ORIGINAL ARTICLE

Assessment of Serum Human GADD45A and Peripheral Nerves Examinations in Fibromyalgia Patients

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Abstract

Background: ***Fibromyalgia is a disorder defined by chronic, widespread musculoskeletal pain.***

Aim: ***To evaluate serum GADD45A levels in fibromyalgia patients, evaluate peripheral nerves through nerve conduction and neuro-ultrasound, and investigate if there is a correlation between serum GADD45A levels and clinical parameters.***

Subjects and methods: ***The present research involved fifty cases of fibromyalgia (FM) in the Rheumatology and Rehabilitation and Psychiatric departments of Al Zahraa University Hospital.***

Results: ***Serum GADD45A level can be used for assessment of fibromyalgia syndrome in the studied patients at a cut-off>1.812 (AUC =0.819 and P value<0.001) with 90.00% sensitivity, 66.00% Specificity, 72.6 %PPV, and 86.8 % NPV.Nerve cross-sectional area can be used for assessment of fibromyalgia syndrome in the studied patients at a cut-off>3.3 mm2 (AUC =0.718 and P value<0.001) with 100.00% Specificity, 40.00% sensitivity, 62.5% NPV, and 100.0% PPV. A positive correlation was discovered among Serum GADD45A level and (PDQ, FIQ, and Nerve cross-sectional area). A correlation was discovered between Serum GADD45A level and (Age, BMI, and disease duration) in the studied Case group. The nerve conduction study showed statistically significant differences between the two groups. Nerve cross-sectional area was significantly greater in the case group compared to the control group (P value<0.001). 25(50%) patients had neuropathy in the studied case group.***

Conclusion: ***Clinical examination, ultrasound, and serum GADD45A levels are crucial for identifying and assessing fibromyalgia, with sural nerve CSA being the optimal cut-off for neuropathic pain features.***

Keywords: FM; GADD45A; Fibromyalgia Syndrome

1. Introduction

Fibromyalgia (FM) is a condition defined by chronic, widespread musculoskeletal pain, potentially accompanied by muscle or joint stiffness, as well as additional symptoms including exhaustion, depression, anxiety, and sleep disturbances.[1]

The fibromyalgia condition is defined by a complex of symptoms, which identify it as FM according to several diagnostic criteria given in the past few years .[2]

This pain amplification disorder significantly affects society by reducing work productivity, increasing disability and injury compensation claims, and leading to the overuse of healthcare resources .[3]

Pathophysiological pathways, including central nervous system sensitization, were reported. Magnetic resonance imaging investigations have demonstrated a loss in gray matter volume in areas associated with pain processing, along with changes in descending pathways of pain modulation and functional connectivity .[4]

Th aim of this study was assessment of serum GADD45A level in fibromyalgia patients, assessment of peripheral Cutaneous nerves by nerve conduction study and neuro-ultrasound in fibromyalgia patients and assessment if the correlation was discovered among serum GADD45A concentration and clinical parameters in fibromyalgia cases.

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2. Patients and methods

The present research involved fifty cases with fibromyalgia (FM) attending the Rheumatology and Rehabilitation and psychiatric departments of Al Zahraa University Hospital.

All studied case groups were divided into two subgroups: Group Ia (n=25) with a high score (>19), complaining of neuropathic pain. Group Ib (number= twenty-five): with a Low score (<12), absence of neuropathic pain. Control group (number =fifty) (II) Fifty age and gender, matched, apparently healthy. The fibromyalgia condition is defined by a complex of symptoms, which identify it as FM according to several diagnostic criteria given in the past few years 2. This pain amplification disorder significantly affects society by reducing work productivity, increasing disability and injury compensation claims, and leading to the overuse of healthcare resources 3. Pathophysiological pathways, including central nervous system sensitization, were reported. Magnetic resonance imaging investigations have demonstrated a loss in gray matter volume in areas associated with pain processing, along with changes in descending pathways of pain modulation and functional connectivity.

