

Anti-glutamic acid decarboxylase antibody (GAD) syndromes may have more aggressive disease course in African Americans and early onset of presentation compare to Caucasians group

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ABSTRACT

Anti-Glutamic acid decarboxylase antibodies (GAD) are increasingly diagnosed in the clinic and this antibody related syndromes can manifest commonly as autoimmune encephalitis, Stiff person syndrome and cerebellar ataxia. However, it is unclear if the race has role in age of incidence, presentation and severity of symptoms of anti-GAD associated conditions. In our cohort of 40 patients who were anti-GAD positive, we observed that the age at which the anti-GAD titers turned out to be positive was significantly lower in African Americans (AA) compared to Caucasians (Cau) irrespective of the type of conditions. However, the age at symptoms onset didn't differ significantly different between these groups. Furthermore, AA anti-GAD positive patients had seizures as their initial presentation that was significantly higher in incidence compared to Cau indicating that AA have more aggressive form of autoimmune phenomenon for reasons unknown. Future studies to explore the variations in autoimmune process and their phenotypes may aid in understanding anti-GAD syndromes differently between these racial groups.

1. Introduction

Anti-Glutamic acid decarboxylase antibodies (Anti-GAD) associated autoimmune conditions are increasingly diagnosed in outpatient clinics and there has been a greater interest to understand them better. GAD is an intracellular enzyme expressed by central neuronal and pancreatic islet cells which mediates the formation of gamma-aminobutyric acid (GABA) from L-glutamic acid. While the GABA exerts paracrine functions in pancreatic islets, it acts as an inhibitory neurotransmitter in the central nervous system. Anti-GAD is associated with various neurological syndromes such as stiff person syndrome (SPS), autoimmune encephalitis (AE), cerebellar ataxia mimicking Miller Fisher syndrome and autoimmune epilepsy [1–3]. GAD65 and GAD67 are the two forms of GAD with similar mechanism but are present at different locations [4]. GAD67 is synthesized across all neurons and produces GABA that helps in synaptogenesis and protect the nerve cells from injury but does not participate in neurotransmission. GAD65 is located specifically at the nerve terminals and produces GABA which participates in neurotransmission at the synapses. Anti-GAD syndrome manifestations are usually due to the rare antibodies formed by B cells against GAD65 leading to reduced neurotransmission at synapses. It is unclear how

multiple manifestations occur but may be due to variability in epitope recognition by the antibody [5,6].

Stiff person syndrome (SPS) has extreme muscle stiffness, rigidity and painful spasms in the trunk and limbs, severely impairing mobility [7,8]. Cerebellar ataxia associated with anti-GAD presents with lack of coordination of voluntary muscle movements [9,10]. Cerebellar ataxia can also rarely present with acute neurological findings - acute onset of bilateral external ophthalmoplegia, vertigo antedating ataxia, down-beat nystagmus, “dancing-eye syndrome”, dysarthria, mild to no limb weakness, ptosis, facial palsy, or bulbar palsy [1,11]. Epilepsy in anti-GAD positive patients usually presents with simple partial or complex partial seizures with minimal correlation with seizure frequency and antibodies titers [12]. Autoimmune encephalitis particularly limbic encephalitis presents with headache, irritability, sleep disturbance, delusions, hallucinations, agitation, seizures, psychosis, and short-term memory deficits [13]. It is unclear if GAD65 have more sub-genotypes that are syndrome specific and are expressed periodically at times of exacerbations.

In addition to neurological presentations, more than one third of all cases are found to be associated with other autoimmune disorders such as diabetes mellitus, about 5–10% are associated with others including

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antithyroid, antinuclear and anti-parietal cell antibodies [2,7]. Few studies have reported the presence of GAD in the nerve terminal of neuromuscular junctions [14]. Also, few case-reports have been published on anti-GAD associated ataxia as an extrahepatic manifestation of HCV infection [15]. It is unclear if anti-GAD Ab are independently and solely responsible for the prior mentioned clinical manifestations. Furthermore, even the therapy options for management of these anti-GAD syndromes remain uniform without targeted therapy and that include GABAergic drugs for symptomatic treatment and first-line and second-line immunotherapies that include corticosteroids, immunoglobulins, plasma exchange or immunomodulating agents [8,16].

