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# SERUM MATRIX METALLOPROTEINASE-2 AS A BIOMARKER FOR DIAGNOSIS OF IDIOPATHIC EPILEPSY

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## ABSTRACT

**Background:** Epilepsy is a common serious neurological disorder. Medical histories and electroencephalogram (EEG) are not always sufficient for epilepsy diagnosis; therefore, exploring novel methods for the accurate diagnosis of epilepsy is of great importance. Recent studies indicate that Matrix metalloproteinases (MMPs) especially MMP-2 is sensitive to seizures thus; MMP-2 may be a potential biomarker for epilepsy diagnosis. **Subject and method**: Thirty four epileptic patients older than 2 years subjected to: Detailed medical history, general and neurological examination, routine laboratory studies, EEG , Brain magnetic resonance imaging (MRI), and serum MMP-2 level measurement . Thirty four age and sex matched healthy controls were selected and their serum MMP-2 were obtained. **Results:** serum MMP-2 levels were statistically significantly low in patient with idiopathic epilepsy compared to control group .Levels were less in patient with focal epilepsy than those with generalized epilepsy.Serum MMP-2 was lower in drug resistant epileptic patients and highest in newly diagnosed patients with negative correlation observed between duration of epilepsy and MMP-2 levels. Sensitivity of MMP-2 as biomarker was 85.29% with 97.06 % specificity. **Conclusion:** MMP-2 levels decreased in patients with epilepsy especially those with focal seizures. This tool may be a helpful diagnostic biomarker for epilepsy with a good sensitivity and specificity.

**Keywords:** Epilepsy biomarker, MMP-2. Matrix metalloproteinases.

## INTRODUCTION

Epilepsy is one of the most common serious neurological disorders which affects about 50 million people worldwide each year [1].with a prevalence of 5-10 cases per 1,000 [2]. The diagnosis of epilepsy is largely based on a patient's detailed, reliable medical history, and electroencephalogram (EEG) may help in the diagnosis. However, medical histories are not always sufficient, making diagnosis difficult in some cases. Therefore, exploring novel methods for the accurate diagnosis of epilepsy is of great importance [3]. Matrix metalloproteinases (MMPs) represent a family of zinc-dependent proteases with many substrates, including, cytokines, extracellular matrix components, receptors, and cell motility factors [4].

They are the main proteolytic enzyme group involved in remodeling the extracellular matrix and maintaining the integrity of cell membrane**.** They play an important role in regulating organ development including muscles and nerves, maintaining normal physiology in adulthood, and they also take part in repair after injury in the nervous system [5]. Based on function and structure, MMPs can be subdivided into 5 groups: **(i) collagenases** (MMPs 1,8 and 13); **(ii) gelatinases A and B** (MMPs 2 and 9); **(iii) stromelysins-1 and -2** (MMPs 3 and 10); (iv) **classical MMPs** (MMP-7,20,12) and19 .lastly **(v) membrane-type MMPs** (MTMMPs 1,3,4,and 11) [6].

The most commonly expressed MMPs in the brain are MMP-2 and MMP-9 [7].

Recently, advances have been made regarding the role of MMPs in both autoimmune and non-autoimmune neurological disorders including multiple sclerosis, myasthenia gravis, ischemic stroke, amyotrophic lateral sclerosis, migraine, Alzheimer dementia and epilepsy [8].

Metalloproteinases have been implicated in seizure-induced cell death, breakdown of the blood-brain barrier, neuroinflammation, and aberrant synaptic plasticity, all of which occur during epileptogenesis [9], also, MMP-2 is activated in the brain in the kainic acid rat seizure model. Thus, MMP-2 may be a potential diagnostic biomarker for epilepsy in human serum. Recent studies indicate that MMP-2 and 9 is generally sensitive to seizures [10] [11].

## AIM OF THIS WORK

we aimed to assess serum matrix metalloproteinase -2 (MMP-2) levels in patients with idiopathic epilepsy and evaluate its role as a biomarker for diagnosis of idiopathic epilepsy.