A control group was included for comparison.

Methods

All cases have been exposed to: Complete history taking, clinical investigation: General examination, musculoskeletal, neurological examination and diagnosis of fibromyalgia according to 2016 modified American College of Rheumatology Diagnostic Criteria for Fibromyalgia, assessment of fibromyalgia with: Widespread Pain Index (WPI), symptom Severity Scale (SSS), fibromyalgia Impact Questionnaire (FIQ): The FIQR had twenty-one numerical rating scales, each with eleven points, assessing three health domains: nine items for physical function, ten for symptoms, and two for overall impact, over the preceding 7 days. The final score ranged from zero to one hundred, with elevated values indicating greater intensity of symptoms and pain as assessed by the questionnaire. The PDQ involved describing a patient's pain pattern, irradiation, and characteristic symptoms of neuropathic pain. The final score ranged from -1 to 38, indicating the probability of neuropathic pain. Scores between -1 and 18 are considered ambiguous, electrophysiological studies: Neurophysiological testing involved subject comfort, alcohol rubbing, and recording using Nihon Kohden Neuropak EMG apparatus at 25°C, recording at a fixed room temperature, musculoskeletal ultrasound: All subjects were examined using a 7-11 MHz linear phased array transducer (Xario200, Toshiba ultrasound machine, Tochigi, Japan),routine laboratory investigations including CBC, ESR, CRP and specific laboratory included serum GADD45A level ,it used the kits for serum GADD45A ELISA Kit (BT LAB Bioassay Technology Laboratory Cat No 1525Hu) and analysed by sandwich ELISA Detection technique and sural nerve sensory conduction study: The sensory nerve action potential (SNAP) peak to peak amplitude and latency were determined by placing the stimulating electrode over the calf, recording electrode 14 cm apart, and ground electrode above the ankle ,the sensory nerve action potential (SNAP) was defined as abnormal when it was absent unilaterally, prolonged peak latency, decreased SNAP amplitudes or if the involved/healthy side amplitude ratio was <50%, uultrasonographic assessment: Sural nerve CSA has been examined at calf level, 14 cm proximal to the lateral malleolus apex. Identified on ultrasound examination, it was a small structure near the small saphenous vein. Measurement of CSA at this level was used in protocols for polyneuropathies during vasculitis. Sural nerve CSA was measured unilaterally and considered the final mean of three measurements.

Ethical consideration

The research exposed to be accepted by the medical ethics and committee of faculty of Medicine for Girls Al Azhar University. Full counselling about the procedure, purpose and importance of the test were fully explained to all participants prior to be investigated and an informed consent was obtained.

Statistical analysis

Statistical analysis has been conducted using SPSS version 26 (IBM Inc., Chicago, IL, USA). Quantitative data were expressed as mean and standard deviation (SD) and compared between the two groups using an unpaired Student's t-test. Qualitative variables have been expressed as frequency and percentage (%) and evaluated using the Chi-square test or Fisher's exact test, as applicable. The correlation among several factors was assessed utilizing the Pearson coefficient. A receiver operating characteristic curve (ROC curve) analysis was utilized to diagnose fibromyalgia syndrome in the analyzed groups and assess neuropathy in the examined case group. A two-tailed P value less than 0.05 was deemed statistically significant. The research utilized an independent-samples t-test, Chi-square test, Fisher's exact test, Pearson's correlation coefficient, scatter plot, ROC curve analysis, and a 95% confidence interval with a 5% margin of error to compare two means, evaluate the correlation among parameters, and identify the optimal cut-off value.

3. Results

Table 1 showed that age was statistically insignificantly in Case group than Control group. Sex and BMI were statistically significant variant among both groups.

