Autoimmune epilepsy: clinical features, management and outcomes

Divyanshu Dubey MD[1], Ryan Hays MD[1], Puneet Gupta MD[1], Mark Agostini MD[1], Kan Ding MD[1], Paul Van Ness MD[1], Steven Vernino MD PhD[1]

[1] University of Texas Southwestern Medical Center, Dallas, Texas

Background

•Despite increased recent research interest, no clear guidelines exist for the diagnosis or management of autoimmune epilepsy.
•Autoantibodies associated with encephalitides, as well as with epilepsy, include those directed against

- •Membrane antigens: anti-VGKc, anti-NMDA and antii-AMPA, anti-P/Q type VGCcand anti-$GABA_B$
- •Intracellular neuronal antigens: anti-Hu, anti–Ma2, anti-CRPM-5, etc.

•For the intracellular antigens, the pathophysiology of autoimmunity is T-cell mediated, rather than antibody-mediated as with surface antigen-related autoimmunity. Mechanism for encephalitis among patients with anti-GAD and anti-thyroid antibodies remain unclear.

Objective

•We hypothesized, earlier diagnosis as well as earlier treatment initiation would lead to better Responder Rate for autoimmune epilepsy patients.

•Additionally we evaluated the response to immunomodulatory therapy among patients with or without underlying malignancy.

Methods

•Retrospective chart review using data from two teaching hospitals [Parkland Memorial Hospital (PMH) and UT Southwestern University Hospital (UTSW)] from January 2008 through December 2013.

• Patients were screened by selecting charts with a primary diagnosis corresponding to the ICD-9 code of encephalitis (323.0) during the hospital encounter.

•Cases included in the study were patients presenting with new onset seizure activity, plus atleast two of the following:

(1) Presence of CSF findings consistent with inflammatory involvement of brain parenchyma (lymphocytic pleocytosis or elevated CSF protein > 50).
(2) MR image showing signal changes consistent with encephalitis (mesial temporal FLAIR signal changes).
(3) Presence of autoimmune/paraneoplastic antibodies in serum or CSF which have been associated with autoimmune encephalitis in previous studies (Hu, CRMP, VGKC, NMDA, GAD, amphiphysin, GABA, glycine, ANNA, PCA-2, striational, gAChR, P/Q type calcium channel antibody).
(4) Response to immunomodulatory therapies.

• Cases were excluded if there was evidence of another identified cause of the patient's symptoms:

(1) Presence of CSF viral/bacterial/fungal antigens or antibodies or DNA PCR which could explain underlying acute inflammatory brain parenchymal changes.
(2) Presence of metabolic abnormalities which could have precipitated seizures (severe renal or hepatic failure, malignant hypertension, severe hypo/hyperglycemia).
(3) Presence of brain structural lesions such as stroke, tumor, traumatic lesions, heterotopias, mesial temporal sclerosis, vascular malformation, abscess or infectious lesion which could have precipitated the presenting seizures.

•Cases selected based on inclusion and exclusion criteria that did not have a pre-specified antibody were further divided based on the presence or absence of high titers of TPO antibodies (>100 IU/ml).

•Clinical data was analyzed using SPSS 21 software. Categorical variables were analyzed using Chi Square. Normative data and non-normative data were analyzed using independent t-test and Mann-Whitney U test respectively. Due to multiple comparisons Bonferroni correction was utilized and p- value of < 0.05 was considered statistically significant.

Results

•34 patients were included in the study. Mean age of patients was 44.94 years and 64.7% (22) of the patients were males.

•Electrographic seizures were documented in 64.7% (22) of patients in our institution. Twelve patients had clinical or electrographic evidence of seizures at an outside hospital.

•22 had unilateral and 4 had bilateral temporal lobe onset, while 8 had extra-temporal onset/multiple ictal foci.

•29.4% (10) patients had only electrographic seizures, without clinical correlate, while 44.1% (15) patients were discovered to have focal status epilepticus on VEEG monitoring.

•Median number of seizures during initial prolonged VEEG monitoring was 8 (range 0 to 48)

• Median number of anti-seizure medications used was 2 (range 1 to 5)

•94.1% (32) patients received immunomodulatory therapies, including high dose corticosteroids (96.8%), plasmapheresis (62.5%), IVIG (34.4%), Rituximab (21.8%), mycophenolate (15.6%), cyclophosphamide (12.5%).

•Median time to clinic follow-up post discharge was 53.50 days (19 to 101 days).

•63.3% (19) of patients had 50% reduction in seizure frequency at the first clinic visit, following inpatient management of acute episode.

•6 (17.6%) patients had complete resolution of seizures on initial clinic follow up.

•Patients without an underlying malignancy had a better RR ($p<0.05$).

•Time from symptom onset to EEG ($U= 56.00$, $p<0.05$), symptom onset to CSF ($U= 56.50$, $p<0.05$) and symptom onset to MRI ($U= 41.00$, $p<0.005$) was significantly lower among patients who had a favorable Responder Rate.

•Duration symptom of onset to diagnosis ($U= 48.00$, $p<0.005$) and duration of symptom onset to immunomodulatory therapy ($U= 43.00$, $p<0.005$) was also significantly lower among patients who had ≥ 50% reduction of seizures.

•Even following adjustment of baseline characteristics (age gender, race, type of antibody) time from symptom onset to diagnosis (CI 0.82-0.98, $p<0.05$) and time from symptom onset to immunomodulation (CI 0.83-0.99, $p<0.05$) continued to be significantly lower in group showing clinic improvement.