Given the variability in presentation of symptoms and uncertainty in independent association of anti-GAD with the disease course, the relevance of basic characteristics like ethnicity and gender in the incidence of anti-GAD associated syndromes is not well studied. In a cohort of 40 patients at our center, we analyzed variations in age of incidence and initial anti-GAD positivity for significant differences between Caucasians (Cau) and African Americans (AA).

2. Method

Forty anti-GAD positive patients from our neurology clinic were included in this retrospective study. Pertinent neurological syndromes included seizure with autoimmune encephalitis AE ($n = 24$), SPS ($n = 7$), CA ($n = 2$) and limbic encephalitis ($n = 7$). Twenty-two AA and 18 Cau patients were enrolled in our study and their ages at symptom onset and at time when anti-GAD positivity was detected were noted. We included patients with established diagnosis of anti-GAD associated syndrome including autoimmune epilepsy, cerebellar ataxia, or stiff person syndrome. Their anti-GAD titer was > 100 -fold above reference level. Exclusion criteria include patients with seizures due to other risk factors including CNS infections, penetrating traumatic brain injury, stroke, intracranial hemorrhage and other neurological conditions. We excluded patients who were tested for Anti-GAD as part of diabetes evaluation panel.

Chi-square test was performed to evaluate the variation in incidence of seizures between the ethnic groups. Independent t -test with bootstrapping was applied to analyze the variations in age of initial anti-GAD positivity between the ethnic groups. Data is represented as mean \pm standard error of mean and p -value $< .05$ was considered to be statistically significant.

3. Results

The seizure incidence in anti-GAD positive patients was significantly higher in AA patients compared to Cau patients ($p = .01$, $\chi^2 = 6.07$, Table 1). The age at which anti-GAD titers were positive was significantly lower in AA patients (39.33 ± 4.2 years) compared to Cau patients (52.72 ± 2.84 years, p -value = .01, Fig. 1). The age of symptoms onset was also lower in AA (33.5 ± 0.5 years) when compared to Cau (40.1 ± 0.4 years), however, this was not statistically

significant (p -value = .15). The anti-GAD titer range was 10–1442 nmol/L in AA vs 11.7–999 nmol/L in Cau group.

4. Discussion

In this study we observed the overt presentation of anti-GAD antibody syndrome at a younger age in the AA population than Cau population. Furthermore, AA patients were anti-GAD positive at significantly younger age compared to Cau. The age at which the symptoms were more evident that alerted the neurologists for exploration of anti-GAD panel was lower in AA than Caucasians. This suggests that AA may have more aggressive form of autoimmune phenomenon compared to Cau. Most of the case series with anti-GAD antibody syndromes have not included data on AA populations. In a study done by Saiz *et al* in Spain, the mean age at diagnosis of SPS was 56 years (range 14–77 years) and cerebellar ataxia was 59 years (range 39–77 years), which is comparable to our Cau population [2]. Their study consisted of 61 patients with high anti-GAD antibodies, 22 (36%) had SPS, 17 (28%) had cerebellar ataxia, 11 (18%) had other neurological disorders (epilepsy - 4, PNS - 4; idiopathic limbic encephalitis - 2; myasthenia gravis - 1), and 11 (18%) isolated DM1. Patients with SPS and cerebellar ataxia had the same high frequency in female patients (86% of CA and 94% of SPS), but our patients did not have SPS and ataxia in sufficient numbers to reaffirm this difference.

Our study included 40 anti-GAD positive patients, 7 with a diagnosis of stiff person syndrome (SPS), 2 with cerebellar ataxia (CA), 7 with limbic encephalitis and the remaining 24 with seizure with autoimmune encephalitis (AE). Epilepsy patients have very low prevalence as a manifestation of anti-GAD antibody syndrome, $< 10\%$. The study done by Fernandes *et al.* included 12 patients, 9 had SPS and its variants, 2 had epileptic seizures (one from the SPS group and the other from the cerebellar ataxia group), 3 had acquired secondary cerebellar ataxia associated with anti-GAD antibodies, and there were no cases of limbic encephalitis [17]. Ataxia associated with anti-GAD antibodies is a rare condition and is considered to be a component of a polyglandular autoimmune syndrome in patients with circulating anti-GAD antibodies (10%) according to Brice and Pulst, however in a series of 62 patients with anti-GAD detected at the Mayo Clinic, 39 (63%) were identified as having cerebellar ataxia [9].