Table 1. Demonstration of demographic data of the studied groups

		CASE GROUP (NUMBER=FIFTY)	CONTROL GROUP (NUMBER=FIFTY)
AGE (YEARS)	Mean ± SD	45.94 (±7.919)	39.62 (±6.99)
	Range	30-59	28-55
SEX	Male	4(8%)	5(10%)
	Female	46(92%)	45(90%)
BMI(KG/M^2)	Mean ± SD	33.58 (±5.71)	34.12 (±4.73)
	Range	24-45	27-42

BMI: Boy mass index

Table 2 showed that, PDQ, FIQ and nerve cross-sectional area were statistically significant higher in cases with neuropathy compared to cases without neuropathy (P-value<0.001).

Table 2. Relation among neuropathy and disease clinical parameters PDQ and FIQ

		IA(NUMBER=TWENTY-FIVE)	IB (NUMBER=TWENTY-FIVE)	P VALUE
PDQ	Mean ± SD	24.16 (±4.78)	7.04 (±3.02)	<0.001*
	Range	19-37	2-12	
FIQ	Mean ± SD	53.16 (±12.46)	39.16 (±5.89)	<0.001*
	Range	38-77	28-50	

*: Significant as P value <0.05, PDQ: Pain detects questionnaire, FIQ: Fibromyalgia impact questionnaire.

Table 3 showed that, nerve conduction study was statistically insignificant different between both groups. Nerve cross-sectional area was significantly greater in Case group compared to Control group (P value<0.001). 25(50%) patients had neuropathy in the studied Case group.

Table 3. Assessment of peripheral cutaneous nerve of the examined groups

		CASE GROUP (NUMBER=FIFTY)	CONTROL GROUP (NUMBER=FIFTY)	P VALUE
NERVE CONDUCTION STUDY	Normal	40(80%)	44(88%)	0.290
	Abnormal	2(4%)	0(0%)	
	Lost	8(16%)	6(12%)	
NERVE CROSS-SECTIONAL AREA (MM^2)	Mean ± SD	3.47 (±1.35)	2.49 (±0.44)	<0.001*
	Range	1.8-7.2	1.7-3.3	
NEUROPATHY	Yes	25 (50%)	----	-----

Table 4 showed that ,according to sural sensory nerve conduction in patient group, the mean peak latency was 2.06±0.80 ms (range: 1.2-4.2 ms), and only 6% of them showed prolonged peak latency, while control showed a mean of 1.92±0.64 ms (range: 1.1-4 ms) with insignificant variance (P-value >0.05).The mean amplitude in patients' group was 15.06± 4.17 mv (range: 8-26.5 mv). 6% of them showed decreased amplitude, while controls showed a mean of 15.84±4.06 mv (range: 8.5-27 mv) with insignificant variance among the two groups (P-value >0.05),

Table 4. Comparison between patients and controls regarding Sural sensory nerve conduction study.

SURAL SENSORY		PATIENT GROUP (NUMBER=FIFTY)	CONTROL GROUP (NUMBER=FIFTY)	TEST VALUE	P-VALUE
LATENCY (MS)	Mean±SD	2.06±0.80	1.92±0.64	1.933	0.054
	Range	1.2-4.2	1.1-4		
	Affected	3 (6%)	0 (0.0%)	1.343	0.246
	Normal	47 (94%)	50 (100.0%)		
AMPLITUDE (μV)	Mean±SD	15.06±4.17	15.84±4.06	1.895	0.059
	Range	8-26.5	8.5-27		
	Affected	3 (6%)	0 (0.0%)	1.343	0.246
	Normal	47(94%)	50 (100.0%)		

Using: t-Independent Sample t-test for Mean±SD;

p-value >0.05 is insignificant; *p-value <0.05 is significant;

**p-value <0.001 is highly significant

Table 5 showed that ,serum GADD45A level can be used for assessment fibromyalgia syndrome in the studied patients at cut off >1.812 (AUC =0.819 and P value<0.001) with 90.00% sensitivity, 66.00% Specificity, 72.6 %PPV and 86.8 % NPV.Nerve cross sectional area can be used for assessment of fibromyalgia syndrome in the studied patients at cut off >3.3 mm2 (AUC =0.718 and P value<0.001) with 100.00% Specificity, 40.00% sensitivity, 62.5% NPV and 100.0% PPV.

