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RESEARCH

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Potential use of microRNA-590 biomarkers verses plasma calcitonin gene-related peptide for diagnosis of migraine

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Abstract

Background Many biomarkers have been investigated for migraine diagnosis, giving insights into the pathophysiology of migraine, treatment response, and for the development of new treatment strategies. Over the years, many substances, for example, neurotransmitters, neuropeptides, glio transmitters, and hormones, have been suggested as possible biomarkers for migraine. The literature demonstrates that miRNAs may play a role in migraine. The aim of this study was to compare serum mi RNA and calcitonin gene-related peptide in Migraineurs. 43 Migraineurs and 43 age and sex-matched controls were included in the study serum miRNA 590 of Migraineurs and controls were assessed by high content serum miRNA arrays. miRNA was compared to serum calcitonin gene-related peptide in both groups. Expression of miRNA-590 in serum is detected by real time PCR (q-PCR) Measurement of serum CGRP by ELISA (enzyme-linked immunosorbent assay) technique.

Results 43 patients (86% females) mean age was 35.56 ± 9.45 and 43 controls (93% females) mean age was37.26 ± 9.15 which were age and sex matched with no statistically significant difference regarding age and sex (fisher extract) FE $p = 0.483$, $p = 0.400$, respectively. Regarding the level of miR-590-5p among patients and controls, Table 1 shows that miR-590-5p was significantly higher among cases (mean = 5.90 ± 21.22) than among controls mean = 3.32 ± 5.73 and $*p = 0.027$ reading the level of CGRP among patients and controls Table 2 shows that CGRP was significantly higher among cases (mean = 172 ± 110) than among controls mean = 66.43 ± 8.89 and $*p \leq 0.001$. Regarding the relation between migraine type with miR-590-5p and CGRP among cases miR-590-5p had a higher mean among cases with episodic migraine mean = 11.58 ± 32.40 in comparison with chronic migraine mean = 1.81 ± 1.68 and this was statistically significant $*p = 0.013$.

Conclusions MicroRNA-590 can be used as a biomarker of migraine and has a comparable result to CGRP.

Keywords Migraine, Headache, micro-RNA, CGRP

Background

Migraine has been included among the top ten cause of disability [1].

The diagnosis of migraine is based upon the classification of headaches by the International Headache Society (3rd edition of the International Classification of Headache Disorders [ICHD-3]) [2] .

Many biomarkers have been investigated for migraine diagnosis, giving insights into the pathophysiology of migraine, treatment response, and for the development of new treatment strategies. Over the years, many

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Table 1 Comparison between the two studied groups according to miR-590-5p and CGRP

	Cases (*n* = 43)	Control (*n* = 43)	U	*P*
miR-590-5p				
Mean ± SD	5.90 ± 21.22	3.32 ± 5.73	669.0*	0.027*
Median (Min.–Max.)	1.56 (0.25–140)	0.58 (0.06–22.32)		
CGRP				
Mean ± SD	172 ± 110	66.43 ± 8.89	0.0*	< 0.001*
Median (Min.–Max.)	148 (99.5–813)	63.0 (54.1–82.4)		

SD: Standard deviation; *U*: Mann Whitney test; *p*: *p* value for comparing between the two studied groups

*Statistically significant at p ≤ 0.05

Table 2 Distribution of the studied cases according to different parameters in cases group (*n* = 43)