## SUBJECTS AND METHODS

This study was carried out on 34 epileptic patients as prospective case control study. Patients selected from neurology department inpatient and out patient at Zagazig University Hospitals during the period from September 2017 to April 2018 beside 34 healthy controls. **Inclusion criteria:** Patients older than 2 years and diagnosed with Idiopathic epilepsy. Epilepsy was diagnosed according to ILAE criteria 2010 [12].

**Exclusion criteria**

1. Seizures due to electrolyte disturbances, metabolic causes, drug intoxication, encephalitis, trauma.
2. History of any systemic autoimmune disease.
3. Active neurological disorder or structural brain lesion (e.g. arteriovenous malformation, brain tumors).
4. History of alcohol or substance abuse in the previous 12 months
5. Active co-morbid psychiatric illness or intake of any psychotropic medication in the previous 6 months
6. History of epilepsy surgery.
7. History of pseudo seizures.

All patients were asked about their, age at seizure onset, seizure frequency, seizures semiology, current and past anti epileptic drug (AED) use. Patient classified into three categories according to seizure frequency, treatment response. These categories were:

**(1)** Newly diagnosed epilepsy (NDE) (duration of less than 1 year)

**(2)** Non-drug-resistant (NDR) epilepsy (active or occasional seizures which, improved by treatment)

**(3)** Drug-resistant (DR) epilepsy which defined by failure of adequate trials of two tolerated, appropriately chosen and used in appropriate dose (whether as mono therapies or in combination) to achieve sustained seizure freedom that means seizure-free for more than one year, or has sporadic seizures separated by a period three times the longest interval between seizures prior to the treatment [13].

**Control group:** Thirty four healthy individuals (age and sex matched) with no history of epilepsy or other medical, neurological or psychiatric disorders.

**All patients and controls were subjected to the following:**

1. Written informed consent signed by the patient.
2. Full history taking according to epilepsy sheet which is consistent with the current guidelines of international league against epilepsy
3. Thorough general and neurological examination
4. Routine laboratory investigations; complete blood picture, liver and kidney function testes, blood glucose level, serum electrolytes and erythrocyte sedimentation rate.
5. **Electroencephalography (EEG):** Interictal EEG was done for 30 minutes at Neurology department, Zagazig University Hospitals using 18 channels digital EEG Nicolet Biomed alliance works. Electrodes were arranged according to the international 10-20 system of surface electrodes placement using mono and bipolar montages. It was carried out under standard conditions i.e. the patients were lying supine, completely relaxed in a quiet dark room. The EEG tracing were analyzed

carefully as regards the background activity, presence of any generalized or focal abnormalities, revised and reported by nNeurology department staff members.

6. **Magnetic resonance imaging of the brain:** was done at MR unit of Radiology Department of Faculty of Medicine, Zagazig University Hospitals using closed Atcheiva MRI scanner, Philips 1.5 tesla .MRI sequences at slice thickness 5mm first (using MR head coil) . Images were revised and reported by Radiology department staff members.
7. **Serum matrix metalloproteinase -2 (MMP-2) levels** will be assessed interictally. Five milliliters of blood was collected from the antecubital vein into vacutainer tubes without anticoagulants. Blood was incubated at room temperature for 30 min to clot before centrifugation for 15 minutes at 1000 cycle /min at Clinical pathology department , Zagazig university hospitals. Serum removed for assay immediately or stored at ≤ -20 °C. Assays were performed using RayBio® Human MMP-2 enzyme-linked immunosorbent assay for quantitative measurement of human MMP-2 in serum. Normal serum level of MMP-2 in serum is 81-151ng\ml [14].

## STATISTICAL ANALYSIS

All data were collected, tabulated and statistically analyzed using SPSS 22.0 for windows (SPSS Inc., Chicago, IL, USA) and MedCalc 13 for windows (MedCalc Software bvba, Ostend, Belgium). Continuous variables were expressed as the mean ± SD & median (range), and the categorical variables were expressed as a number (percentage). All tests were two sided. P-value < 0.05 was considered statistically significant (S), P-value < 0.001 was considered highly statistically significant (HS), and p-value > 0.05 was considered statistically insignificant (NS) [15].

