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Correlation between serum levels of fibroblast growth factor-21 and the severity of migraine headache in patients undergoing sodium valproate treatment

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Hamed Cheraghmakani[1], Mehrdad Afzalinezhad[2], Monireh Ghazaeian[2,3], Parham Mortazavi[2], Narges Karimi[1], Sahar Fallah[4]

[1] Department of Neurology, School of Medicine, Mazandaran University of Medical Sciences, Sari, Iran
[2] Department of Clinical Pharmacy, School of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran
[3] Pharmaceutical Sciences Research Center, Mazandaran University of Medical Sciences, Sari, Iran
[4] Department of Biostatistics, School of Health, Mazandaran University of Medical Sciences, Sari, Iran

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Biomarkers; Mitochondria; Headache; Efficacy; Safety

Abstract

Background: Mitochondrial metabolism disruption increases neuron excitability and reduces migraine attack threshold. This study investigates whether serum fibroblast growth factor-21 (FGF-21) levels in chronic migraine relate to headache severity and response to sodium valproate treatment.

Methods: This pilot study involved 30 patients with chronic migraine treated with sodium valproate. Serum FGF-21 levels were assessed at baseline and after 12 weeks of treatment. Pain severity and disability were evaluated using visual analogue scale (VAS) and Migraine Disability Assessment (MIDAS). Paired t-test was used for the quantitative variables. The qualitative variables were evaluated using Pearson's chi-square test and Fisher's exact test. Moreover, correlation coefficients were calculated. A $P < 0.05$ was considered statistically significant.

Results: Mean age of the patients was 42.9 ± 11.3 years. There was a significant reduction in headache severity between baseline and the end of the study regarding VAS scores (8.50 ± 1.50 vs. 5.30 ± 2.20, $P < 0.001$). The same reduction was observed in MIDAS during the study (61.20 ± 33.20 vs. 20.31 ± 17.07, $P < 0.001$). However, there was no significant changes in serum levels of FGF-21 over three months (299.53 ± 479.80 vs. 491.33 ± 456.64, $P = 0.810$), nor any relationship between these levels and headache severity scores (MIDAS: $P = 0.658$, VAS: $P = 0.708$).

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Corresponding Author: Monireh Ghazaeian
Email: ghazaeianm@gmail.com

Conclusion: The results of this study did not show a significant correlation between FGF-21 serum levels and changes in VAS and MIDAS throughout the study. Further research on various mitochondrial pathways can provide valuable insights into the migraine pathophysiology and help identify more effective biomarkers for monitoring therapeutic regimens.

Introduction

Migraine is the sixth most significant cause of disability in individuals.[1] It ranks among the top ten global causes of years lived with disability (YLDs)[2] that are widely underdiagnosed and undertreated.[3]

This neurobiological condition is characterized by a heightened sensitivity of the brain, which is thought to have a genetic origin.[4,5] However, the exact mechanism behind this hyperexcitability is unclear. Regarding the pathophysiology of migraine, there is some evidence that metabolic variations can initiate pain-signaling in the trigeminovascular system. Moreover, genetic mutations of metabolic enzymes in both mitochondrial and nuclear loci play an important role in the severity and disability of migraine.[6-8] Several clinical trials have shown that agents such as riboflavin,[9] coenzyme-Q10,[10] and L-carnitine[11] that affect metabolic pathways could have beneficial effects on migraine.

