

## Cerebrospinal Fluid Level of Glutamic Acid Decarboxylase (GAD) Antibody in Patients with Encephalitis

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### ABSTRACT

**Background:** Assaying the Glutamic Acid Decarboxylase (GAD) antibody in patients with encephalitis in cerebrospinal fluid and blood serum and its role in autoimmune encephalitis in children.

**Objective:** This study aimed at screening for GAD antibody in CSF of children presenting with acute encephalitis with non bacterial cause mostly autoimmune. **Participants and methods:** study is a pilot prospective study, conducted in the Pediatric department, Children's Hospital, Ain Shams University. Fifty patients diagnosed with encephalitis exhibited at least one sign of parenchymatous brain dysfunction such as altered consciousness, personality or behavior change, seizure, paresis, or ataxia. Encephalitis was defined as the presence of encephalopathy plus at least two of four findings: (1) fever (body temperature >38°C); (2) abnormal cerebrospinal fluid examination (pleocytosis >5 white blood cells/mL and/or increased protein content >40 mg/dL) with negative cerebrospinal fluid culture; (3) abnormal electroencephalography findings compatible with encephalitis such as diffuse or focal slow activity, or periodic lateralized epileptiform discharges; and (4) abnormal results of neuroimaging, including computed tomography and magnetic resonance imaging<sup>(10)</sup>, with age ranged from 6-144 Months; followed up in the period from September 2014 till March 2016. Basic clinical evaluation and laboratory investigations were done, GAD antibody level was measured in CSF and blood serum. **Results:** GAD receptor antibody titer was done in CSF which range from (36 - 368 ng/l) with median of 64.83 (57.93-74.48), while in serum it range from (42.76-900) ng/l) with median 89.5 (58.62-154.5). It was found that 6/50 (12%) patients had high GAD receptor antibody titer were high in CSF. The other 44/50 (88%) patients had low GAD antibody titer. In serum samples of twenty patients we had 8/20 (40%) patients had high GAD antibody titer and the rest were low GAD antibody titer 12/20 (60%). Significant occurrence of DCL, hospitalization plus mechanical ventilation and long term sequel were detected in patients with high GAD antibody titer. EEG findings; Two patients showed generalized epileptogenic activity, one patient had diffuse cortical dysfunction and two patients had multifocal epileptiform discharge and the rest of patients had normal findings. Eighty six percent had normal MRI findings, while 7 patients (14%) had non specific findings; 3 patients had transient cortical meningeal enhancement, 2 patients had high intensity in medial temporal lobe, one had abnormal signal intensity in medial temporal lobe and one patient had global brain atrophy. **Conclusion:** GAD Abs are directed against an intracellular antigen. The proposed pathogenic mechanisms of neurological disease in patients with antibodies directed against intracellular proteins is not clear. The present study emphasizes the importance of studying the CSF of patients with encephalitis suspected to be mediated by GAD autoimmunity. Both serum and CSF level must be assessed simultaneously as CSF level may change rapidly with fluctuation of disease. There are great efforts to be done to define the role of these GAD antibodies and to determine how they affect central nervous system function. These studies must be carried out so that appropriate treatments can be provided for the growing number of patients with possible antibody-mediated conditions.

**Keywords:** GAD, CSF, EEG, MRI, autoimmunity.

### INTRODUCTION

Encephalitis is an acute infection or inflammation of the brain parenchyma that most commonly affects children and young adults. Many aspects of the pathogenesis of acute encephalitis and acute encephalopathy have been clarified in the past decade, although many unknown mechanisms remain to be elucidated. The pathogenesis of encephalitis is divided into infectious or immune mediated mechanisms<sup>(1)</sup>.

Encephalitis refers to an inflammatory disorder of the brain resulting in altered mental status, seizures, or focal neurologic deficits, usually accompanied by signs of inflammation in the cerebrospinal fluid and magnetic resonance imaging (MRI) findings ranging from normal to extensive abnormalities. The causes of encephalitis are numerous, and most patients undergo extensive testing for infectious etiologies without discovery of a causative agent<sup>(2)</sup>.

Autoimmune encephalitis is a type of encephalitis that can result from a number of autoimmune diseases including Rasmussen encephalitis, Systemic lupus erythematosus (SLE), Behcet's disease, hashimoto's encephalopathy and autoimmune limbic encephalitis<sup>(3)</sup>.

