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Antithyroid Antibodies Are Implicated in Epileptogenesis of Adult Patients With Epilepsy

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Abstract: Antithyroid antibodies (Abs) are associated with epilepsy in steroid-responsive encephalopathy, but have been rarely studied in unselected epilepsy patients. This study aimed to characterize the prevalence and associated factors of antithyroid Abs and other auto-Abs in adult patients with epilepsy.

Epilepsy patients without autoimmune disorders were surveyed for antinuclear antibody (ANA), anti-β2 glycoprotein 1 antibody (aβ2GP1), anticardiolipin IgG Ab, antimicrosomal antibody (AMA), antithyroglobulin antibody (ATA), and thyroid function test.

Of 319 patients, 75 (23.5%) were positive for at least 1 Ab. The most common Ab was anticardiolipin antibody (aCL) (30/319, 9.4%), followed by AMA (24/319, 7.5%), ANA (18/319, 5.6%), aβ2GP1 (18/319, 6.5%), and ATA (6/319, 3.25%). Antimicrosomal Abs were significantly more frequent in patients who were female, older at disease onset, older at the time of study, and had unknown seizure etiology. The presence of aCL was significantly associated with more frequent seizures. Most patients with antithyroid Ab were female and had focal seizures with unknown etiology.

The association of different auto-Abs with different factors suggests that they may have different roles in adult patients with epilepsy. Recurrent seizures and certain antiepileptic medications may cause the production of aCL. The role of antithyroid Abs in adult focal epilepsy with unknown cause, especially in females, warrants further evaluation because of the potential implications on treatment.

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The authors confirm that they have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. The research has been carried out in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Kaohsiung Chang Gung Memorial Hospital (98-1251B).

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Abbreviations: Abs = antibodies, aβ2GP1 = anti-β2 glycoprotein 1 antibody, aCL = anticardiolipin antibody, AEDs = antiepileptic drugs, AMA = antimicrosomal antibody, ANA = antinuclear antibody, ATA = antithyroglobulin antibody, HE = Hashimoto encephalopathy, SREAT = steroid-responsive encephalopathy associated with antithyroid Ab, T4 = thyroxin, TSH = thyroid stimulating hormone.

INTRODUCTION

Immunologic mechanisms are involved in the pathogenesis of epilepsy.[1,2] There is evidence of elevated prevalence of various autoimmune antibodies (Abs) among both adult and pediatric patients with epilepsy.[3–8] The role of these Abs in epilepsy patients remains uncertain. Abs against neuronal membrane proteins, such as anti-*N*-methyl-D-aspartate receptor Abs and antivoltage-gated potassium channel Abs, have been confirmed as causative factors of autoimmune encephalopathy, where seizures are part of the features.[9,10] The responsiveness to immunotherapy in these patients further supports the concept of autoimmune epilepsy.

The role of autoimmunity in epileptogenesis for patients without encephalopathy seems to be more complicated. It is suggested that auto-Abs are capable of binding to brain component and interacting with ion-channels or neurotransmitters, thereby affecting neuronal membrane stability.[11] On the contrary, recurrent seizures have been suggested to affect cytokine production and induce antiphospholipid Ab formation.[3] Moreover, previous case reports revealed that the use of antiepileptic drugs (AEDs) can induce Ab formation, whereas recent cohort studies dispel the association.[4,5,7,8]

Antithyroid Abs have been recently associated with status epilepticus and encephalopathy known as steroid-responsive encephalopathy associated with antithyroid Ab (SREAT) or Hashimoto encephalopathy (HE).[12] The presence and role of antithyroid Abs in unselected epileptic patients remains far from clear. Our aim is to characterize the prevalence of antinuclear antibody (ANA), antiphospholipid Abs, and antithyroid Abs in unselected adult patients with epilepsy, and to correlate their existence with clinical demographic data and AEDs therapies.

METHODS

Subjects

This was a single center observational study. Patients of Chinese ethnicity with epilepsy aged >15 years were recruited from epilepsy outpatient clinics of the Department of Neurology of Kaohsiung Chang Gung Memorial Hospital. Patients with preexisting diagnosed autoimmune disorder were excluded from the study.

