quantitative PCR (RT-qPCR) for miR-130b-3p (ID:MS00003451), miR-148a-3p (ID:MS00003556) and RNU6 (housekeeping gene) (ID:MS MS00033740) expression profiling was done using specific miRNA primers (cat. No. 218300 Qiagen, Hilden, Germany) and miScript SYBR Green PCR Kit (cat. No. 218073 Qiagen, Hilden, Germany). Reaction mix per sample per primer was as follows; SYBR Green PCR Master Mix 12.5 µl, primer assay 2.5 µl, miScript Universal Primer 2.5 µ, of RNase-free water 2.5 µl and 1 ng cDNA. Q-PCR. The thermal protocol was 95ºC for 15 minutes (initial activation phase), followed by 40 cycles of 15 seconds at 94ºC (denaturing), 30 seconds at 55ºC (annealing) and 30 seconds at 70ºC (expansion). Florescence collection was at the expansion process. The QPCR process was carried by Rotor-Gene Q real time PCR system (Qiagen, Hilden, Germany), Rotor-Gene Q programmed software was used to analyze the final product and $2^{-\Delta\Delta Ct}$ equation was used for calculations. Validity of Q-PCR results were confirmed by the melting curves and to ensure accuracy and reliability, randomly selected samples were duplicated[15].

Statistical methods:

Analysis of data was performed using SPSS version 21 software for Windows. Qualitative data was presented as frequencies and quantitative data was presented as mean and standard deviation (SD). Nonparametric distributed data such as relative miR-130b-3p and miR-148a-3p expression were presented as median and interquartile range (IQR). One-Way ANOVA analysis was used for multiple group comparisons. Pearson's correlation coefficient was used for correlating miRNA expression with other quantitative parameters. A p-value of < 0.05 was considered statistically significant.

RESULTS

The current study included three groups: 100 LN patients, 50 JSLE patients without LN and 50 age and sex matched HC, general characteristics and laboratory variables of the studied population are presented in table (1) with no significant difference concerning age and sex of the participants.

Table 1: General characteristics and laboratory variables of the three studied groups

Characteristics	LN (no. = 100)	JSLE (no. = 50)	HC (no. = 50)	p value
Age (years) *	11.9 ± 2.7	11.0 ± 3.1	11.1 ± 2.6	0.1
Male:Female ratio	1:5	1:6	1:5	0.8
JSLE duration (years) *	3 ± 2.1	2.6 ± 1.3	-	0.1 (LN and JSLE)
SLEDAI-2K score *	6.3±6	2.1±1.2	-	0.001(LN and JSLE)
LN duration (years) *	2.5 ± 1.9	-	-	-
Renal SLEDAI score *	4.6±4.8	-	-	-
Creatinine (mg/dl) *	0.7±0.5	0.4 ± 0.1	0.4±0.9	0.001(LN and other groups)
ACR (mg/g)*	386± 433	16±6.9	4.6 ±7.4	0.001(LN and other groups)
C3 (mg/dl) *	47±44.7	100±43.9	-	0.001(LN and JSLE)
C4 (mg/dl) *	14.5±17.8	41.7±46.8	-	0.001(LN and JSLE)

*Values are expressed as mean ± SD.
JSLE: Juvenile Systemic Lupus Erythematosus; LN: Lupus nephritis; HC: healthy control; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; ACR: Albumin/creatinine ratio; C: Complement component.

Table 2 shows that relative expression of serum miR-130b-3p significantly decreased in LN and JSLE compared to HC group (p=0.001), while no significant difference appeared in the relative expression between LN and JSLE groups.

Relative expression of serum miR-148a-3p shows decreased expression in LN patients and JSLE patients compared to controls, while further elevated expression was detected in LN patients compared to SLE patients (Table 2).