	n. (%)
Migraine type	
Chronic	25 (58.1%)
Episodic	18 (41.9%)
Chronic illness	13 (30.2%)
Type of illness (*n* = 13)	
Diabetes	2 (15.4%)
Hypertension	3 (23.1%)
Cholesterol	2 (15.4%)
Thyroid	3 (23.1%)
Polyarthralgia	1 (7.7%)
Osteo Malacia	1 (7.7%)
Facial palsy	1 (7.7%)
Drugs	
Abortive	29 (67.4%)
Prophylactic	26 (60.5%)
Topiramate	21 (48.8%)
Tryptizol	10 (23.3%)
Ketolac	8 (18.6%)
Oral contraceptives	4 (9.3%)
Triptan	18 (41.9%)
Inderal	3 (7%)
Compliance	20 (46.5%)
Status migrainosis	11 (25.6%)
Duration of migraine (years)	
Mean ± SD	8.81 ± 7.81
Median (Min.–Max.)	6 (1–30)
Number of headache /months	
Mean ± SD	15.86 ± 10.54
Median (Min.–Max.)	15 (1–30)
Severity of migraine	
Mean ± SD	8.26 ± 1.33
Median (Min.–Max.)	8 (5–10)

substances, for example, neurotransmitters, neuropeptides, glio transmitters, and hormones, have been suggested as possible biomarkers for migraine [3].

The literature demonstrates that miRNAs play a role in migraine [4].

RNA molecules that do not code for proteins control the expression of genes. MiRNAs are a large class of non-coding RNA molecules that have been the subject of much research in recent years. Through their formation of RNA-induced silencing complexes, miRNAs contribute significantly to post-transcriptional gene control by lowering the levels of mRNA. miRNAs seem to have a role in pain signaling as well: patients with fibromyalgia and complicated regional pain syndrome have all been shown to have dysregulated miRNAs [5].

The plasma CGRP level can differentiate migraine from non-migraine headache. It may also serve as a reference for the therapeutic strategy [6].

CGRP levels are valuable peripheral indicators of migraine because they are linked to the expression of several miRNAs in plasma. It is possible that CGRP plays an epigenetically controlled basic function in the transmission of inflammatory pain [7].

Several clinical pharmacological studies also support the notion that CGRP plays a causative role in migraine. First, intravenous infusion of CGRP produces a migraine-like headache in volunteers [8]. Second, a CGRP receptor antagonist, olcegepant (BIBN4096BS), is effective in treating acute migraine attacks [9] and anti-CGRP or anti-CGRP receptor monoclonal antibodies are approved for migraine prevention [10, 11].

MiR-590-5p, a density-sensitive microRNA, has been shown to prevent tumorigenesis in colorectal cancer [12]; in addition, miR-590-5p has the power to inhibit the inflammatory molecular transmission cascades [13, 14].

Furthermore, alterations in miRNA expression patterns may control neuroinflammation, nerve regeneration, and aberrant ion channel expression, contributing to the etiology of both inflammatory and also neuropathic pain [15] The aim of this study is to compare serum mi RNA and calcitonin gene-related peptide in Migraineurs.

Methods

43 Migraineurs and 43 age and sex-matched controls were included in the study serum miRNA 590 of Migraineurs and controls was assessed by high content serum miRNA arrays. miRNA was compared to serum calcitonin gene-related peptide in both groups.

The diagnosis of migraine is based upon the classification of headaches by the International Headache Society (3rd edition of the International Classification of Headache Disorders (ICHD-3).

Any history of any tumor was an exclusion criteria.

Expression of miRNA-590 in serum is detected by real time PCR (q-PCR).

Measurement of serum CGRP by ELISA (enzyme-linked immunosorbent assay) technique.

Ethical approval was obtained from the University ethical committee (EC) which operates according to the International Conference of Harmonization Good Clinical Practice (ICH GCP) and applicable local and institutional regulations and guidelines [16].

A written informed consent was obtained from all subjects prior to recruitment to the study.

Results

Regarding the sociodemographic data, Table 3 shows that we studied 43 patients (86% females) mean age was 35.56 ± 9.45 and 43 controls (93% females) mean age was37.26 ± 9.15 which were age and sex matched with no statistically significant difference regarding age and sex(fisher extract) FEp = 0.483, $p = 0.400$, respectively.

There was no statistically significant difference regarding weight and height, mean weight among cases was 81.36 ± 15.05 kg, while among controls was 83.35 ± 11.88 kg. mean height among cases was 166 ± 6.56 cm, while among controls was 164 ± 8.63 cm, $P = 0.498$, $p = 0.510$, respectively.