Clinical information was obtained by interviews and review of medical recordings by experienced epileptologists (M-HT and Y-CC). A structured questionnaire was used to record the demographic data, which included age, sex, possible etiology, physical/neurologic examination results, past medical history, seizure type, duration of epilepsy, current AED therapeutic state, seizure frequency on the last visit, electroencephalography findings, and results of neuroimaging studies. Clinical seizures and epileptic syndromes were defined according to the latest International League Against Epilepsy Classification/Organization of Seizure and Epilepsies.[13] In this study, intractable epilepsy was defined as a failure of 2 adequate AEDs to achieve seizure freedom.[14] Seizure freedom is defined as freedom from seizures for the past 12 months before study. The study protocol was approved by the Ethics Committee of Chang Gung Memorial Hospital and all of the participants provided written informed consent.

Assessment of Serum Antibodies and Thyroid Functions

Blood samples were collected from patients in the outpatient clinic during interictal state for antimicrosomal antibody (AMA), antithyroglobulin antibody (ATA), ANA, anti-β2 glycoprotein 1 antibody (aβ2GP1), anticardiolipin antibody (aCL), and thyroid function test.

The AMA and ATA were examined by particle-agglutination assay (SERODIA-AMC and SERODIA-ATG; Fujirebio Inc, Tokyo, Japan). ANA was examined by indirect immunofluorescence assay (ANA test kit; Immuno Concepts, Sacramento, CA). Enzyme-linked immunosorbent assay was used to measure the aCL-IgG and aβ2GP1-IgG (Varelisa Cardiolipin Antibodies and Varelisa β2-glycoprotein 1; Pharmacia & Upjohn, Freiburg, Germany). aCL was expressed in U/mL, whereas aβ2GP1 was expressed in GPL/mL. Values $\geq$10 were considered positive.

Free thyroxin (T4) and thyroid stimulating hormone (TSH) were examined by chemiluminescent competitive immunoassay (ADVIA Centaur FrT4 and TSH-3 test kits; Bayer Healthcare, New York City, NY) on the Bayer ADVIA Centaur immunoassay system (Bayer Healthcare). Free T4 value between 0.89 and 1.76 ng/dL and TSH value between 0.35 and 5.5 uIU/mL were considered normal.

Statistical Analysis

Outcome measures were defined as positivity and negativity of various Abs according to the cutoff value. Categorical clinical data, including sex, seizure type, and etiology classification between positive and negative groups, were analyzed by χ^2 or Fisher exact test. Ordinal data such as age at the study, age at seizure onset, duration, and number of AEDs between the 2 groups were analyzed by the Mann–Whitney *U* test. For paired comparison of etiology classifications, *P* values were adjusted using Bonferroni correction. To identify independent factors for Ab positive, we performed logistic regression including significant variables ($P < 0.05$) in univariate analysis. All statistical analyses were conducted using the R software, version 3.1.1.[15]

RESULTS

There were 319 patients enrolled, including 170 males and 149 females. Their mean age at the study was 36.52 years (range, 15–84 years) and mean age of onset was 19.45 years (range, 0.1–77 years). Regarding seizure type, 265 (83.1%) patients were classified as focal, 44 (13.8%) generalized, and 10 (3.1%) undetermined. In terms of etiology, 148 (46.4%) of the patients were structural/metabolic, 51 (16%) were genetic, and 120 (37.6%) were unknown. Moreover, 158 (49.5%) had intractable epilepsy. The mean number of AEDs used was 1.96.

On the basis of the results of Ab positivity (Figure 1), 75 patients (23.5%) were positive for at least 1 Ab. The most common Ab was aCL in 30 (9.4%), followed by AMA in 24 (7.5%), ANA in 18 (5.6%), aβ2GP1 in 18 (5.6%), and ATA in 6 (1.9%). Fourteen patients were positive for >1 Ab, including 3 with both AMA and ATA, 2 with aCL and AMA, 2 with ANA and ATA, and 1 each with ANA+aβ2GPI and aβ2GPI+aCL. Three patients had 3 Abs: ANA+aβ2GPI+aCL, β2GPI+aCL+AMA, and aβ2BPI+AMA+ATA, whereas 2 patients had 4 Abs: ANA+aβ2GPI+aCL+AMA and ANA+aCL+AMA+ATA.