## RESULTS

our study was conducted on 34 epileptic patients; their mean age was 15.23± 8.34 years, beside 34 controls with the mean age of 17.97±10.05 years. Patient group included 19 males (55.8 %) and 15 females (44.2 %) with 34 healthy controls of same number and male to female percentage. Age of onset of epilepsy in case group ranged between 3 to 22 years old with mean age of 9.38± 4.86 years; epilepsy duration ranged from 1 to 23 years. The most prevalent presentation of our patients was partial epilepsy 61.77% compared to 38.23% with generalized seizures. 38.2% of our patients are treated with two anti epileptic drugs while 5.9% were treated by four drugs, 35.2 % belong to Non drug resistant prognostic group while 32.4 % belong to newly diagnosed epilepsy group and drug resistant group respectively.

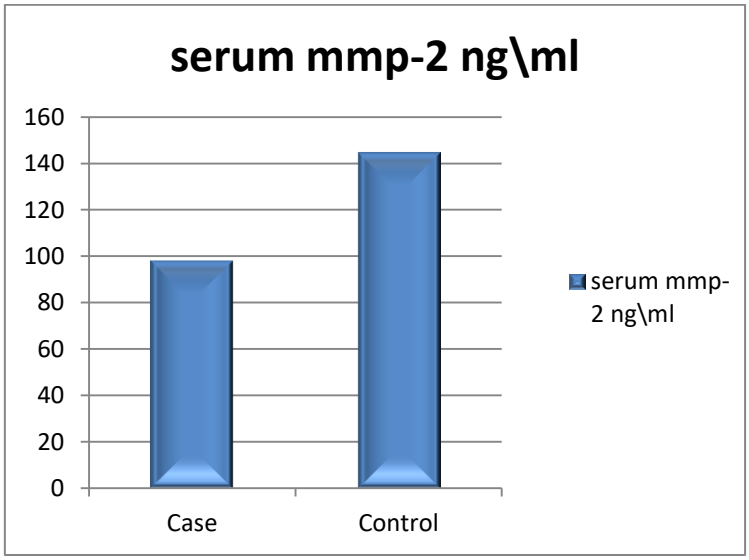


**Figure 1** Serum MMP2 in patient and control group

**Table 1** Serum MMP-2 level difference and gender in case and control groups.

| sex | Group | N | Mean± SD | Median | Minimum | Maximum | P value |
|---|---|---|---|---|---|---|---|
| **Males** | **Case** | 19 | 96.44 ±13.00 | 98.00 | 69.3 | 124 | <0.001 HS |
| | **Control** | 19 | 145.91±15.92 | 147 | 120.9 | 169.5 | |
| **Females** | **Case** | 15 | 105.63±24.48 | 100.80 | 79.6 | 135.8 | <0.001 HS |
| | **Control** | 15 | 143.66±17.93 | 139.5 | 114.2 | 177.5 | |

HS: highly significant

**Table 2** Serum MMP-2 level difference and age groups in case and control groups.

| sex | Group | N | Mean± SD | Median | Minimum | Maximum | P value |
|---|---|---|---|---|---|---|---|
| **≤ 20 years** | **Case** | 26 | 102.74 ± 26.50 | 98.40 | 69.30 | 128.20 | <0.001 HS |
| | **Control** | 25 | 147.50± 18.06 | 145.95 | 125.80 | 177.50 | |
| **>20 years** | **Case** | 8 | 99.11±13.43 | 98.0 | 77.50 | 135.80 | <0.001 HS |
| | **Control** | 9 | 137.83±31.36 | 140.85 | 114.9 | 170.6 | |

HS: highly significant

**Table 3** Serum MMP-2 level difference and gender in patients.

| | N | Mean± SD | Median | Minimum | Maximum | P value |
|---|---|---|---|---|---|---|
| Male | 19 | 96.44 ±13.00 | 98.00 | 69.3 | 124 | 0.499 NS |
| Female | 15 | 105.63±24.48 | 100.80 | 79.6 | 135.8 | |
| Total | 34 | 100.50±19.18 | 98.2 | 69.30 | 135.8 | |