Regarding the clinical characteristics of the patients, 58.1% of cases were classified as chronic migraine, while 41.9% were episodic.

30.2% of patients suffered from chronic illnesses.

67.4% of patients were treated with abortive medication, while 60.5% were on prophylactic medication.

Mean duration of migraine was 8.81 ± 7.81 years, while the severity of migraine using visual analogue score was 8.26 ± 1.33.

Regarding the level of miR-590-5p among patients and controls, Table 1 shows that miR-590-5p was significantly higher among cases (mean = 5.90 ± 21.22) than among controls mean = 3.32 ± 5.73 and $^{*}p = 0.027$.

Regarding the level of CGRP among patients and controls, Table 2 shows that CGRP was significantly higher among cases (mean = 172 ± 110) than among controls mean = 66.43 ± 8.89 and $^{*}p \leq 0.001$

Regarding the relation between migraine type with miR-590-5p and CGRP among cases miR-590-5p had a higher mean among cases with episodic migraine mean = 11.58 ± 32.40 in comparison with chronic migraine mean = 1.81 ± 1.68 and this was statistically significant, $^{*}p = 0.013$.

In addition, CGRP was higher among episodic migraine mean = 192 ± 157 than chronic migraine mean = 158 ± 56.42, yet this was not statistically significant $p = 0.15$ (see Table 4).

Table 3 Comparison between the two studied groups according to different parameter

	Cases (*n* = 43)	Control (*n* = 43)	*P*
Gender			
Male	6 (14%)	3 (7%)	$^{FE}p = 0.483$
Female	37 (86%)	40 (93%)	
Age (years)			
Mean ± SD	35.56 ± 9.45	37.26 ± 9.15	0.400
Median (Min.–Max.)	37 (16–61)	40 (18–51)	
Residence			
Alexandria	39 (90.7%)	39 (90.7%)	$^{FE}p = 1.000$
Rural	4 (9.3%)	4 (9.3%)	
Marital status			
Single	6 (14%)	6 (14%)	$^{MC}p = 1.000$
Married	36 (83.7%)	37 (86%)	
Divorced	1 (23%)	0 (0%)	
Education			
High school	10 (23.3%)	6 (14%)	0.598
Collage	21 (48.8%)	21 (48.8%)	
Can read	8 (18.6%)	9 (20.9%)	
Illiterate	4 (9.3%)	7 (16.3%)	
Employment	18 (41.9%)	21 (48.8%)	0.516
Smoking	6 (14%)	12 (27.9%)	0.122
Weight (kg)			
Mean ± SD	81.36 ± 15.05	83.35 ± 11.88	0.498
Median (Min.–Max.)	80 (58–125)	84 (65–100)	
Height (cm^2)			
Mean ± SD	166 ± 6.56	164 ± 8.63	0.510
Median (Min.–Max.)	166 (146–183)	165 (146–183)	

SD: Standard deviation; t: Student t-test; U: Mann Whitney test; χ^2: Chi square test; MC: Monte Carlo; FE: Fisher Exact; *p*: *p* value for comparing between the two studied groups

Table 4 Relation between migraine type with miR-590-5p and CGRP in cases group (*n* = 43)

	Migraine type		U	*P*
	Chronic (*n* = 25)	Episodic (*n* = 18)		
miR-590-5p				
Mean ± SD	1.81 ± 1.68	11.58 ± 32.40	124.5*	0.013*
Median (Min.–Max.)	0.87 (0.25–6.0)	2.69 (0.50–140)		
CGRP				
Mean ± SD	158 ± 56.42	192 ± 157	167.5	0.157
Median (Min.–Max.)	142 (124–418)	160 (99.5–813)		

SD: Standard deviation; U: Mann Whitney test; *p*: *p* value for comparing between Chronic and Episodic

*Statistically significant at $p \leq 0.05$

Regarding the Correlation between miR-590-5p, CGRP and different parameters, Table 5 shows that as the number of attacks of headache increases, both miR-590-5p ($^{*}p \leq 0.001$) and CGRP increase ($^{*}p = 0.042$), and this was statistically significant.