Associations of Antibody Positivity With Clinical Factors

The comparison of the demographic data between Ab positivity and negativity revealed no association of any Ab positivity with age, sex, disease duration, seizure types, and etiology and frequency of seizure (Table 1). There is also no association between Ab positivity and intractability to medical treatment.

As for individual Abs, the positivity of AMA was significantly more frequent in female than in male (11.4% vs 4.3%) patients ($P = 0.02$), older age at the study ($P = 0.003$), older age of disease onset ($P = 0.009$), and unknown etiology ($P = 0.04$) as compared to structural, whereas ANA was associated with genetic etiology ($P = 0.01$). On the contrary, aCL was associated with higher seizure frequencies ($\geq$1 seizure/mo) ($P = 0.04$). Multivariate analysis showed that female gender remained significantly associated with the positivity of AMA (odds ratio: 3.4, $P = 0.015$).

Associations of Antibody Positivity With Antiepileptic Drugs Use

The number of AEDs was not significantly associated with the presence of any Abs (Table 2). However, aCL and overall

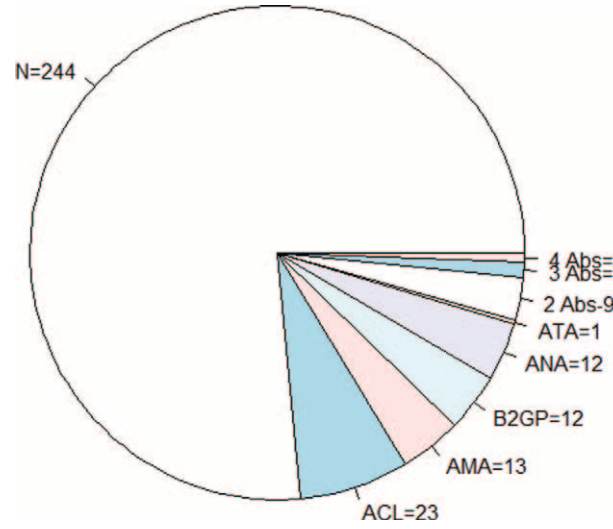

FIGURE 1. Prevalence of antibody in epilepsy patients. Abs = antibodies, aCL = antinuclear antibody, aβ2GP1 = anti-β2 glycoprotein 1 antibody, AMA = antimicrosomal antibody, ANA = antinuclear antibody, ATA = antithyroglobulin antibody.