NS: Non significant

**Table 4** Serum MMP-2 level difference and age group in patients.

| sex | N | Mean± SD | Median | Minimum | Maximum | P value |
|---|---|---|---|---|---|---|
| **≤ 20 years** | 26 | 102.74 ± 26.50 | 98.40 | 69.30 | 129.80 | 0.834 NS |
| **>20 years** | 8 | 99.11±13.43 | 98.0 | 77.50 | 135.80 | |
| Total | 34 | 100.50±19.18 | 98.2 | 69.30 | 135.8 | |

NS: Non significant

**Table 5** Serum MMP-2 levels and epilepsy type

| | N | Mean± SD | Median | Minimum | Maximum | P value |
|---|---|---|---|---|---|---|
| Focal | 13 | 79.54 ±19.12 | 82.70 | 69.30 | 101.10 | 0.003 S |
| Generalized | 21 | 100.2± 18.24 | 98.40 | 77.5 | 138.8 | |
| Total | 34 | 100.50±19.18 | 98.2 | 69.30 | 135.8 | |

S: significant

**Table 6** Serum MMP-2 level and anti-epileptic drugs number.

| | N | Mean± SD | Median | Minimum | Maximum | P value |
|---|---|---|---|---|---|---|
| One drug | 9 | 107.1± 22.94 | 105.24 | 97 | 138.8 | 0.12 NS |
| Two drugs | 13 | 96.90 ± 11.77 | 96.8 | 77.5 | 124 | |
| Three drugs | 10 | 92.65±17.37 | 88.25 | 69.3 | 130.8 | |
| Four drugs | 2 | 88.60±4.10 | 88.35 | 85.5 | 91.20 | |
| Total | 34 | 100.50±19.18 | 98.2 | 69.30 | 135.8 | |

NS: Non significant

**Table 7** Serum MMP-2 level and epilepsy prognostic category

| | N | **Mean± SD** | **Median** | **Minimum** | **Maximum** | **P value** |
|---|---|---|---|---|---|---|
| NDE | 11 | 119.7± 20.29 | 108.24 | 100.6 | 138.8 | <0.001 HS |
| NDR | 12 | 96.20 ± 7.57 | 97.2 | 85.7 | 107.8 | |
| DRE | 11 | 85.93±8.27 | 87.20 | 69.3 | 98.4.8 | |
| Total | 34 | 100.50±19.18 | 98.2 | 69.30 | 135.8 | |

NDE: newly diagnosed epilepsy NDR: non drug resistant epilepsy
DRE : drug resistant epilepsy HS: highly significant

**Table 8** Correlation between serum MMP-2 and patient age, age of epilepsy onset, disease duration and number of anti epileptic drugs. (N= 34)

| | | | **Serum MMP (ng/ml)** |
|---|---|---|---|
| | **Age (years)** | R | .030 |
| | | p-value | .867 |
| | **Age at epilepsy onset** | r | -.198 |
| | | p-value | .263 |
| | **Duration of epilepsy** | r | -.483** |
| | | p-value | .004 |
| | **Number of Anti-epileptic drugs** | r | -.550** |
| | | p-value | .01 |

