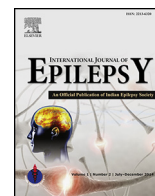




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Research paper

Plasma tetranectin as a potential clinical biomarker for epilepsy and correlation with clinical and social characteristics

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ABSTRACT

Background: Tetranectin concentration has been identified as a biomarker of several types of metastatic and malignant cancers. The role of tetranectin has also been seen in some neurological disorders. We aimed to estimate the plasma tetranectin concentration in different groups of people with epilepsy (PWE) followed-up for a year. As a secondary objective, the clinical and social characteristics were also correlated with the tetranectin levels.

Methods: We enrolled 90 subjects grouped as Newly-diagnosed epilepsy (NDE), Drug-effective epilepsy (DEE), and Drug-refractory epilepsy (DRE) and an age-gender matched control group (n = 30). The plasma samples were collected thrice at the six-month interval and were analysed for the tetranectin concentration using S-ELISA.

Results: The mean plasma tetranectin levels at the baseline test were significantly lower for the DEE (6.294 ± 0.806) and DRE (7.572 ± 0.545) groups compared with control group (9.71 ± 0.628) but not the NDE group (8.651 ± 0.859 vs. 9.71 ± 0.628; p > 0.05). On a year of follow-up, the tetranectin levels for the NDE group significantly decreased (p < 0.001) matching with that of the DEE and DRE group. Multivariate linear regression analysis showed that gender (p = 0.035) in the DRE group and seizure type (p = 0.040) and diet (p = 0.046) for the NDE group were significantly correlated.

Conclusion: The plasma tetranectin level in PWE significantly decreased as the disease progressed irrespective of the stage of epilepsy. Thus, tetranectin could be considered as a potential progressive biomarker for epilepsy. The study outcome suggests further investigation for the possible link of tetranectin levels with clinical and social parameters.

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1. Introduction

Epilepsy is a neurological disorder characterised by chronic, recurrent, unpredictable occurrence of seizures which affects nearly 50 million of the world's population.^{1,2} Despite increasing global health awareness, the gap between the incidence and prevalence of epilepsy in developed and developing nations still exists. Highlighting this fact about 80% of the total global burden of epilepsy is in developing countries.³ India has a prevalence rate of 6–10 million cases of epilepsy per year with the incidence rate of 27.3/100,000 per year.^{4,5}

The biomarkers identified for epilepsy revolves around two major mechanisms, i.e. epileptogenicity and epileptogenesis. Epileptogenicity biomarker identifies the genetic and molecular modulations; whereas biomarker for epileptogenesis deals with the development and progression of the disease.⁶ Epilepsy with its complexity and different clinical types do not have a unique biomarker. Identification of a potential blood biomarker in people with epilepsy (PWE) could be an important diagnostic tool along with the other epileptic molecular, EEG and imaging biomarkers.

Tetranectin is a glycoprotein which is encoded by CLEC3B gene (C-type lectin domain family 3, member B) in human.⁷ Its role has been perceived prominently in the regulation of fibrinolysis, tissue growth, and proteolytic processes; presented in a variety of cells including monocytes, neutrophils, fibroblasts and osteoblasts.^{7,8} As a biomarker, tetranectin has been found to be downregulated with the progression of metastatic cancer (oral cancer, lymph node cancer) as well as in solid malignant cancer (breast, colonic and ovarian cancer).^{9,10} Furthermore, studies have shown the role of tetranectin in various neurological disorders such as multiple

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sclerosis, Parkinson disease, Alzheimer's disease, and epilepsy. Particularly studies mentioned that the level of CSF tetranectin increases while serum tetranectin level decreases in people with epilepsy compared with the healthy control.^{11,12}

The research for the precise physiological role of tetranectin in epilepsy is still under investigation. This exploratory study was aimed to estimate and correlate the plasma tetranectin concentration in different groups of PWE at different clinical stages followed up for a year. The secondary objective was to correlate the clinical and social parameters with the proposed biomarker.