Fibroblast growth factor-21 (FGF-21) is a circulating hormone (hepatokine) generated by the liver that has beneficial effects on glucose and lipid metabolism in mice. FGF-21 is also expressed in adipocytes and the pancreas. It controls glucose and lipid metabolism in various tissues and the brain via pleiotropic effects.[12] This hormone is also a potential biomarker of mitochondrial disorders and its increased serum levels can be indicative of metabolic dysfunction.[13]

There is evidence suggesting that mitochondrial dysfunction and impaired metabolic mechanisms may be associated with triggers for migraine attacks.[14] As a result of alterations in mitochondrial and metabolic pathways, the levels of oxidative stress biomarkers begin to rise.[15] Among these biomarkers is FGF-21, the secretion of which is influenced by mitochondrial oxidative stress.[16] Additionally, it is important to note that clinical evidence indicates serum levels of FGF-21 are influenced by various conditions, such as diabetes, ketogenic type, obesity, physical activity, hypertension (HTN), liver disease, and autoimmune diseases.[17] With regards to the potential involvement of mitochondria in the pathophysiology of migraine, it is reasonable to consider that the levels of biomarkers associated with metabolic dysfunction may undergo changes following the administration of therapeutic regimens targeting mitochondrial pathways in patients with chronic migraine. We hypothesize that if the therapeutic agents prove to be efficacious, there will be a decrease in the serum levels of FGF-21 that corresponds appropriately with the clinical response.

Valproic acid (VPA) alters the activity of the neurotransmitter gamma-aminobutyrate (GABA) in the human brain by potentially increasing its inhibitory activity through a variety of mechanisms: inhibition of GABA degradation, inhibition of GABA transaminobutyrate [4-aminobutyrate aminotransferase (ABAT)], increased GABA synthesis, and decreased turnover.[18] Additionally, VPA inhibits N-methyl-D-aspartate (NMDA)-mediated excitation, Na+ and Ca2+ channels (voltage-dependent L type CACNA1 types C, D, N, and F), and voltage-gated sodium channels (SCN).[15] Apart from its anticonvulsant and mood-stabilizing properties, VPA is effective in treating migraine headaches, clinical depression, schizophrenia, and absence seizures.[19-21] Previous experience in bipolar mood disorder has demonstrated that higher serum levels of FGF-21 are associated with resistance to mood stabilizing effects of sodium valproate and increased rate of metabolic side effects.[22]

Considering the mentioned data, the aim of this study was, first, to evaluate the serum levels of FGF-21 in patients with chronic migraine who were treated with sodium valproate and, second, to determine any relationship between headache improvement and changes in FGF-21 serum levels.

Materials and Methods

Study setting: This pilot study was performed on patients with chronic migraine who had referred to the neurology clinic of Ibne Sina Hospital in Sari City, Iran, between October 2019 and March 2021. This research was approved by the Institutional Review Board and the Ethics Committee of Mazandaran University of Medical Sciences, Sari (IR.MAZUMS.REC.1399.034) and was registered in the Iranian Registry of Clinical Trials (IRCT20190804044429N3).

Patient population: The recruited patients were 18 to 60 years old and had recently been diagnosed with chronic migraine (with or without

aura) based on the International Classification of Headache Disorders, 3rd Edition-Beta[3] Version (ICHD-3β) and were candidate for sodium valproate prophylaxis treatment. The exclusion criteria were headache other than chronic migraine, pregnancy, lactation, liver and kidney disease, cardiovascular disease (CVD), diabetes, and concomitant use of other prophylactic drugs.

Study intervention and outcome measurement: Sodium valproate was administered (500-1000 mg daily) for migraine prophylaxis. Demographic characteristics of patients and the results of related laboratory tests were recorded. Fasting levels of FGF-21 were measured at the beginning of the study before initiation of sodium valproate and at the end of the 12th week. FGF-21 was measured by enzyme-linked immunosorbent assay (ELISA) method (Human FGF-21 ELISA Kit, Eastbiopharm Co., Ltd., China) at the same time (i.e., in the morning while fasting) for all recruited patients.

In addition to recording the side effects of the prescribed drugs during the study period, we assessed their effectiveness in improving migraine symptoms 4 and 12 weeks after treatment. The severity of the patient's disability due to headache was also assessed based on the Migraine Disability Assessment (MIDAS) questionnaire, and the patient's pain intensity was measured with visual analogue scale (VAS). The questionnaires were filled out before treatment and three months after treatment.