Table 5. Role of serum GADD45A level and nerve cross sectional area for diagnosis of fibromyalgia syndrome of all the studied patients

VARIABLES	CUT OFF	SENSITIVITY	SPECIFICITY	PPV	NPV	AUC	P VALUE
SERUM GADD45A LEVEL	>1.812	90.00%	66.00%	72.6 %	86.8 %	0.819	<0.001*
NERVE CROSS SECTIONAL AREA (MM^2)	>3.3	40.00%	100.00%	100.0%	62.5%	0.718	<0.001*

*: Significant as P value <0.05, NPV: Negative predictive value, PPV: Positive predictive value, AUC: Area under the curve

Table 6 showed that, a positive association was discovered among Serum GADD45A level and (PDQ, FIQ and Nerve cross-sectional area). A no correlation was discovered between Serum GADD45A level and (Age, BMI and disease duration) in the studied Case group.

Table 6. Correlation among serum GADD45A level and other variables of the examined case group

	SERUM GADD45A LEVEL	
	r	P value
AGE (YEARS)	0.096	0.509
BMI (KILOGRAMME PER METER SQUARE)	0.164	0.255
DISEASE DURATION (YEARS)	0.052	0.722
PDQ	0.569	<0.001*
FIQ	0.536	<0.001*
NERVE CROSS-SECTIONAL AREA (MM^2)	0.497	<0.001*

*: Significant as P value <0.05, r: Pearson coefficient, BMI: Body mass index, PDQ: Pain detects questionnaire, FIQ: Fibromyalgia impact questionnaire.

Table 7 showed that ,serum GADD45A level can be used for assessment of neuropathy in the studied case group at cut off >2.318 (AUC =0.815 and P value<0.001) with 84.00% sensitivity, 68.00% Specificity, 72.4% PPV and 81% NPV.Nerve cross sectional area can be used for assessment and prediction of neuropathy in the studied case group at cut off >3.1mm2 (AUC =0.950 and P value<0.001) with 88.00% sensitivity, 96.00% Specificity, 95.7% PPV and 88.9% NPV.

Table 7. Role of serum GADD45A level and nerve cross sectional area for diagnosis of neuropathy of the studied case group.

VARIABLES	CUT OFF	SENSITIVITY	SPECIFICITY	PPV	NPV	AUC	P VALUE
SERUM GADD45A LEVEL	>2.318	84.00%	68.00%	72.4%	81%	0.815	<0.001*
NERVE CROSS SECTIONAL AREA (MM^2)	>3.1	88.00%	96.00%	95.7%	88.9%	0.950	<0.001*

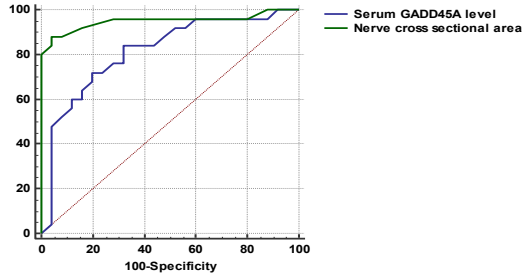

Figure 1. ROC curve of serum GADD45A level and nerve cross sectional area for diagnosis of neuropathy of the studied case group.

4. Discussion

Our study revealed a high prevalence of fibromyalgia in females. There were 46 (92%) females and 4 (8%) males, with an elevation of the severity value and impact on life, which was assessed by FIQ, while there was no significant difference from the healthy group according to other demographic data.

Ruschak et al.,[5] stated that the outcomes possess minimal statistical significance, and we believe it essential for increasing the male sample size in the research to facilitate a more comprehensive examination of these specificities.

In our study showed that, PDQ and FIQ were statistically significant higher in patients with neuropathy than patients without neuropathy.