Autoimmune encephalitis involves paraneoplastic and nonparaneoplastic causes. Paraneoplastic autoimmune encephalitis is associated with autoantibodies to onconeural antigens and, less often, to cell membrane antigens. Nonparaneoplastic autoimmune encephalitis may be associated with systemic autoimmune disorders, autoantibodies to cell membrane antigens such as voltage-gated potassium channel complex, and less frequently, autoantibodies to intracellular antigens such as glutamic acid decarboxylase. Anti-GAD antibodies target an enzyme called Glutamic Acid Decarboxylase. This enzyme is responsible for converting glutamic acid to GABA, a chemical neurotransmitter found in high concentration in central nervous system, Anti-GAD antibodies are particularly common in diabetes mellitus and autoimmune diseases such as thyroid disease and rheumatoid arthritis. Classic presentation of autoimmune encephalitis includes the rapid development of irritability, short-term memory loss, depression, sleep disturbances, hallucinations, seizures and Confusion<sup>(4)</sup>.

Definitive diagnosis of anti-GAD encephalitis is established by demonstrating antibodies in patients' serum and CSF or CSF only and usually the CSF titer is higher than the serum titer.

The treatment for anti-GAD antibodies is corticosteroids or prednisone to reduce the abnormal immune response. If this is ineffective infusion of immunoglobulin intravenously (IVIG) or a procedure called plasma exchange can be used. It is sporadic and occurs without a seasonal pattern. Outcomes vary between those who are able to return to their former work and lifestyle (with perhaps only a slight change in their abilities) to those left profoundly disabled, physically, cognitively or both<sup>(5)</sup>.

## OBJECTIVE

This study aimed at evaluating the level of GAD antibody in CSF of children presenting with acute encephalitis with nonspecific cause mostly autoimmune encephalitis. The ultimate

objective was to study the prognostic gain from adding this marker to the work up of this disease.

## PARTICIPANTS AND METHODS

The study is a pilot prospective study, conducted in the Pediatric department, Children's Hospital, Ain Shams University.

Fifty patients previously diagnosed as cases of autoimmune encephalitis, they were studied and followed up in the period from September 2014 till March 2016, with regular clinical and laboratory evaluation.

### Inclusion Criteria

- 1) Age: Above 6 months' old
- 2) Normal neurodevelopmental history

### Exclusion Criteria

- 1) Electrolyte disturbance that might be implicated in altering the mental status.
- 2) Recent history of head trauma.
- 3) Patients receiving drugs that might affect the mental status.
- 4) Delayed neuro-development.
- 5) MRI brain showing structural brain lesion e.g. ADEM, neurodegenerative disease, or brain tumor
- 6) Cases of bacterial meningitis or encephalitis, i.e. turbid CSF, or neutrophilia in the CSF or other evidences of bacterial etiology.

### Control group:

Twenty infants and children presenting to the outpatients clinic with complaints other than encephalopathy or neurological symptoms and signs of comparable age and sex to the patients' group were included as the control group. Serum samples were collected from them.

## INTERVENTION

Enrollment of patients according to predetermined exclusion and inclusion criteria.

*All patients were subjected to the following:*

### 1) Full history taking

*With special emphasis on the following data*

- Demographic data: name, age, sex, parental consanguinity, similar condition in the family
- Fever with its character.
- Recent history of vaccination
- URTI symptoms (rhinitis, cough, others).
- GIT symptoms (vomiting, diarrhea, abdominal pain)
- Neurological symptoms: convulsion, mental delay, squint, weakness, lateralization, and abnormal pupillary reaction to light.

**2) Full clinical examination:**

- General examination and vital data monitoring
- Detailed neurological examination.