At first, the Kolmogorov-Smirnov test was done to check the distribution status of data. Then we reported the quantitative variables as mean [standard deviation (SD)] in accordance with their normal or non-normal distribution, respectively. Qualitative variables were presented as frequency and percentage. Paired t-test was used for comparing the quantitative variables. On the other hand, the qualitative variables were evaluated using Pearson's chi-square test and Fisher's exact test; P-values were calculated when needed. Moreover, Pearson or Spearman correlation coefficient was used to evaluate the association between variables. All analyses were performed in SPSS software (version 22, IBM Corporation, Armonk, NY, USA), and $P < 0.05$ was considered statistically significant.

Following the results of the study by Shakiba et al.,[23] the effects of sodium valproate on migraine headache duration, at least 25 patients were calculated based on G*Power software. Finally, we considered 30 patients assuming attrition rate of 20%.

Results

A total of 84 patients were evaluated for their eligibility to participate in the study. Of this population, 54 patients were excluded due to coronavirus disease 2019 (COVID-19) conditions and non-acceptance of study protocol. At the end of the study (week 12), 30 patients had completed clinical data and the FGF-21 test (Figure 1). Baseline demographics and routine laboratory tests were recorded. In case of body mass index (BMI), as a possible confounding factor, despite significant increase from baseline to the end of the study, there was no statistically significant correlation between FGF-21 serum levels and BMI (Table 1).

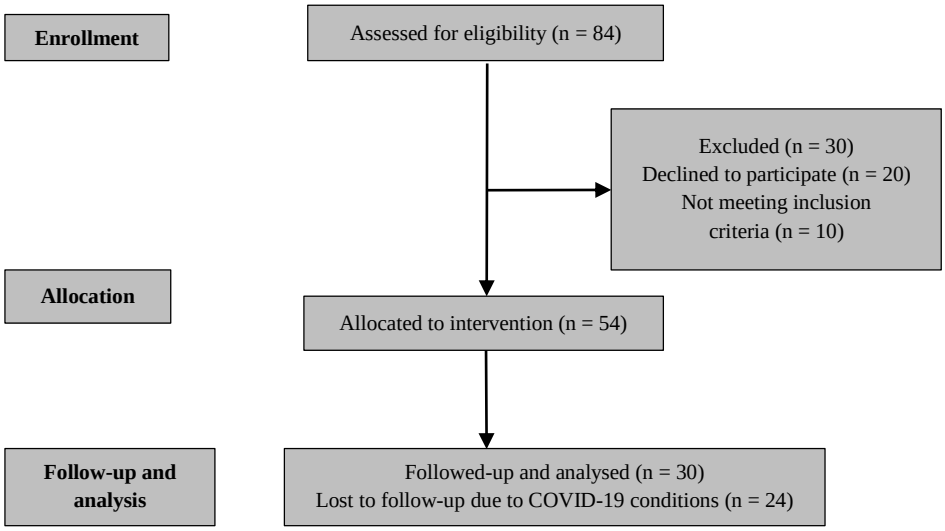

Figure 1. Study flowchart

Table 1. Demographic and laboratory data of patients during the study period

Variable	Baseline	Week 12	P
Age (year)	42.90 ± 11.30	-	-
Sex	Women: 25 (83.3) Men: 5 (16.7)	-	-
BMI (kg/m^2)	27.30 ± 4.10	27.70 ± 4.30	0.016
PLT (per micro-liter)	273111.10 ± 66519.00	255074.07 ± 65695.00	0.003
WBC (per micro-liter)	5702.89 ± 2730.69	6027.19 ± 2600.10	0.632
TSH (pg/ml)	3.10 ± 1.80	4.60 ± 1.30	0.601
Free T4 (pg/ml)	5.20 ± 4.30	5.20 ± 4.50	0.970
ALT (IU/l)	20.33 ± 7.92	21.74 ± 8.16	0.392
AST (IU/l)	17.37 ± 4.57	18.00 ± 3.68	0.471
Total bilirubin (mg/dl)	0.64 ± 0.25	0.66 ± 0.21	0.563
Direct bilirubin (mg/dl)	0.21 ± 0.07	0.22 ± 0.06	0.801
FBS (mg/dl)	95.11 ± 20.70	96.66 ± 13.78	0.651
LDL-C (mg/dl)	112.70 ± 29.46	109.22 ± 31.00	0.582
Triglyceride (mg/dl)	140.00 ± 52.80	144.74 ± 53.22	0.601
Total cholesterol (mg/dl)	192.11 ± 34.30	187.52 ± 29.49	0.401