R: Ratio r: correlation coefficient
N: number

**Table 9** Correlation between serum MMP2 and number of antiepileptic drugs

| **Number of anti epileptic drugs** | | Mean difference | Std err | Sig P value | 95% confidence interval | |
|---|---|---|---|---|---|---|
| | | | | | Lower bound | Upper bound |
| **One drug** | Two drugs | 20.18 | 8.31 | 0.16 | -6.42 | 46.78 |
| | Three dugs | 24.43 | 9.41 | 0.11 | -4.10 | 52.96 |
| | Four drugs | 28.47 | 8.17 | 0.04 | 1.05 | 55.89 |
| **Two drugs** | One drug | -20.17 | 8.31 | 0.18 | -46.78 | 6.42 |
| | Three dugs | 4.25 | 6.39 | 0.98 | -15.07 | 23.57 |
| | Four drugs | 8.30 | 4.36 | 0.54 | -11.08 | 27.68 |
| **Three drugs** | One drugs | -24.47 | 9.42 | 0.12 | -52.96 | 4.10 |
| | Two dugs | -4.25 | 6.39 | 0.98. | -23.57 | 15.07 |
| | Four drugs | 4.05 | 6.21 | 0.98 | -16.98 | 25.08 |
| **Four drugs** | One drug | -28.47 | 8.17 | 0.04 | -55.89 | -1.05 |
| | Two drugs | -8.30 | 4.36 | 0.54 | -27.68 | 11.08 |
| | Three dugs | -4.05 | 6.21 | 0.98 | -25.18 | 16.98 |

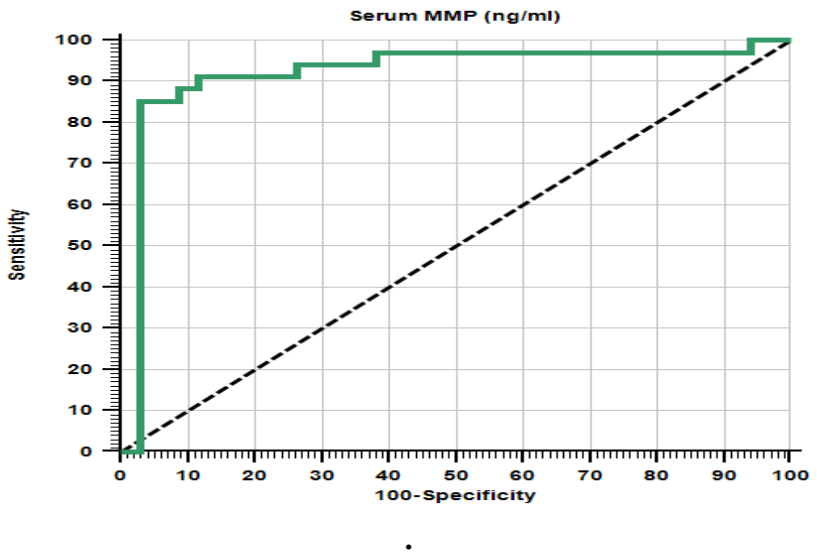


**Figure 2** ROC curves used to evaluate the serum MMP-2 as a biomarker for epilepsy diagnosis

Area under the ROC curve (AUC): 0.922 Standard Error [a] : 0.0345
95% Confidence Interval [b] : 0.831 to 0.973 z statistic : 12.220
Significance level P (Area=0.5) : <0.0001

## DISCUSSION

We found a statistically significant difference in serum MMP-2 in between patient and control groups being higher in control group with mean of 144.99 ±14.71 ng/ml compared to 98.44±14.71 ng/ml in the case group.

These results consistent with the study of **Wang et al, 2016** which concluded diminish in serum MMP-2 levels in people with epilepsy. This phenomenon concerning MMP-2 and its relation to epileptogenesis worth further investigations [16].

Previous studies noted that MMP-2 levels were not changed in animal brain tissue with epilepsy [17] [18] [19]. **Hoehna et al., 2012** study was conducted on rat models and measure activity of MMP-2 and MMP-9 in rat brain influenced by pilocarpine and showed raise MMP-9 activity [17].

**Li et al, 2013**[11] detected increased MMP-9 protein and activity levels in CSF from adult epilepsy patients with generalized tonic–clonic seizures compared to age-matched nonepileptic individuals. Levels of MMP-9 were also increased in serum from patients after seizures.

**Mizoguchi et al., 2011** [18] studied the effect of pentylenetetrazole (PTZ) induced kindled seizure on mice hippocampus which also emphasis the role of MMP-9 on seizure development with non statistically significant role proven for MMP-2. Although previous study deny any role of MMP-2 in neuronal cell death in epilepsy [20] , MMP-2 can contributes in structural remodeling in epileptogenesis since MMP-2 mRNA, protein, and activity are increased after seizures [21] [22] .These studies applied to symptomatic epilepsy while study was for idiopathic epilepsy.