**3) Laboratory investigations including:**

- Complete blood picture
- C-reactive protein.
- Random blood glucose
- Electrolytes: calcium, potassium, and sodium
- Liver function tests: AST, ALT, ALP, PT, serum albumin and serum bilirubin.
- Renal functions: serum urea and creatinine.
- Serum samples for quantitative measurement of GAD antibody level by enzyme linked immunosorbent assay (ELISA).
- Lumber puncture and CSF examination for:
  - 1) Cell type and count.
  - 2) Glucose, proteins, and LDH levels.
  - 3) Culture and sensitivity.
  - 4) Quantitative measurement of GAD antibodies by enzyme linked immunosorbent assay (ELISA): Simultaneous serum and CSF samples were planned but this could not be achieved for all patients due to the bad general condition of some for which the CSF samples had to be postponed.
  - 5) Neuroimaging: CT or MRI brain.
  - 6) Electroencephalogram.

***Patients were closely followed up for at least 4 months for:***

- 1) Time till they regain full conscious
- 2) Signs of morbidity as neurological squeal; motor, mental, linguistic deficit, pseudobulbar palsy, behavioral changes and hemiparesis.
- 3) resolution : regain complete and age matched neurodevelopmental skills.

For the blood samples withdrawn from the control infants and children; quantitative serum levels OF GAD antibody were done.

**The study was approved by the Ethics Board of Ain Shams University and an informed written consent was taken from their relatives.**

**Statistical analysis**

Data were analyzed using Statistical Program for Social Science (SPSS) version 20.0. Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

**The following tests were done:**

- Independent-samples t-test of significance was used when comparing between two means.
- Chi-square ( $X^2$ ) test of significance was used in order to compare proportions between two qualitative parameters.

- Pearson's correlation coefficient (r) test was used for correlating data.
- Probability (P-value)
  - P-value <0.05 was considered significant.
  - P-value <0.001 was considered as highly significant.
  - P-value >0.05 was considered insignificant.

**RESULTS**

Fifty patients previously diagnosed as cases of autoimmune encephalitis, 32 of them were males (64%), and 18 were females (36%), their median age was 24(12-16) months, ranging between 6 and 144 months. Comparison patient group and control group according to (age , sex) indicating matching of both groups.

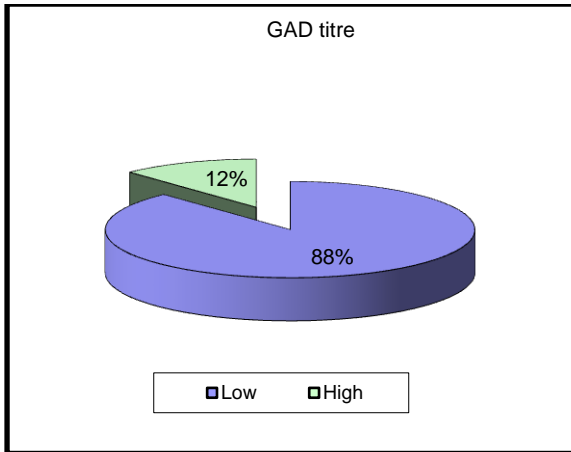
As regard constitutional symptoms in our patients group 82% had fever, 34% with diarrhea,62% with vomiting,42% with URTI.

Moving to neurological manifestation our patients had 100%of DCL and convulsions. EEG finding; 46% of patient group not available ,44% are normal finding, 10% had abnormal finding; two patients indicate generalized epileptogenic activity, one patient had diffuse cortical dysfunction and two patient had multifocal epileptiform discharge . Eighty six percent (43) of the patients had normal MRI findings. While 7 patients (14%) had nonspecific findings;3 patients had transient cortical meningeal enhancement, 2 patients had high intensity in medial temporal lobe, one had abnormal signal intensity in medial temporal lobe and one patient had global brain atrophy. Cerebrospinal fluid analysis of the patients' group had normal cerebrospinal fluid (CSF) glucose, protein and cell count. GAD (glutamic acid decarboxylase) antibody titer in CSF, Six patients (6/50) (12%) was high titer (more than 93 ng/l) while forty four (88%) was low titer of glutamic acid decarboxylase anti body (GAD) (less than 93ng/l).Cut off point =93ng/l which is the mean of control group as ( table ,figure (1)).