Data are presented as mean ± standard deviation (SD) or number (percent)
BMI: Body mass index; PLT: Platelet; WBC: White blood cell; TSH: Thyroid-stimulating hormone; Free T4: Free thyroxine; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; FBS: Fasting blood sugar; LDL-C: Low-density lipoprotein cholesterol

Although there were significant differences in platelet count during the study, the differences were not clinically significant (both levels were in normal range). The clinical and laboratory findings during the study period are presented in table 1.

Compared with the baseline, the mean score of MIDAS in patients decreased significantly at the end of the study (61.20 ± 33.20 vs. 20.31 ± 17.07, P < 0.001) (Table 2). A similar reduction was also observed for VAS from baseline until the end of the study (8.50 ± 1.50 vs. 5.30 ± 2.20, P < 0.001) (Table 2). Regarding serum FGF-21 levels, there was no significant change between baseline and after 3 months of treatment with sodium valproate (P = 0.810) (Table 2).

Table 2. Serum fibroblast growth factor-21 (FGF-21) levels, Migraine Disability Assessment (MIDAS), and visual analogue scale (VAS) before and after twelve weeks of sodium valproate therapy

Variable	Baseline	Week 12	P
FGF-21	299.53 ± 479.80	491.30 ± 456.60	0.810
MIDAS	61.20 ± 33.20	20.30 ± 17.07	< 0.001
VAS	8.50 ± 1.50	5.30 ± 2.20	< 0.001

Data are presented as mean ± standard deviation (SD)
FGF-21: Fibroblast growth factor-21; MIDAS: Migraine Disability Assessment; VAS: Visual analogue scale

The correlation between serum FGF-21 level and headache severity was investigated according to VAS and MIDAS scores before and after sodium valproate intake, and the results did not show any statistically significant link (Table 3).

Table 3. Fibroblast growth factor-21 (FGF-21) serum level correlation with headache severity scores and body mass index (BMI)

Variables	Coefficient of correlation	P
FGF-21 MIDAS	-0.015	0.940
FGF-21 VAS	-0.153	0.437
FGF-21 BMI	0.207	0.291

FGF-21: Fibroblast growth factor-21; MIDAS: Migraine Disability Assessment; VAS: Visual analogue scale; BMI: Body mass index

Moreover, the relationship between the changes seen in serum levels of FGF-21 and headache severity scores during the study periods was not significant (Table 4).

Table 4. The correlation between the amount of changes in fibroblast growth factor-21 (FGF-21) serum level and headache severity scores during the study period

Variables	Coefficient of correlation	P
FGF-21 (baseline) MIDAS (baseline)	-0.280	0.801
FGF-21 (baseline) VAS (baseline)	-0.114	0.302
FGF-21 (week 12) MIDAS (week 12)	-0.790	0.658
FGF-21 (week 12) VAS (week 12)	-0.074	0.708

FGF-21: Fibroblast growth factor-21; MIDAS: Migraine Disability Assessment; VAS: Visual analogue scale

Discussion

The main goal of our study was to investigate whether serum levels of FGF-21, as one of the mitochondrial dysfunction biomarkers, were related to the severity of migraine headache and therapeutic response to sodium valproate. The results of our study showed that the improvement in MIDAS and VAS during the study-though confirmed the clinical response to sodium valproate – was not correlated with. Furthermore, the baseline serum levels of FGF-21 in patients with chronic migraine who were candidate to receive prophylaxis treatment were not different from those people without migraine.