Discussion

In the current study, we aimed to identify new factors that can aid in diagnosis and might be targets for treatment in migraine. We aimed to identify the relation between migraine and CGRP and micro-RNA590, if it had a potential relation to acute and chronic migraine.

The current study showed that micro-RNA 590 had a positive correlation with migraine headache and correlated positively with number of headache attacks.

Long acknowledged for their worth and significance, viable biomarkers for migraine have been proposed in a variety of forms, including biological samples, electrophysiological patterns, and brain imaging.

The ability to objectively test migraine biomarkers can help with diagnosis, deepen our understanding of its pathophysiology, and increase the effectiveness of therapy.

However, to the best of our knowledge, scarce studies in literature studied micro-RNA in relation to migraine headache.

A short-chain noncoding RNA molecule called microRNA (miRNA) is (about 22 nucleotides in length). It controls the translation of the target gene's protein from a specific mRNA by inhibiting complete base pairing [17].

Gallelli and colleagues [4] in 2017 mentioned that miR-590-5p was found to be altered in migraine patients. This micro-RNA, in mice, is modulated by celecoxib, while in human is dysregulated in the complex regional pain syndrome, condition where migraine assumes a risk factor for its development.

For a clinical perspective, miR-590-5p can have an interesting double meaning. It can be used as a biomarker for all types of pain, including migraines, as well to gauge how well a pharmacological treatment is working. In the juvenile group, where disease diagnosis and monitoring might be difficult, this may be relevant [18].

Table 5 C or relation between miR-590-5p, CGRP and different parameters in cases group ($n = 43$)

	miR-590-5p		CGRP	
	r_s	P	r_s	*p*
Duration of migraine (years)	− 0.154	0.324	− 0.076	0.626
Number of headache/months	0.534	< 0.001*	0.311	0.042*
Severity of migraine	0.046	0.772	− 0.158	0.310

r_s: Spearman coefficient; *Statistically significant at $p \leq 0.05$

In 2015 a study by Reham and colleagues, in a mouse model, showed that miR-590-5p,represents miRNAs that were drastically upregulated only in the mice treated with celecoxib alone [19].

This is contrary to our results which show that micro RNA 590 correlated positively with severity and frequency of headache.

In a recent study by Wen Q and colleagues in 2021, this study was performed on mice and found upregulated miR-155-5p in the TNC (trigeminal nucleus caudalis) participates in the central sensitization of chronic migraine [20].

Small sample size was a limitation to our study, also we were not to specify if micro-RNA was upregulated due to migraine or due to pain medication, so further studies are needed to compare drug naïve and patients under treatment.

Conclusion

MicroRNA-590 can be used as a biomarker of migraine and has a comparable result to CGRP.

Abbreviations

RNA	Ribonucleic acid
ICHD-3	3rd edition of the International Classification of Headache Disorders
ELISA	Enzyme-linked immunosorbent assay
PCR	Polymerase chain reaction
CGRP	Calcitonin gene-related peptide
TNC	Trigeminal nucleus caudalis

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Author contributions

HME: idea of the research revision of the manuscript. RAS: micro RNA and ELISA were performed by her. DEG: Revision of the results and the manuscript and the corresponding author. All authors have read and approved the manuscript.

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Availability of data and materials

The research data supporting the results reported in the article is totally available upon request from the corresponding author.

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from the Ethics Committee (EC) of Faculty of Medicine which is constituted and operates according to the International Conference on Harmonisation-Good Clinical Practice ICH GCP guidelines (Food and Drug Administration guideline) and applicable local and institutional regulations and guidelines which govern EC operation. IRB NO 0304988.

Informed consent

A written informed consent was obtained from all subjects prior to recruitment to the study. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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