2. Materials and methods

2.1. Subjects and Ethics committee approval

The study was designed as a cross-sectional study and carried out in the Department of Neurology, Out Patient Department (OPD) at the University Hospital (Govind Ballabh Pant Hospital), New Delhi, during July 2011–January 2013. A total of 300 people diagnosed with epilepsy were screened based on their type of seizures defined in the International League Against Epilepsy (ILAE) in 1981, clinical history, neurological examination, EEG, and imaging (CT scan and MRI). As per the inclusion and exclusion criteria, 90 patients were enrolled and classified into three groups namely, Newly-diagnosed epilepsy (NDE, n=30), Drug-effective epilepsy (DEE, n=30), and Drug-refractory epilepsy (DRE, n=30). People who had one unprovoked seizure with high risk of relapse within past three months were defined as the NDE group; those who were seizure free for \geq three years while taking a single anti-epileptic drug (AED) or combination to treat epilepsy were categorized as DEE group; and those in whom no seizure control was there since the last two months while having three AEDs were grouped as DRE group. An age, gender, and sample size-matched control group (n=30) with no evidence of neurological disorders or any history of seizures or exposure to AEDs was recruited. The study protocol was approved by the Institutional Ethics Committee, Maulana Azad Medical College (MAMC) & Associated Hospitals, New Delhi.

2.2. Procedure

Each selected subject and the parents/guardians in case of children were subjected to sign the Informed Consent Form. The individual subject's clinical and social characteristics were entered in the Subject History Sheet. Blood samples were collected in 2 ml EDTA vacutainers at the initial baseline and then twice after every six months. Samples were processed by centrifuging for 10 min at 2000 g to collect the plasma. The plasma was aliquot and stored at -80°C until the analysis was done. The plasma tetranectin concentration at different time points was determined using a Human CLEC3B sandwich ELISA kit (Bio-medical Assay Co. Ltd, Beijing, China). The assay procedure was followed according to the user manual provided by the manufacturer. A dilution of 1:100 was prepared for plasma samples and optical density was read at 450 nm using UV Spectrophotometer (PerkinElmer Lambda-20 Double-beam UV-vis spectrophotometer). The analysis was carried out at the Neurobehavioral Pharmacology Lab, Faculty of Pharmacy, Department of Pharmacology, Jamia Hamdard (Hamdard University), New Delhi, India.

2.3. Statistical analysis

The plasma tetranectin concentrations were expressed as mean \pm SD. The clinical and social characteristics of the study subjects were compiled as percentages. Differences between the variables from the three groups were assessed using one-way

Table 1

Clinical characteristics of the three groups of people with epilepsy.

Clinical characteristics	NDE	DEE	DRE
Age, yrs			
Mean	19.8	24.97	23.2
Range	6–52	13–46	7–45
Sex, n (%)			
Male	24 (80.00)	19 (63.33)	27 (90.00)
Female	6 (20.00)	11 (36.66)	3 (10.00)
Onset of seizures, n (%)			
\leq 3 mo	30 (100.00)	0	0
\leq 5 yrs	0	17 (56.66)	1 (3.33)
6–15 yrs	0	11 (36.66)	20 (66.66)
16–30 yrs	0	2 (6.66)	10 (33.33)
Family history, n (%)			
Yes	7 (23.33)	4 (13.33)	5 (16.66)
No	23 (76.66)	26 (86.66)	25 (83.33)
Frequency of seizures, n (%)			
1–2/mo	30 (100.00)	0	11 (36.66)
3–5/mo	0	0	19 (63.33)
1–2/yrs	0	0	0
1/3–4 yrs	0	19 (63.33)	0
1/5–10 yrs	0	11 (36.66)	0
Last episode, n (%)			
$<$ 1–2 mo	30 (100.00)	0	30 (100.00)
$<$ 1–5 yrs	0	18 (60.00)	0
$<$ 6–10 yrs	0	12 (40.00)	0
Types of seizures, n (%)			
GTCS	17 (56.66)	19 (63.33)	11 (36.66)
Complex partial seizures	6 (20.00)	4 (13.33)	5 (16.66)
Seizure with 2 ^o generalization	6 (20.00)	5 (16.66)	10 (33.33)
Multiple seizures	1 (3.33)	2 (6.66)	5 (16.66)
AEDs history, n			
1	8	13	18
2	13	9	24
3	10	9	9
4	1	2	4
5	1	0	9
6	0	1	2
7	0	0	2
8	0	0	1