TABLE 1. Association of Antibody Positivity and Clinical Characteristics

	Overall			ANA			aCL			aβ2GP1			AMA			ATA		
	Pos	Neg	*P*	Pos	Neg	*P*	Pos	Neg	*P*	Pos	Neg	*P*	Pos	Neg	*P*	Pos	Neg	*P*
Sex (n)																		
Male/female	34/41	136/108	ns	9/9	161/140	ns	15/15	155/134	ns	9/9	161/140	ns	7/17	163/132	0.02	2/4	168/145	ns
Age (y)	37.6 ± 13.9	36.2 ± 12.7	ns	39.6 ± 16.4	36.3 ± 12.7	ns	36.2 ± 12.1	36.6 ± 13.1	ns	33.8 ± 10.9	36.7 ± 13.1	ns	43.5 ± 12.3	36 ± 12.9	0.003	41.8 ± 16.2	36.4 ± 12.9	ns
Age of onset (y)	19.7 ± 14.3	19.4 ± 14.1	ns	17 ± 12.8	19.6 ± 14.2	ns	20 ± 13.1	19.4 ± 14.2	ns	14.8 ± 12.5	19.7 ± 14.2	ns	26.9 ± 14.4	18.9 ± 13.9	0.009	29.5 ± 13.6	19.3 ± 14.1	ns
Duration (y)	17.9 ± 13.7	17 ± 10.7	ns	23.2 ± 19.2	16.9 ± 10.8	ns	17.3 ± 12	17.2 ± 11.4	ns	20.6 ± 12.5	17 ± 11.4	ns	15.6 ± 12.1	17.4 ± 11.4	ns	12.8 ± 8.8	17.3 ± 11.5	ns
Seizure type (n, %)		ns			ns			ns			ns			ns			ns	
Generalized	9 (20.5)	35		5 (11.4)	39		3 (6.8)	41		0	44		1 (2.3)	43		0	44	
Focal	66 (25)	199		13 (4.9)	252		27 (9.1)	238		18 (6.8)	247		23 (8.7)	242		6 (2.3)	259	
Undetermined	0	10		0	10		0	10		0	10		0	10		0	10	
Etiology (n, %)		ns			0.02			ns			ns			0.02			ns	
Genetic	14 (27.5)	37	ns*	7 (13.7)	44	0.01*	4 (7.8)	47	ns*	3 (5.9)	48	ns*	4 (7.8)	47	ns*	1 (2)	50	ns*
Unknown	34 (28.3)	86	ns*	6 (5)	114	ns*	11 (9.2)	109	ns*	10 (8.3)	110	ns*	14 (11.7)	106	0.04*	4 (3.3)	116	ns*
Structural/metabolic	27 (18.2)	121		5 (3.4)	143		15 (10.1)	133		5 (3.4)	143		6 (4.1)	142		1 (0.7)	147	
Seizure frequency (n, %)																		
<1/mo	49 (23)	164	ns	11 (5.2)	202	ns	15 (7)	198	0.04	14 (6.6)	199	ns	18 (8.5)	195	ns	5 (2.3)	208	ns
≥1/mo	26 (24.8)	79		7 (6.7)	98		15 (14.3)	90		4 (3.8)	101		6 (5.7)	99		1 (1)	104	
Intractable epilepsy (n, %)																		
Yes/no	38/75	120/244	ns	10/18	148/301	ns	14/30	144/289	ns	11/18	147/301	ns	10/24	148/295	ns	2/6	156/313	ns

Values expressed as mean ± standard deviation. aβ2GP1 = anti-β2 glycoprotein 1 antibody, aCL = anticardiolipin antibody, AMA = antimicrosomal antibody, ANA = antinuclear antibody, ATA = antithyroglobulin antibody, Neg = negative, ns = not significant, Pos = positive.

* Compared to structural/metabolic, *P* values were adjusted with Bonferroni correction.

TABLE 2. Association Between Antiepileptic Drugs and Antibody Positivity

		Overall			ANA			aCL			aβ2GP1			AMA			ATA		
n (%)		Pos	Neg	*P*	Pos	Neg	*P*	Pos	Neg	*P*	Pos	Neg	*P*	Pos	Neg	*P*	Pos	Neg	*P*
AED number	≤1	25	84	ns	7	102	ns	8	101	ns	3	106	ns	7	102	ns	2	107	ns
	2	32	98		7	123		13	117		11	119		12	118		3	127	
	≥3	28	62		4	76		9	71		4	76		5	75		1	79	
PHT	Y/N	28/47	50/194	0.005	5/13	74/228	ns	14/16	64/225	0.006	3/15	75/226	ns	9/15	65/230	ns	3/3	74/239	ns
CBZ	Y/N	17/58	82/163	ns	3/15	95/206	ns	6/24	92/197	ns	7/11	91/210	ns	5/19	93/202	ns	1/5	97/216	ns
VPA	Y/N	24/51	88/156	ns	8/10	104/197	ns	9/21	103/186	ns	6/12	106/195	ns	6/18	106/189	ns	0/6	112/201	ns
LTG	Y/N	22/53	84/160	ns	5/13	101/200	ns	9/21	97/192	ns	8/10	98/203	ns	6/18	100/195	ns	2/4	104/209	ns
TPM	Y/N	15/60	34/210	ns	3/15	46/255	ns	7/23	42/247	ns	4/14	45/256	ns	6/18	41/254	ns	2/4	47/266	ns
LEV	Y/N	27/48	98/146	ns	5/13	120/181	ns	16/14	109/180	ns	7/11	118/183	ns	7/17	118/177	ns	1/5	124/189	ns
PHB	Y/N	4/71	22/222	ns	1/17	25/276	ns	0/30	26/263	ns	2/16	24/277	ns	1/23	25/270	ns	1/5	25/288	ns
OXC	Y/N	12/63	26/218	ns	2/16	36/265	ns	7/23	31/258	ns	3/15	35/266	ns	2/22	36/259	ns	1/5	37/276	ns
GBP	Y/N	3/72	4/240	ns	0/18	7/294	ns	1/29	6/283	ns	1/17	6/295	ns	1/23	6/289	ns	0/6	6/306	ns
VGB	Y/N	2/73	9/235	ns	0/18	11/290	ns	1/29	10/279	ns	2/16	9/292	ns	0/24	11/284	ns	0/6	11/302	ns