Our explanation of decreased serum MMP-2 compared to high enzymatic activity in brain tissue may be due to consumption of peripheral MMP-2 and shifting intobrain to share in the process of epileptogenesis, such hypothesis worth future studies by combined serum and animal brain tissue sampling.

Our study reported that serum MMP-2 was not affected by age of both epilepsy and control groups. Serum MMP-2 has been investigated in studies of myasthenia gravis and migraine. Both reported increased serum MMP-2 levels compared to healthy controls, with no effect of age on MMP-2 levels[23] [24] [25] .On the other hand the study of **Wang** and colleagues[16] on 2016 show decrease in serum MMP-2 by age in both epilepsy and control groups.

This discrepancy may be attributed to several factors. First, the methods used to measure MMP-2 levels differed between the studies. In the current study, we examined

MMP-2 concentrations by ELISAs while the study of Wang and colleagues used Luminex technology, which has a much higher sensitivity, throughput, and efficiency than enzyme-linked immunosorbent assays (ELISAs) [26]. In addition, Wang study uses larger sample sizes and a larger age range (2-79 years) than our study [16].

Our study agreed with **Wang et al, 2016** [16] who found non statistically significant sex difference in serum MMP-2 between male and female gender among patients and controls.

Serum MMP-2 in our study was found to be statistically significantly lower in patient with focal epilepsy compared to patient with generalized epilepsy. The only study, as fare as we know, concerned with such relation [15], showed non statistically significant difference in both groups.it was done on larger sample size including wider age range with idiopathic, symptomatic and cryptogenic epilepsy patients, with a better measurement technology ( Luminex assay)

We next determined whether serum MMP-2 levels were affected by various clinical characteristics within the epilepsy group. Levels of MMP-2 were assessed in relation to disease duration, prognostic category, age at onset, and number of AED used.

Our study agreed with **Wang et al, 2016** [15], who found that MMP-2 was not affected by antiepileptic medication number.

in Multiple linear regression analysis ,we found a statistically significant negative correlation between age at onset and MMP-2 levels, serum MMP-2 is highly affected by patient prognostic category being lowest (85.93±8.27 ng/ml) in drug resistant epileptic patients and highest (119.7± 20.29 ng/ml) in the newly diagnosed patients.as shown by previous study of **Wang et al., 2016** [16].

To evaluate the utility of MMP-2 levels in discriminating cases of epilepsy from normal controls, we performed ROC curve analysis, when the cut-off value of MMP-2 concentration of 111.5 ng/ml was chosen, the sensitivity and specificity for distinguishing epileptic from control subjects were 85.29 and 97.06 %, respectively, and the AUC was 0.922.

**Wang** and colleagues[16] came to nearly similar results as cut-off value of MMP-2 concentration was 175.40 ng/ml, the sensitivity and specificity for distinguishing epileptic from control subjects were 71.13 and 62.66%, respectively, and the AUC was 0.697.

Another study evaluated the role of MMP-2 in a variety of neurodevelopmental processes and neurological disorders, but little is known about the precise role of MMP-2 in the pathogenesis of epilepsy [27].

Another study of **Mirshafiey and colleagues in 2014** [28] suggested that down regulation of MMP-2 may inhibit blood-brain-barrier (BBB) breakdown and migration of inflammatory cells into the CNS.

Our data showed that in epileptic subjects, MMP-2 levels are lowest in epileptic patients' especially drug-resistant ones. MMP-2 is involved in the repair process following CNS injury, but MMP up regulation in neurologic conditions may be results in pathology. Therefore, the down regulation of MMP-2 may be neuroprotective in patients with epilepsy. However, the precise role of MMP-2 in the pathogenesis of epilepsy remains to be established [29].

## CONCLUSION

Epilepsy is a major health burden. We need reliable biomarkers for diagnosis due to a wide range of epilepsy mimics. Our study demonstrated that serum MMP-2 levels were decreased in patients with epilepsy especially those with focal seizures. This tool may be a helpful diagnostic biomarker for epilepsy with a good sensitivity and specificity.

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