1-VPA, 2-CBZ, 3-PHT, 4-PB, 5- CB, 6- LTG, 7- LVT, 8- TP. NDE: Newly-diagnosed epilepsy, DEE: Drug-effective epilepsy, DRE: Drug-resistant epilepsy, mo: Months, yrs: Years.

ANOVA followed by Tukey-Kramer Multiple Comparison post hoc test. A multivariate linear regression was executed to identify the correlation of the factors with the biomarker level. The GraphPad InStat version 3.0 for Windows (GraphPad Software, San Diego, California, USA, www.graphpad.com) was used and a p value of <0.05 was considered as statistically significant.

3. Results

3.1. Clinical and social characteristics

Table 1 shows the summarised clinical characteristics. The mean age of the study population among the three groups was 22.65 years. The age range for the NDE group was 6–52 years, the DEE group 13–46 years, and for the DRE group 7–45 years. The sex ratio varies from group to group basis, on the one hand, the DEE group had more male subjects than female (63.33% vs. 36.66%), whereas, both the DRE and NDE groups had only 10% and 20% of the female subjects included, respectively. A fair role of family history was found with a percentage of 17.77%. The NDE group had GTCS with 56.66% as the most common type of seizure; seizures with secondary generalisation and complex partial seizures shared 20% each. For the DEE group, the most common type of seizure was GTCS (63.33%) followed by seizures with secondary generalisation and complex partial seizures. A mixed ratio for the DRE group was there; GTCS and seizures with secondary generalisation shared the

same percentage (36.66% and 33.33%), trailed by complex partial seizures, and multiple seizures with 16.66%. The AEDs history implied that valproic acid (VPA), carbamazepine (CBZ), and phenytoin (PHT) were the drug of choice as monotherapy; whereas, clobazam (CB) > phenobarbitone (PB) > lamotrigine (LTG) > levetiracetam (LVT) were used as adjuvants for polytherapy regimen in the DRE group.

The social characteristics are presented in Table 2. The majority of the study population were either had an education below 10th grade (NDE: 70.00%, DEE: 43.33%, and DRE: 53.33%) or illiterate (NDE: 10.00%, DEE: 6.66%, and DRE: 30.00%). A higher percentage of subjects belong to student category in the NDE group (56.66%) whereas, in the DRE group, 60% of the population were not working. A relation with the marital status was found with the OPD reporting, about 3/4th of the studied population was single and only 1/4th of those were married.

3.2. Plasma tetraectin concentrations

The mean plasma concentrations of tetraectin in three tests are shown in Table 3. The mean concentrations of the NDE group (8.651 ± 0.859) was comparable to the control group (9.71 ± 0.628), whereas concentrations of the DEE (6.294 ± 0.806) and DRE (7.572 ± 0.545) group were significantly decreased compared with the control group in the first test as baseline ($p < 0.001$). At the first follow-up of six months, the plasma tetraectin level of the DRE group reduced further but the for the NDE group it remained more or less unchanged ($p > 0.05$). In the final test analysis at one-year follow-up, though the plasma tetraectin level of the DEE and DRE group remained unchanged to that in the previous tests; levels of the NDE group decreased significantly in comparison with the control group ($p < 0.001$).

3.3. Multivariate linear regression

To establish the relationship between the tetraectin plasma concentration as a dependent variable and the predictor variables, we performed a multivariate linear regression model. The data from the baseline test (Test-1) was considered for each group. The tetraectin concentration being the dependent variable was

Table 2
Social characteristics of the three groups of people with epilepsy.