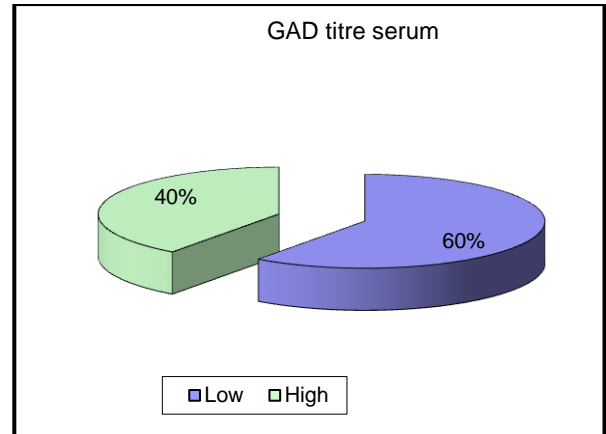
**Table (1):** GAD antibody titer in Cerebrospinal fluid of the patients' group (n=50)

GAD CSF		Patients'group Total no. = 50
Low titer (less than 93ng/l)	Mean -62.88	44 (88%)
High titer (more than 93 ng/l)	Mean	
	-167.16	6 (12%)

GAD; glutamic acid decarboxylase antibody



**Fig. (1):** GAD antibody titer in Cerebrospinal fluid of the patients' group.



**Fig. (2):** Serum anti GAD antibody titer of patient group

Basically, we compared the 2 main groups (high and low titer) of patients with each other in CSF;diarrhia was common in patients with high titer compared to patients with low titer of GAD anti body and the difference was statistically significant ( $p<0.05$ ), While vomiting and upper respiratory tract infection were non statistically significant difference.Fever ,MRI, EEGand CSF analysis were compared between both group with statistically insignificant difference.

Twenty serum samples of the studied patients: serum GAD antibody titer ranged from (42.76-900) with median 89.5 (58.62- 154.5) and 8 patients had high titer of GAD antibody (40%) (more than 93 ng/l) and 12 patients had low titer of GAD anti body (60%) in serum As showing in (table, figure 2) (less than 93 ng/l). Both group were compared according to age, sex, constitutional symptoms, EEG, MRI and csf analysis with statistically insignificant difference.

**Table (2):** Serum anti GAD antibody titer of patients 'group

GAD Titer serum	patients' group
	Total no. = 20
Median (IQR)	89.5 (58.62 – 154.5)
Range	42.76 – 900
Low	12 (60%)
High	8 (40%)

GAD: glutamic acid decarboxylase  
 Low GAD titer;<93 ng /l  
 High GAD titer;≥93 ng/l

### DISCUSSION

Encephalitis is a potentially life-threatening neurological condition caused by inflammation of the brain parenchyma.The frequency and severity of encephalitis is highest among younger children. In nearly half of the cases of acute encephalitis in children a definitive cause is not found, though infection is the most important known cause <sup>(6)</sup>.

Encephalitis is a neurological syndrome that may present in association with cancer, infection, or as an isolate clinical condition often accompanying autoimmune disorders <sup>(7)</sup>.Autoimmune encephalitis (AE) is an expanding group of inflammatory brain conditions defined by the presence of autoantibodies against cell-surface proteins such as neuronal receptors or synaptic proteins. AE is important to suspect and diagnose, as early immune therapy appears to improve outcomes. With this aim, consensus criteria have been recently proposed to diagnose AE<sup>(8)</sup>.

Encephalitis is a significant cause of morbidity and mortality worldwide. In order to find the etiology of the disorder patients frequently undergo extensive testing but despite this, the cause remains unknown in about 60% of the cases. The discovery that several forms of encephalitis result from antibodies against neuronal cell surface or synaptic proteins, and that they are potentially treatable has led to a paradigm shift in the diagnostic approach of encephalitis <sup>(9)</sup>.

Encephalitis was defined as the presence of encephalopathy plus at least two of four findings:

- 1- Fever (body temperature>38C).
- 2- Abnormal cerebrospinal fluid examination (pleocytosis>5 white blood cells/mL and/or

increased protein content >40 mg/dL) with negative cerebrospinal fluid culture.

- 3- Abnormal electroencephalography findings compatible with encephalitis such as diffuse or focal slow activity, or periodic lateralized epileptiform discharges.
- 4- Abnormal results of neuroimaging, including computed tomography and magnetic resonance imaging<sup>(10)</sup>.