Bennett et al.,[6] study expressed confidence in the utilization of the FIQ, as it evaluates the status, progress, and prognosis of cases and is a commonly utilized instrument in healthcare settings.

Our study showed that, according to the sural cross-sectional area by neuromuscular ultrasound, the mean was 3.47 (±1.35), ranging from 1.8 to 7.2 mm^2 in the case group. The nerve cross-sectional area was significantly greater in the Case group compared to the Control group, and was statistically significantly higher in patients with neuropathy compared to cases without neuropathy. Nerve cross sectional area can diagnose neuropathy in the studied case group at cut off >3.1mm.

Study done by Tsiami et al.,[7] stated the value of small fiber neuropathy in fibromyalgia, All cases underwent a detailed rheumatologic and neurologic physical examination and were requested to complete questionnaires assessing depression, pain, sleep quality, neuropathic symptoms, quality of life , and daytime sleepiness.

In our study showed, according to sural sensory nerve conduction in patient group, insignificant variance. The mean amplitude in patients' group with insignificant variance among the two groups in our results, also there is insignificant different between patients with neuropathy and patients without neuropathy.

Supporting by study done by GRAYSTON et al.,[8] Neuropathic pain characteristics may result from abnormalities in the somatosensory system of small nerve fibers, that are undetectable by routine clinical instrumental tests, including electrophysiological studies.

Salaff et al.,[9] When compared to clinical judgment in cases showing symptoms indicative of small fiber neuropathy , nerve conduction investigations generally yield normal results.

Our investigation indicated that tiny fiber pathology, as identified using skin biopsies and corneal confocal microscopy, was present in almost two-thirds of fibromyalgia cases, indicating the presence of subgroups.

Salaff et al.,[9] comparing them with clinical judgment. A sural nerve cross-sectional area of three mm^2 serves as the ideal threshold for identifying neuropathic pain characteristics suggestive of small fiber neuropathy, in comparison to clinical assessment.

Marshall et al.,[10] This investigation verifies the presence of SFN in a particular group of individuals with fibromyalgia. We further demonstrate that a selected group of individuals with fibromyalgia shows symptoms of small fiber neuropathy despite the absence of anatomical small fiber neuropathy. These cases have heightened mechanical pain sensitivity, as well as symptoms of depression and anxiety.

In our research, a positive correlation was discovered among Serum GADD45A level and (PDQ, FIQ, and Nerve cross-sectional area). No correlation among Serum GADD45A level and (Age, BMI, and disease duration) in the studied Case group.

In our study, serum GADD45A level was assessed and revealed that it is significantly higher in the Case group compared to the Control

group, and can diagnose fibromyalgia syndrome in the studied patients at a cut-off of>1.812, 90.00% sensitivity, and 66.00% Specificity. A positive correlation was discovered among Serum GADD45A level and (PDQ, FIQ, and Nerve cross-sectional area). Serum GADD45A level can diagnose neuropathy in the studied case group at a cut-off>2.318 with 84.00% sensitivity, 68.00% Specificity.

According to these findings, other investigations identified a significant elevation in GADD45A expression in human skeletal muscle samples from cases with traumatic nerve injury, with denervation periods varying from two to forty-eight months Bongers et al.,[11]

Plyusnina et al.,[12] studied the increase of Drosophila melanogaster lifespan attributed to D-GADD45 overexpression in the nervous system indicates that GADD45 overexpression likely enhances the recognition and repair of deoxyribonucleic acid damage, as evidenced by the deoxyribonucleic acid comet assay, which demonstrated a statistically significant reduction in spontaneous deoxyribonucleic acid damage in larva neuroblasts.