Table 2: Relative expression of serum miR-130b-3p and miR-148a-3p in three studied groups

Parameter	LN (no. = 100)	JSLE (no. = 50)	HC (no. = 50)	p value
miR-130b-3p	0.52 (0.15-0.7)	0.55(0.25-1.1)	0.85 (0.64-1.5)	0.1(LN and JSLE) 0.001(LN and HC) 0.001(JSLE and HC)
miR-148a-3p	0.9 (0.46-2.5)	0.65 (0.28-1.8)	1.4 (0.94-2)	0.03 (LN and JSLE) 0.18 (LN and HC) 0.006(JSLE and HC)

Data presented in the form of median (interquartile range).
LN: Lupus nephritis; JSLE: Juvenile Systemic Lupus Erythematosus; HC: healthy control.

Our results show strong positive correlation between miR-130b-3p and miR-148a-3p in diseased groups (LN and JSLE) (r=0.75, p=0.001).

When we compared the studied miRNAs with clinical and laboratory parameters of the patients' (LN and JSLE) groups, miR-130b-3p 3p showed inverse correlation with serum creatinine while miR-148a-3p showed inverse correlation with JSLE duration, both miRNAs did not show any correlation with age of onset, ACR, C3, C4, SLEDAI-2k (Table 3).

Table 3: Correlation of serum miR-130b-3p and miR-148a-3p with clinical and laboratory data in the diseased group (LN+JSLE)

Parameter	miR-130b-3p (r)	miR-130b-3p (P)	miR-148a-3p (r)	miR-148a-3p (P)
Age of JSLE onset	0.1	0.07	0.06	0.3
Disease duration	-0.1	0.06	-0.1	0.02
SLEDAI-2K score	0.02	0.7	0.01	0.7
ACR	-0.24	0.73	0.04	0.5
Creatinine	-0.1	0.01	-0.12	0.08
C3	0.1	0.13	-0.004	0.9
C4	0.05	0.48	-0.03	0.6

r: Pearson's correlation coefficient.
LN: Lupus nephritis; JSLE: Juvenile Systemic Lupus Erythematosus; HC: healthy control; ACR: Albumin/creatinine ratio; C: Complement component; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

Since miR-148a-3p showed significant increased expression in LN compared to JSLE patients we tried to find correlation between its levels and renal parameters in LN group and it revealed significant negative correlation with serum creatinine and significant negative correlation with renal disease duration but not with ACR, C3, C4 or renal SLEDAI (Table 4).

Table 4: Correlation of serum miR-148a-3p with renal parameters in LN patients

Parameter	miR-148a-3p (r)	miR-148a-3p (P)
LN duration	-0.27	0.006
Renal SLEDAI score	0.01	0.9
ACR	0.09	0.3
Creatinine	-0.2	0.01
C3	0.1	0.2
C4	-0.03	0.7

r: Pearson's correlation coefficient.
LN: Lupus nephritis; JSLE: Juvenile Systemic Lupus Erythematosus; HC: healthy control; ACR: Albumin/creatinine ratio; C: Complement component; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

DISCUSSION

JSLE is an autoimmune mediated chronic systemic inflammatory disease. Pathogenesis of the disease is unclear and multifactorial with environmental, genetic and epigenetic factors interacting together to generating immune dysfunction. JSLE is tougher than adult onset SLE with increased rate of morbidity and mortality as a result of earlier and more aggressive organ damage in addition to increased disease activity[16]. LN affects up to 80% of JSLE and it is the most fatal complication that repeatedly leads to end-stage renal disease and death[17]. Early diagnosis and proper intervention affect the course of JSLE and LN drastically[18]. Variation of clinical picture and eventually pathophysiology between juvenile and adult onsets of the disease is raising an urgent need to study the underlying causes from the juvenile onset perspective with targeting new biomarkers and specific pathways for early diagnosis and targeted treatment[16].