•Patients with the VGKc antibody more commonly had MRI changes (78%) consistent with encephalitis, compared to those with NMDA-R antibody (28.5%) patients; this difference was statistically significant ($p = 0.02$).

•The type of autoimmune antibody (VGKc or NMDA) was not associated with a difference in RR.

Table 2: Depicting Study outcomes

Median Values	≥50% Reduction in seizures	<50% Reduction in seizures	P value
Duration of symptom onset to diagnosis (days)	16	95	<0.005
Duration of symptom onset to Lumbar puncture	17.5	48	<0.05
Duration of symptom onset to MRI	14	74	<0.01
Duration of symptom onset to EEG	12	34	<0.005
Duration of symptom onset to Immunomodulation therapy	19	100.5	<0.005

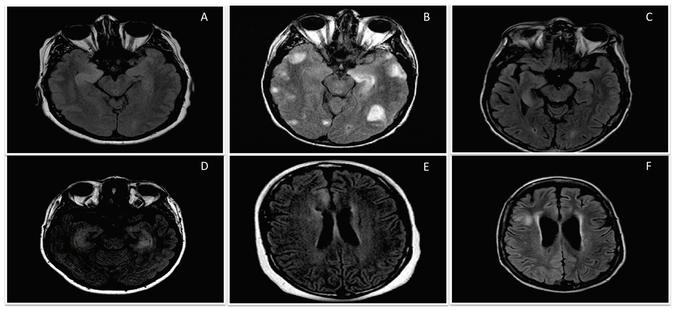

Figure 1: 42 yo female with VGKc antibody: MRI showing bilateral temporal FLAIR hyperintensities (A); 43 yo male with VGKc antibody; MRI showing multifocal FLAIR abnormalities (B); 53 yo male with $GABA_B$ receptor antibody: MRI depicting right medial temporal FLAIR hyperintensity (C); 32 yo male with no underlying paraneoplastic/autoimmune antibody: MRI depicting bilateral medial temporal FLAIR hyperintensities (D); 26 yo female with NMDA-R antibody: MRI depicting frontal lobe FLAIR hyperintensities (E,F).

Antibody	Cases	Age (yrs)	Sex	Race	Malig.	Initial symptom	MRI pattern	Electrographic seizure onset	Mean AEDs	FNCSE	RR
VGKc	8	56	M 7 F 1	CA 5 AA 2 HP 1 OT 0	3 (breast Ca, thymoma, lymphoma)	Seizures (25%); speech changes (12.5%); altered mentation (12.5%)	NL 0 UT 4 BT 2 ET 1	UT 6 BT 1 ET 1	2.00 (SD 1.00)	2	5 (62.5%)
NMDA	7	29	M 4 F 3	CA 3 AA 1 HP 3 OT 0	2 (ovarian teratoma)	Seizures (28.6%); altered mentation (14.3%)	NL 5 UT 1 BT 0 ET 1	UT 5 BT 1 ET 1	2.00 (SD 1.00)	2	3 (42.9%)
GAD	4	50	M 1 F 3	CA 3 AA 1 HP 0 OT 0	1 (prostrate Ca)	Memory loss (33.3%), movement disorder (16.7%)	NL 2 UT 0 BT 2 ET 0	UT 2 BT 2 ET 0	1.00 (SD 4.00)	2	2 (50%)
$GABA_B$	2	37	M 1 F 1	CA 1 AA 0 HP 1 OT 0	1 (SCC lung)	Seizures (100%)	NL 0 UT 1 BT 0 ET 1	UT 1 BT 0 ET 1	4.00 (SD 0.00)	2	1 (50%)
Anti-thyroid	5	55	M 3 F 2	CA 4 AA 1 HP 0 OT 0	0	Seizures (20%); movement disorder (20%)	NL 2 UT 1 BT 0 ET 2	UT 2 BT 0 ET 3	2.00 (SD 1.00)	3	2 (40%)
None	8	42	M 6 F 2	CA 4 AA 1 HP 1 OT 2	2(testicular Ca, ADCA lung)	Seizures (62.5%); altered mentation (12.5%)	NL 1 UT 4 BT 2 ET 1	UT 6 BT 0 ET 2	3.00 (SD 1.00)	4	5 (62.5%)

Table 1: Demographic, clinical and electrographic characteristics of patients included in the study

Table legend: VGKc *voltage gated potassium channel antibody*; NMDA *N-methyl-D-aspartate receptor antibody*; GAD *glutamic acid decarboxylase receptor antibody; $GABA_B$ γ-aminobutyric acid B receptor antibody*; M *Male*; F *Female*; CA *Caucasian*; AA *African American*; HP *Hispanic*; OT *Other*; Malig. *presence of underlying malignancy*; Ca Cancer; ADCA Adenocarcinoma; SCC small cell cancer; NL *Normal*; UT *unilateral temporal*; BT *bilateral temporal*; ET *extra-temporal*; AEDs *anti-epileptic drugs*; FNCSE *focal non-convulsive status epilepticus*; RR *50% seizure reduction in response to therapy*

Conclusions

•This study highlights important clinical aspects of autoimmune epilepsy.
•Early diagnosis is likely the most critical step for affected individuals, and the summarization of the common clinical and electrographic presentations provided herein may aid in that diagnosis.
•Our study demonstrates that timely initiation of immunomodulatory agents helps reduce seizure frequency.
•The patients without an underlying malignancy tend to respond better to such therapy.
•Future prospective studies will be necessary to determine the ideal immunomodulatory treatment regimen for patients based on clinical presentation and antibody-type.

References

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