In the current study, analysis of data revealed that, The range of age in patients group was (6-144) months (64% males & 36% females) and this percentage which is high in males patients may be due to our mistake during collecting data which was more from male gender, in comparison with those in control group, it ranged from 7 months to 144 months (70% males & 30% females), with no significant statistical difference as regarding age or sex ( $P > 0.05$ ) indicating matching of two groups for comparison. But some studies Coming in accordance with those of **Incecik *et al.*** who found that, 60% of the diseased children were males, their median age was 8.3 years. But, it comes against the results of **Malter<sup>(11)</sup>** who reported the older female predominance among his studied group of children having the same disease.

Eighty two percent of the included patients had fever on presentation (60% low fever & 22% high fever), 34% with diarrhea, 62% with vomiting and 42% with upper respiratory tract infection, which was in agreement with that of **Incecik<sup>(12)</sup>**, who documented similar results among their study groups of children. The disease associated with a characteristic syndrome that develops in several stages of illness and recovery, as first reported by **Iizuka<sup>(13)</sup>**, **Sansing<sup>(14)</sup>** unfortunately our study missed the observation of psychiatric symptom.

Moving to the clinical data of the patients group, starting with the neurological signs & symptoms, all patients had history of convulsions or convulsions along the course of their disease. Seizures are common in autoimmune encephalitis and may be a presenting symptom. It may occur at any stage of the illness. Autoantibodies to two important inhibitory receptors in the brain, GABA-B and GABA-A receptors (at high titer) convey a high risk of severe seizures and intractable status epilepticus<sup>(15)</sup>. In agreement with our results, **Albert<sup>(16)</sup>**, **Wright & Vincent<sup>(17)</sup>** and **Mishra<sup>(18)</sup>** reported that convulsions was appeared in high

percentage of their studied group patients with encephalitis.

Regarding EEG findings in patients group, it was done to 27 patients, showing that, 44% of patients had normal finding and 5% had generalized epileptogenic activity, diffuse cortical dysfunction in one patient and multifocal epileptiform discharge in two patients this in accordance with **Gultekin<sup>(19)</sup>** and **Incecik<sup>(20)</sup>** who found that, autoimmune encephalitis mostly had nonspecific slowing and epileptiform activity arising from temporal lobes in EEG.

Regarding neuroimaging data, only 14% had positive MRI changes this comes in relative agreement with **Titulaer<sup>(21)</sup>** who found that, the brain MRI is normal in approximately 60% of the patients with autoimmune encephalitis and shows nonspecific findings in the rest including cortical-subcortical FLAIR changes in brain or posterior fossa, transient meningeal enhancement, or areas of demyelination. Also, **Albert<sup>(16)</sup>** documented that, pediatric patients with definite autoimmune encephalitis have a narrow spectrum of MRI abnormalities.

Looking for laboratory investigations, analysis of CSF in patient group revealed that mean of CSF glucose level, ( $80.50 \pm 26.70$ ) mmol/l, mean of protein ( $26.40 \pm 10.43$ ) mg/dl, median of cell number 3 (0-8). Most autoimmune encephalitis Associated with cerebrospinal fluid (CSF) lymphocytic pleocytosis that is usually milder than that found in viral etiologies. Patients with viral and autoimmune encephalitis have normal glucose levels and normal or mildly increased protein concentration. **Finelli<sup>(22)</sup>**, Indicated that, in the majority of patients, the CSF shows a mild-to-moderate pleocytosis, increased protein concentration and mild increase in the CSF glucose level, **Skillback<sup>(23)</sup>**, **Blennow and<sup>(24)</sup>** **Norgren<sup>(25)</sup>** revealed that, CSF protein, glucose and cells increased non-specifically in patients with brain disorders (e.g. encephalitis) and their levels may normalize when the disease process has abated spontaneously or due to treatment.

According to the level of GAD antibodies in the CSF (high GAD-titer in 12% of cases, while 88% of the same group had low GAD titer), patient group was divided into two subgroups: group with high level of CSF GAD-Abs (6 patients; 66.4% females & 33.3% males, with age ranging from (6-108) months) and group with low level of CSF GAD-Abs (44 patients; 68.2% males & 31.8% females with age ranging from (3 - 144) months).