4. Conclusion

Clinical examination and exclusion of other causes of neuropathy are the main steps in the identification and assessment of fibromyalgia. Small fiber neuropathy can't be detected using standard instrumental assessments, including electrophysiological studies, in individuals with fibromyalgia. Ultrasound, an appropriately user-friendly technology, may detect morphological alterations in peripheral nerve systems in cases of fibromyalgia. A sural nerve cross-sectional area of three mm^2 is the best threshold for identifying neuropathic pain characteristics suggestive of small fiber neuropathy in cases with fibromyalgia. Serum GADD45A level can be a promising biomarker to predict and evaluate the neuropathy and neurocognitive symptoms in fibromyalgia.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

All authors have a substantial contribution to the article

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Conflicts of interest

There are no conflicts of interest.

References

1. Jurado-Priego LN, Cueto-Ureña C, Ramírez-Expósito MJ, Martínez-Martos JM. Fibromyalgia: A Review of the Pathophysiological Mechanisms and Multidisciplinary Treatment Strategies. Biomedicines. 2024 Jul 11;12(7):1543.
2. Salaffi F, Di Carlo M, Farah S, Atzeni F, Buskila D, Ablin JN, et al. Diagnosis of fibromyalgia: comparison of the 2011/2016 ACR and AAPT criteria and validation of the modified Fibromyalgia Assessment Status. Rheumatology (Oxford). 2020 Oct 1;59(10):3042-3049.
3. Grayston R, Czanner G, Elhadd K, Goebel A, Frank B, Üçeyler N, et al. A systematic review and meta-analysis of the prevalence of small fiber pathology in fibromyalgia: Implications for a new paradigm in fibromyalgia etiopathogenesis. Semin Arthritis Rheum. 2019 Apr;48(5):933-940.
4. Cagnie B, Coppieters I, Denecker S, Six J, Danneels L, Meeus M. Central sensitization in fibromyalgia? A systematic review on structural and functional brain MRI. Semin Arthritis Rheum. 2014 Aug;44(1):68-75
5. Ruschak I, Montesó-Curto P, Rosselló L, Aguilar Martín C, Sánchez-Montesó L, Toussaint L. Fibromyalgia Syndrome Pain in Men and Women: A Scoping Review. Healthcare (Basel). 2023 Jan 11;11(2):223.
6. Bennett RM. Clinical manifestations and diagnosis of fibromyalgia. Rheum Dis Clin North Am. 2009 May;35(2):215-32.
7. Tsiami S, Enax-Krumova E, Sturm D, Vorgerd M, Buehring B, Braun J, et al. POS0262 VALUE OF SMALL FIBER NEUROPATHY IN FIBROMYALGIA PATIENTS IN A RHEUMATOLOGICAL SETTING. doi.org/10.1136/annrheumdis-2023-eular.6381.
8. Grayston R, Czanner G, Elhadd K, Goebel A, Frank B, Üçeyler N, et al. A systematic review and meta-analysis of the prevalence of small fiber pathology in fibromyalgia: Implications for a new paradigm in fibromyalgia etiopathogenesis. Semin Arthritis Rheum. 2019 Apr;48(5):933-940.
9. Salaffi F, Di Carlo M, Farah S, Atzeni F, Buskila D, Ablin JN,et al. Diagnosis of fibromyalgia: comparison of the 2011/2016 ACR and AAPT criteria and validation of the modified Fibromyalgia Assessment Status. Rheumatology (Oxford). 2020 Oct 1;59(10):3042-3049.
10. Marshall A, Rapteas L, Burgess J, Riley D, Anson M, Matsumoto K, et al. Small fibre pathology, small fibre symptoms and pain in fibromyalgia syndrome. Sci Rep. 2024 Feb 16;14(1):3947.
11. Bongers KS, Fox DK, Ebert SM, Kunkel SD, Dyle MC, Bullard SA, et al. Skeletal muscle denervation causes skeletal muscle atrophy through a pathway that involves both Gadd45a and HDAC4. Am J Physiol Endocrinol Metab. 2013 Oct 1;305(7):E907-15.
12. Plyusnina EN, Shaposhnikov MV, Moskalev AA. Increase of Drosophila melanogaster lifespan due to D-GADD45 overexpression in the nervous system. Biogerontology. 2011 Jun;12(3):211-26.