Burow et al. investigated the possible role of mitochondrial dysfunction in migraine pathophysiology. They conducted a cross-sectional study on 230 patients with episodic and chronic migraine and measured FGF-21 and growth-differentiation factor-15 (GDF-15) to find any correlation with headache frequency. The results indicated neither biomarkers had any correlation with migraine occurrence. Moreover, they found the link between FGF-21 and increased BMI as a confounding factor.[24] Similar to our study, changes in serum FGF-21 levels were not associated with headache severity in the migraine group. It should be noted that the biomarkers in the study by Burow et al. were not measured simultaneously or in a fasting state, which may have affected the reported levels. Nevertheless, the main point of both studies is that other underlying factors with metabolic and inflammatory nature might contribute to serum levels of FGF-21, but they could not be controlled in either study.

In another case-control study, Mozafarihashjin et al. evaluated the serum levels of biomarkers such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), and prostaglandin E2 (PGE2) in patients with episodic and chronic migraine. From 89 recruited subjects, 23 patients with episodic and 36 patients with chronic migraine were compared with the control group. The results showed the serum levels of these biomarkers in migraine groups were significantly different with the control group, and some biomarkers such as NGF and PGE2 were correlated with headache frequency.[25] Although the nature of the measured biomarkers varied from our study, both studies highlight the important effects of various biomarkers in migraine pathogenesis and future therapeutic pathways.

Similar reports on other biomarkers associated with oxidative stress and mitochondrial function have found energy pathway abnormalities in patients with frequent migraine.[26,27] However, there are only a few therapeutic agents that work well with metabolic pathways in migraine.

In a recent study conducted by He et al., an investigation was carried out to assess the association between FGF-21 and GDF-15 and migraine. The study involved the collection of serum levels of biomarkers from a total of 221 patients with migraine, comprising both chronic and episodic types, as well as a healthy control group. The findings of the study revealed a significant correlation between the severity of migraine disability and headache scores and elevated serum levels of FGF-21 and GDF-15.[28] Despite the positive correlation revealed by the findings, it is important to note that the sampling was carried out without considering the headache status of the patients and the type of medicine they would use for headache relief. Furthermore, it is crucial to differentiate between episodic and chronic migraine in terms of physiopathology, as this distinction has an impact on the clarification of serum levels.

Our study had some limitations. The small sample size did not let us make more definite conclusions about the correlation of specific mitochondrial effects and the severity of migraine symptoms. Furthermore, it was not possible to control the effects of all confounding factors on serum levels of the biomarkers in question. Insufficient control over confounding factors, such as dietary patterns and physical activity, poses challenges in accurately interpreting the results on FGF-21 serum levels. Moreover, our investigation solely concentrated on a single biomarker within the mitochondrial pathway, which may have an influence on the pathophysiology of chronic migraine. Consequently, the obtained results are insufficient to establish a conclusive link between mitochondrial mechanisms and chronic migraine.

However, to the best of our knowledge, this study represents a novel attempt to assess the relationship between FGF-21 serum levels and patients suffering from chronic migraine. The study's strengths lie in its strict patient selection criteria, focusing solely on individuals with chronic migraine headaches. Additionally, the sampling of FGF-21 serum levels was conducted during a consistent fasting period, enhancing the reliability of the results. Furthermore, the study

specifically examined the effects of sodium valproate, a therapeutic agent known to have potential metabolic mechanisms, further adding to its strength.

Conclusion

The results of our study showed that serum levels of FGF-21 in patients with migraine did not have any significant relationship with headache severity and therapeutic response to or tolerability of sodium valproate in these individuals. Further studies with larger sample sizes can be more helpful in determining the key role of mitochondrial pathways in migraine pathophysiology and discovering more specific biomarkers.

Conflict of Interests

The authors declare no conflict of interest in this study.

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