The present result comes in accordance with **Malter**<sup>(11)</sup> who found that, the anti-GAD Ab titer was high in 16% of their study group who diagnosed as autoimmune encephalitis. Also, **Lee & Lee**<sup>(26)</sup> reported that, the GAD-Ab could be negative even in the presence of autoimmune encephalitis.

It was found that, the level of CSF GAD-Ab ranged from (36 to 368 ng/l), **Goran**<sup>(27)</sup> during their study for evaluating the level of anti-GAD in patients in National Institute of Neurological Disorders and Stroke, Bethesda, USA, found that the level of CSF-AB ranged from (30 to 400ng/l), coming in harmony with our results.

In twenty patients only of our 50 patients (of the patient group), GAD-Ab titer was measured in the serum, revealing that, 40% (8/20) of patients had high serum anti-GAD-Ab titer (62.5% males & 37.5% females; their age range was (9-48) months), while 60% (12/20) of patients had low serum GAD-Ab titer, (50% males & 50% females; with age range of (6-144) months).

The main initiating abnormality in GAD antibody encephalitis is the intra-thecal synthesis of GAD antibodies that in turn cause the pathological brain changes that leads to the encephalopathy picture and to the consequently detected CSF GAD antibody and then the serum<sup>(28)</sup>. It was found that, there was no statistical significant difference between low & high levels of GAD Ab in both CSF and serum. It may be referred to that the serum and CSF samples were not all simultaneously withdrawn; serum samples were taken upon admission but CSF samples were sometimes Delayed for few days due to bad general condition of the patients.

This also cannot explain the isolated elevation in serum in some patients without simultaneous CSF, as if we postulated that they had autoimmune encephalitis it is more likely to appear first in the CSF then in the serum and this was not the case. So it is Not logic to diagnose those with only positive serum GAD antibody as having GAD encephalitis<sup>(27)</sup>.

This conclusion accord that of **Saiz**<sup>(5)</sup>, who reported that positive serum anti-GAD-Ab without CSF was linked to many causes as neuropsychiatric disorders like refractory seizures, nystagmus, stiff person syndrome and cerebellar ataxia

On correlating the level of GAD-antibody (high & low) in CSF with clinical signs, it was found that, there was no significant statistical difference between both groups as regarding to

fever, DCL, convulsions and MRI findings, which comes in agreement with that demonstrated by **Rakocevic**<sup>(29)</sup> who found the GAD antibody titers in serum and CSF do not correlate with disease severity or duration, No consistent correlation was found between the serum or CSF GAD antibody titers and disease severity; the titers were high in some patients with mild disease and low in some others with severe disease.

Also in our study, it was found that, fever appeared in 62.5 % of patients with high titer of serum GAD ab, while diarrhea, vomiting and upper respiratory tract infection presented in 37%, 62% and 50% of the same group respectively.

Regarding the neurological signs, convulsions appeared in all patients with high and low titer of serum anti-GAD ab, while MRI changes did not observed in any patient with high titer of serum GAD ab, with no statistical significant difference between groups of low and high serum anti-GAD Ab with these neurological signs.

In the current study, there was no statistical significant correlation between the levels of CSF GAD-Ab titer and the CSF glucose, protein and cells, as it was found that, among the patients who had high titer of GAD-Abs, the CSF glucose level ranged from 62 to 140 mg/dl, while the range of CSF protein & cells were (18-54.32) mg/dl & (0-60) cells/mm<sup>3</sup> respectively.

On correlating the level of CSF GAD-Ab with EEGit, we found that, EEG findings were unremarkable in about 90% of patients having high serum level of GAD-Ab.; one patient had normal finding (12.5%), one patient had generalized epileptiform activity (12.5%) and six patients (75%) not available to done with statistically none significant difference (p- value >0.05). Also **Lancaster**<sup>(15)</sup> declared that there was no correlation between level of GAD-Ab in CSF or serum with EEG findings.

## CONCLUSION

GAD Abs are directed against an intracellular antigen. The proposed pathogenic mechanisms of neurological disease in patients with antibodies directed against intracellular proteins is not clear. The present study emphasized on the importance of studying the CSF of patients with encephalitis suspected to be mediated by GAD autoimmunity. Both serum and CSF level must be assessed simultaneously as CSF level may change rapidly with fluctuation of disease.

## DISCLOSURE

No disclosure of importance in this study.

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