MicroRNAs are nominated as possible pathogenic, diagnostic, prognostic and therapeutic targets in various diseases including malignancy, cardiac, neurological and inflammatory[19]. To the best of our knowledge there is no enough information about the role of microRNAs in the pathogenesis of JSLE and associated LN.

Our main goal from this work was to study expression of serum miR-130b-3p and miR-148a-3p and to demonstrate their possible contribution in the pathogenesis of JSLE and LN in Egyptian children and adolescent patients.

MiR-130b-3p anti-inflammatory role was approved by several studies for example in vascular inflammation[20,21] and in sepsis[22].

In the current study miR-130b-3p showed decreased expression in JSLE and LN patients compared to control group. Underexpression of miR-130b in diseased groups can be explained by weakening of its role as a negative regulator of type I interferon (IFN) signaling through controlling IFN regulatory factor 1[9], leading to increase in Type I IFN. Type I IFN is a critical inflammatory mediator and a key player in JSLE pathogenesis and contributes to high disease activity in JSLE[23] and its role has been also implicated in LN pathogenesis[24]. Our results were also backed up by Han et al.,[9] which found similar results but with renal tissue examination, miR-130b-3p was underexpressed in renal tissues of LN patients and mice with aberrant activation of type I IFN pathway. In vivo application of miR-130b-3p to the renal tissue led to attenuation of type I IFN pathway LN damage, rendering miR-130b-3p a possible novel therapeutic agent for LN. MiR-130b-3p showed inverse correlation with serum creatinine when the two diseased groups were added together this result was similar that of Wang et al.,[25] who found that miR-130b-3p inversely correlates with duration and other parameters of renal affection. Similar to our results miR-130b-3p did not correlate with SLEDAI, the same research group contradicted our results as concerning their serum levels which were upregulated in both SLE and LN, the same for Al-Hasso et al.,[15] who found miR-130b-3p to be increased but non-significantly in SLE patients.

This research revealed significantly decreased expression of miR-148a-3p in JSLE patients compared to controls and LN patients. MiR-148a-3p was elevated in LN cases compared to JSLE but not HC and inversely correlated with duration of LN and serum creatinine.

MiR-148a-3p is a regulator of inflammatory genes expression and its role is contradictory and not totally understood, it either ameliorates or attenuates inflammatory pathways. Concerning our JSLE patients the decrease of miR-148a-3p might have

resulted in uncontrolled inflammatory state through failure in silencing of proinflammatory cytokines like IL-1b, IL-6 and TNF-a[26] or failure in activation of IL-10[27]. Our LN results suggest that dysregulation of miR-148a-3p expression plays an important role in pathogenesis of early stages of LN in children and adolescents. The early elevation of miR-148a-3p noticed in both serum and renal tissue promotes renal tissue damage by down regulating cell survival genes and like phosphatase and tensin homolog (PTEN). Downregulation of PTEN enhances activation of the PI3K/AKT signaling pathway leading to mesangial cells proliferation which is the main pathology of LN. This behavior of miR-148a-3p in LN might render it an early biomarker of the disease and a possible therapeutic target as well[28].

Concerning the significant negative correlation of MiR-148a-3p with duration in LN patients in addition to miR-130b-3p negative correlation with serum creatinine in the diseased groups which can be explained by Neal et al.[29] who stated that significant decrease of circulating miRNAs accompanies renal failure compared to normal and early stages of renal impairment possibly due to increase of RNAses with deterioration of kidney functions.

We found strong positive correlation between serum miR-130b-3p and miR-148a-3p in diseased groups confirming their role in the disease and raising the possibility of concomitant roles.

CONCLUSION

This was the first study to analyze both miR-130b-3p and miR-148a-3p in JSLE and LN and we concluded that both might affect the pathogenesis of JSLE and that miR-148a-3p may significantly contribute in pathogenesis of LN among JSLE patients. Further research is needed to confirm their role as potential biomarkers and therapeutic targets of the studied diseases.

Conflict of interests:
Authors declare no conflict of interest
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