Categorical data were analyzed by χ^2 test or Fisher exact test. aβ2GP1 = anti-β2 glycoprotein 1 antibody, aCL = anticardiolipin antibody, AED = antiepileptic drug, AMA = antimicrosomal antibody, ANA = antinuclear antibody, ATA = antithyroglobulin antibody, CBZ = carbamazepine, GBP = gabapentin, LEV = levetiracetam, LTG = lamotrigine, N = no, Neg = negative, ns = not significant, OXC = oxcarbazepine, PHB = phenobarbital, PHT = phenytoin, Pos = positive, positive, TPM = topiramate, VGB = vigabatrin, VPA = valproate, Y = yes.

Ab positivity were significantly more frequent in patients receiving phenytoin.

Clinical Features of Antithyroid Antibody Positive Patients

The clinical features of 25 patients with positive antithyroid Abs (AMA and/or ATA) (Table 3, details in Supplementary Table) revealed that most (24/25, 96%) of the patients had focal epilepsy. Only 1 had genetic generalized epilepsy. The age at seizure onset ranged from 6 to 64 years, with a female to male ratio of 2:1. Among the 24 patients with focal epilepsy, 15 (62.5%) had unknown etiology despite having brain magnetic resonance imaging study, and 6 patients were due to structural lesions, including previous central nervous system trauma, tumor, hippocampal sclerosis, and vascular malformation.

Ten (40%) were refractory to AEDs treatment. All of the patients underwent thyroid function tests and only 4 had abnormal findings, including 3 with mild hypothyroidism and normal TSH level and 1 with overt hypothyroidism and elevated TSH level.

DISCUSSION

This study demonstrates that the presence of auto-Abs is not uncommon (23.5%) in unselected adult epilepsy patients, which is consistent with previous reports that range from 10% to 40%.[4–8] Moreover, auto-Abs are more commonly seen in patients with unknown etiology (28.3%) rather than in those with structural causes (18.2%). In this study, the presence of different auto-Abs is associated with different clinical factors, suggesting their different roles in adult epilepsy.

Elevated aCL is associated with higher recent seizure frequencies. A previous study has also associated a long duration of epilepsy and poor seizure control with aCL in patients with focal epilepsy.[4] In another study on a pediatric population, aCL is associated with multiple seizure types, younger age of onset, and longer duration.[6] The underlying biology between frequent seizures and aCL remains unclear, although it is hypothesized that longstanding uncontrolled seizure itself can activate cytokine formation, subsequently leading to Ab formation. Alternatively, cardiolipin is an important composition of the inner mitochondrial membrane. Prolonged seizures have been demonstrated to induce oxidative stress and mitochondrial dysfunction, and the ensuing neuronal death.[16,17] Aberrant immune response to exposed inner mitochondrial membrane may lead to aCL formation. Thus, the elevation of aCL in patients may be a maker of seizure-related cell damage.

TABLE 3. Clinical Features of Epilepsy Patients With Antithyroid Antibodies

n = 25	Patient Characteristics
Female/male (%)	17 (68)/8 (32)
Onset age (mean, range in y)	28.5, 6–62
Duration (mean, range in y)	14.4, 2–41
Focal/generalized seizures (%)	24 (96)/1 (4)
Etiology	
Unknown (%)	15 (60)
Structural (%)	6 (24)
Genetic (%)	4 (16)
Refractory epilepsy (%)	10 (40)
Normal thyroid function (%)	21 (84)