Social characteristics	NDE, n (%)	DEE, n (%)	DRE, n (%)
Education			
<10th	21(70.00)	13 (43.33)	16 (53.33)
12th	6 (20.00)	11 (36.66)	5 (16.66)
Graduate & above	0	4 (13.33)	0
Illiterate	3 (10.00)	2 (6.66)	9 (30.00)
Occupation			
Service	7 (23.33)	9 (30.00)	6 (20.00)
Business	0	0	0
Self employed	3 (10.00)	3 (10.00)	0
Student	17 (56.66)	9 (30.00)	6 (20.00)
Not working	3 (10.00)	9 (30.00)	18 (60.00)
Marital status			
Single	21(70.00)	20 (66.66)	25 (83.33)
Married	7 (23.33)	10 (33.33)	5 (16.66)
Personal habits			
Drug abuse	0	0	0
Alcoholic	3 (10.00)	1 (3.33)	1 (3.33)
Smoking	4 (13.33)	1 (3.33)	3 (10.00)
Dietary habits			
Vegetarian	9 (30.00)	11 (36.66)	9 (30.00)
Non-vegetarian	21(70.00)	19 (63.33)	21(70.00)

NDE: Newly-diagnosed epilepsy, DEE: Drug-effective epilepsy, DRE: Drug-resistant epilepsy.

Table 3

Plasma tetraectin concentration in three groups of people with epilepsy and control group.

Group	Tetraectin concentration (µg/ml) mean ± S.D		
	Test-1	Test-2	Test-3
Control	9.71 ± 0.628	9.293 ± 0.857	9.293 ± 0.857
NDE	8.651 ± 0.859 ^{ns}	8.726 ± 0.822 [†]	6.354 ± 0.617 ^{***}
DEE	6.294 ± 0.806 ^{***}	5.832 ± 0.331 ^{***}	6.068 ± 0.776 ^{***}
DRE	7.572 ± 0.545 ^{***}	5.394 ± 0.580 ^{***}	6.151 ± 0.738 ^{***}

The values are shown as the mean ± SD, * $p < 0.05$, *** $p < 0.001$ compared to the Control. One-way ANOVA followed by Tukey-Kramer Multiple Comparison post hoc test. NDE: Newly-diagnosed epilepsy, DEE: Drug-effective epilepsy, DRE: Drug-resistant epilepsy.

correlated with the clinical and social parameters. On comparing the three groups, the multivariate linear regression analysis revealed that overall these factors explained only the 16% to 21% of the total variability. Specifically, a significant correlation was seen for gender ($p = 0.035$) in the DRE group. Whereas, seizure type ($p = 0.040$) and diet ($p = 0.046$) were significantly correlated for the NDE group. On dummy coding moderation with regression analysis, it was evident that males had an inverse relation with the tetraectin under the drug-resistant group. On the other hand, based on the standardised coefficient β people with NDE had GTCS as the most interacted followed by seizures with secondary generalisation, CPS and multiple seizures. Interestingly, the correlation of non-veg or veg diet could not be clearly defined provided with the same p -value of 0.021.

4. Discussion

Our study confirmed that tetraectin has a defined role in the pathophysiology of epilepsy. The plasma tetraectin concentrations in PWE decreased significantly compared with the control group irrespective of the epilepsy state. These results are consistent with other published works. A previous study has stated that tetraectin is present in the normal brain and the CSF tetraectin level gets decreased in temporal lobe epilepsy.¹³ Another study reported that serum tetraectin level decreases while the CSF tetraectin increased in epilepsy and proposed that tetraectin could be a potential biomarker for epilepsy.¹¹

Tetraectin is a kringle 4 protein binding plasminogen; the structure and its role in human physiology have been already worked out. There are study reports stating that tetraectin is present in neuronal cells, myelinated fibres of the white matters in both cerebrum and cerebellum, and CSF of the people with temporal lobe epilepsy (TLE), however, the exact role and mechanism of tetraectin in epileptogenesis are yet not clear.^{11,14}