The study done by Pittock *et al.*, included 62 patients in whom anti-GAD was detected during paraneoplastic autoantibody screening. The study demonstrated that 32% of the patients were African Americans, and 55% of them had multifocal involvement characterized by a predominant brainstem dysfunction [1]. The authors also noted, that, of the 44 patients in the study who were seen at the Mayo Clinic, 10 (23%) were African American, while African Americans make up $< 10\%$ of their total clinic population. There have been no studies so far comparing the age of presentation among AA and Cau population separately.

Our series of anti-GAD patients stands out for a greater incidence of epilepsy compared to other series, but this may be the result of a large

Table 1
Patient demographics.

Ethnicity	AA	Caucasian	p -Value
Number of patients	22	18	
Gender	8 M, 14 F	9 M, 9 F	
Seizure incidence (refractory autoimmune epilepsy)	17	7	0.01*
Other anti-GAD associated conditions	3 SPS, 1 Cerebellar ataxia, 1 limbic encephalitis	4 SPS, 1 Cerebellar ataxia, 6 limbic encephalitis	
Status Epilepticus	4	2	
Avg. Age at symptoms onset	35 \pm 18 years	43 \pm 12 years	0.15
Age at initial anti-GAD positive titer	39.33 \pm 4.2 years	52.72 \pm 2.84 years	0.01*
Anti-GAD titer range	10–1442 nmol/lit	11.7–999 nmol/lit	

M – Male, F – Female, AA – African-American, CAU – Caucasian, Anti-GAD – Glutamic acid decarboxylase, SPS – Stiff person syndrome. Data represents mean \pm standard deviation and * represents significant p -value.

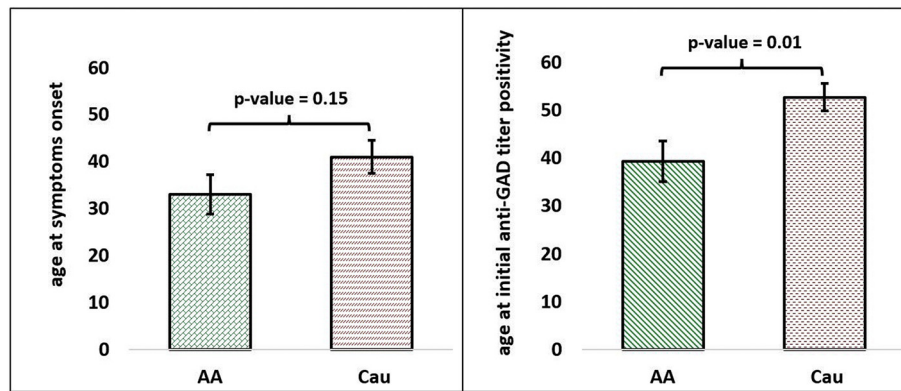


Fig. 1. Bar graphs showing significant difference between age at initial anti-GAD Ab titer positivity between African Americans (AA) and Caucasians (Cau) when the age at onset of symptoms was not significant between those ethnic groups.

epilepsy population in our clinics and frequent screening for autoimmunity in this group. It is notable that while we have similar numbers of AA and Cau with anti-GAD, and both groups have more frequent seizures than in other series, the AA group has twice the seizure incidence of the Cau group. A major strength of our study is our ethnically diverse patient cohort, which allows insight into the role of genetic background in these autoimmune syndromes. A significant limitation is a small sample size.

Overall, our study demonstrates the need for awareness among neurologists of the suspicion of the spectrum of anti-GAD syndromes. A high index of suspicion for anti-GAD should be maintained in patients presenting with new onset seizures, stiffness, encephalopathic features and cerebellar ataxia without other apparent risk factors and having subtle and non-specific neurological symptoms and imaging findings. Our results suggest that the AA population may present at a younger age with these syndromes, with potentially more aggressive phenotypes of anti-GAD syndromes and may have a high incidence of seizures when compared to Cau population. It is also observed that spasticity (SPS) was relatively more common as a presenting feature in Cau, however this was not statistically significant. Validation of our results with prospective, larger scale studies on trending anti-GAD titers can alert physicians to considering anti-GAD syndrome in the differential diagnosis based on ethnicity resulting in earlier detection and therefore appropriate management of these patients with varied presentations of anti-GAD associated syndromes.

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