The association of antithyroid Ab and epilepsy has recently been noted in HE and SREAT.[12] The substantial response to steroid treatment and immunotherapy raises the need for prompt diagnosis.[18,19] The role of antithyroid Abs in patients with epilepsy, but without encephalopathy, has rarely been studied before. In 3 pediatric studies, only 1 patient has been found to have elevated AMA.[6,20,21] In contrast, the present study shows that 7.8% (25/319) of adult epilepsy patients have antithyroid Abs. Previous study suggested that aging is associated with the increase of production of auto-Abs, possibly because of perturbations in the regulatory mechanisms of the immune system.[22] However, later studies argued that thyroid autoimmune phenomena might be related to age-associated disease rather than the consequence of the aging process itself.[23,24] The association of older age in our study could be explained by aging or age-associated disease; nevertheless, patients with unknown etiology are more likely to have positive antithyroid Abs compared to patients with structural lesion cannot be explained by aging process per se. Similar to the current findings, Miro et al[25] recently reported elevated antithyroid Abs in 11/23 (47.8%) patients with adult-onset temporal lobe epilepsy of unknown etiology compared to only 4.3% among those with known etiology. They also observed that elevated antithyroid Abs tend to be seen in middle-aged woman with nonrefractory epilepsy and unknown etiology.

In our study, the preponderance of focal epilepsy with unknown etiology in patients who are positive for antithyroid Abs raises interests as to whether autoimmunity is the underlying cause. Nonetheless, some patients with elevated antithyroid Abs have structural or genetic etiologies, suggesting that antithyroid Abs are not specific in terms of diagnosis. Even in patients with unknown etiology, elevated antithyroid Abs are likely an ''epiphenomenon'' of an underlying autoimmune process that is responsible for recurrent seizures.

The lack of association with disease duration and seizure frequency argues against the hypothesis that antithyroid Abs are induced by recurrent seizures or prolonged AEDs use. The association with older age of onset also explains why antithyroid Abs are more prevalent in this study compared to pediatric cohorts.[6,20,21]

The antigen target of antithyroid Ab within the brain is still unclear. Several antigens within the central nervous system have been reported as epitopes of HE patients such as alpha-enolase, dimethylargininase-I, and aldehyde reductase-I.[26,27] The autoimmune response to these antigens has been hypothesized to lead to vascular or neuronal damage, which causes seizures and cognitive deterioration. The quest for the true autoantigen or a more reliable test continues.

In this study, ANA is more likely to be positive in genetic etiology and tends to be more frequent in generalized seizures (11.4%) than in focal seizures (4.9%). The reasons are unknown, especially because previous studies on the presence of ANA in different seizure types and etiology are controversial.[4,5,7,8,28] Peltola et al[7] found that ANA is more frequently found in newly diagnosed and localization-related refractory epilepsy compared to generalized epilepsy in adults,[7] whereas ANA is reported more frequently in symptomatic/cryptogenic generalized epilepsy in children.[6]

The findings here are in line with the emerging concept where immunity is responsible for a proportion of patients with epilepsy of currently unknown etiology. Recently, several studies reported good response to steroid/immunotherapy in refractory epilepsy patients with clinical and serological evidence suspect autoimmune basis.[19] The response to steroid treatment or immunotherapy cannot be validated as this has not been investigated in our study.

The increasing prevalence of auto-Abs in epilepsy patient is regarded as a consequence of using AEDs. In this study, phenytoin use is associated with the presence of aCL. As aCL is also associated with more severe recent seizures, it is also possible that phenytoin was more commonly prescribed in these patients. Other AEDs are not associated with the increased Abs positivity. Several studies also consistently showed lack of association between AEDs and Abs formation.[4,5,7,8] Our study is limited by lack of normal controls and single ethnicity; more studies on different ethnicity are warranted.

In conclusion, the mechanism for the presence of auto-Abs in patients with epilepsy is likely to be heterogeneous. Antithyroid Ab is different from traditional auto-Abs, which is associated with higher seizure frequencies. In contrast, antithyroid Abs are observed more commonly, although not specifically, in females with late-onset focal epilepsy of unknown etiology. Further immunologic study to identify the true antigen for these patients will facilitate the clinical diagnosis and selection of patients who may benefit from immunotherapy in addition to traditional AEDs.

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