We found that at baseline sampling, the NDE group had comparable tetraectin level as that of healthy control subjects, whereas, the tetraectin levels in the DEE and DRE group were significantly downregulated. On a year of follow-up, the NDE group also showed a declined path similar to that of the DEE and DRE group. This suggests that as the disease advances the plasma tetraectin level decreases irrespective of the state of epilepsy. Furthermore, the Test-1 was the baseline to compare the tetraectin level among the three groups and the control. The significant reduction in the tetraectin concentration points out its existing role in epilepsy. The subjects in the DEE and DRE groups had established history of epilepsy/seizures, in contrast to the NDE subjects at that stage. After a year of follow-up, fall of tetraectin level in the NDE group supported the initial hypothesis. However, the result regarding the DRE group was not in support of previously reported literature in the same context.¹¹ According to that study, lower level of plasma tetraectin in the DRE group was correlated

with the frequency of seizures. The same study showed that the NDE group showed a significant decrease compared with control. However, the subjects were sampled once and were not further followed up. These methodological differences could reflect the differences in result findings. As per our study findings, no difference at the six months follow-up but a significant reduction of tetranectin level in the NDE group after a year suggest that the biomarker levels are affected as the disease progress regardless of the stage of epilepsy.

The study has also highlighted the region-specific patterns amongst the people with epilepsy. During the screening of the study population, data for clinical and social characteristics was recorded. It turns out that there is a skewed gender ratio when it comes to reaching the hospital, as on an average nearly 77.77% of the study population constitute males. The family history of epilepsy among the study population was also evident. Although genetic testing was not performed, the subjects with known family history of epilepsy were counselled as per the case. GTCS being the most common type of seizure reported in the study agrees with other literature published.^{15,16} Besides the 1st generation AEDs (VPA, CBZ, and PHT) used as monotherapy, CB and PB were the drugs of choice as an adjuvant. Various clinical studies have reported LVT as safe and effective add-on drug in people with drug-refractory epilepsy.^{17,18} However, LVT was not commonly prescribed in the study population at our hospital settings. Being illiterate or having a just secondary education was correlated with unemployment among the PWE that directly associates with the different groups of epilepsy. More the frequency of seizures, more the patient, is cut off from the society; be it from education or the workplace. These findings were supported by other studies as well.^{19–21} Another factor that came into notice was the marital status; it turned out that higher proportion of the study subjects were single (75%). The reason for that could be the fewer incidences of seizures occurs in higher ages of life, shifting of the female population after marriage, and societal and family pressure. The condition was worse with female subjects, for whom the stigma of having epilepsy hovers around them. This depicts the mental block of the society, even in the metro city like Delhi. This fact is not new in the country like India, others authors have also reported the same from different parts of the country.^{19–22} The tetranectin levels did not significantly correlate with the clinical and social parameters of the DEE subjects. However, the fact that there was a significant correlation in gender for DRE and type of seizure and diet for the NDE group pointed to dig deep into the concept. Whether these findings can be replicated in large study population or do a non-veg or veg diet would affect the progress of epilepsy in the NDE group.

The present exploratory study firmly concludes that plasma tetranectin level decreases in people with epilepsy as disease advances. Therefore, plasma tetranectin can be considered as a potential candidate for a biomarker of epilepsy that could assist the existing clinical biomarkers. However, with contrasting literature findings of no conclusive difference among the patients with refractory epilepsy per se, open up the future scope of the investigations. A larger sample size, total protein level analysis and prolonged follow-up of DRE and NDE subjects would overcome the limitation of this study. Even with a definite clinical association of tetranectin with epilepsy, further research is required to probe into the mechanism, role and diagnostic characteristic of tetranectin with epilepsy and other neurological disorders.

Conflict of interest

The authors have no conflict of interest.

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