Seizure 29 (2015) 143–147

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Retrospective case series of the clinical features, management and outcomes of patients with autoimmune epilepsy

Divyanshu Dubey *, Niyatee Samudra, Puneet Gupta, Mark Agostini, Kan Ding, Paul C. Van Ness, Steven Vernino, Ryan Hays

Department of Neurology and Neurotherapeutics, University of Texas Southwestern Medical Center, United States

ARTICLE INFO

Article history:
Received 19 January 2015
Received in revised form 21 April 2015
Accepted 23 April 2015

Keywords:
Limbic encephalitis
Paraneoplastic syndrome
Epilepsy
Immunomodulation

ABSTRACT

Purpose: Analyze clinical and electrographic characteristics of patients with autoimmune epilepsy, and evaluate the effect of early diagnosis and treatment on reduction of seizure frequency.
Methods: Observational retrospective case series, conducted using electronic medical data from two teaching hospitals. Clinical data was collected from 2008 to 2013. Cases of new onset seizures were selected based on the presence of laboratory evidence of autoimmunity.
Results: 34 hospitalized patients who presented predominantly due to seizures with concern for autoimmune etiology were identified. Mean age of patients was 44.94 years and 64.7% were males. Autoimmune antibodies were detected in 76.5% (26) of patients as follows: VGKc (8); NMDA-R (7); anti-thyroid (5); GAD (4); $GABA_B$ (2). 22 patients had unilateral temporal lobe onset and 4 had bilateral temporal lobe onset, while 8 had extra-temporal onset/multiple ictal foci. Median number of seizures during initial prolonged vEEG monitoring was 8 (range 0–48); median number of anti-seizure medications used was 2 (range 1–5). 9 patients had an underlying malignancy. 94.1% (32) patients received immunomodulation, as follows: high dose corticosteroids (96.8%), plasmapheresis (62.5%), IVIG (34.4%), rituximab (21.8%), mycophenolate (15.6%), cyclophosphamide (12.5%). 63.3% (19) participants achieved ≥50% seizure reduction (Responder Rate) at first clinic visit. Patients without malignancy had better seizure control ($p < 0.05$). Time from symptom onset to diagnosis ($p < 0.005$) and symptom onset to immunomodulation ($p < 0.005$) was significantly lower among patients who achieved responder rate (RR).
Conclusion: This study highlights certain important clinical and electrographic aspects of autoimmune epilepsy, and the significance of early diagnosis and initiation of immunomodulatory therapy.

1. Introduction

Autoimmune epilepsy is an under-recognized condition without standardized management guidelines [1]. However, identifying an underlying autoimmune etiology for epilepsy is critical, as these patients may remain refractory to conventional anti-seizure medications (ASM). A large population-based study ($n > 2{,}000{,}000$) showed that patients with autoimmune disease constituted 17.5% of patients with epilepsy, and that the presence of an autoimmune disorder may contribute to a fourfold increased risk of epilepsy [2]. It is reasonable to have a high index of suspicion for autoimmune epilepsy in these patients [3]. Despite increased recent research interest, no clear guidelines exist for the diagnosis or management of autoimmune epilepsy. Various immunomodulatory therapies, including steroids, intravenous immunoglobulin (IVIG), cyclophosphamide, and rituximab have been utilized to achieve seizure control in ASM-resistant patients [4].

Epilepsy is a recognized manifestation of autoimmune encephalitis [5]. Autoantibodies associated with encephalitides, as well as with epilepsy, include those directed against neuronal intracellular antigens or neuronal cell surface antigens. Neuronal cell surface antigens include voltage gated potassium channel complex (VGKc), NMDA and AMPA glutamate receptors, and GABA receptors, whereas intra-neuronal autoantibodies include anti-Hu, anti-Ma2, and anti-CRMP-5 [3,6,7]. Intraneuronal antibodies have been shown to be a marker of underlying malignancy [8]. Neuronal cell death associated with these antibodies has shown to be T-cell mediated, rather than direct antibody-mediated as with surface antigen-related autoimmunity [9–11].

Our study is a retrospective case series of 34 patients with varied clinical and electrographic characteristics who were

* Corresponding author at: University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-9047, United States. Tel.: +1-2142839782.
E-mail address: divyanshudubey87@gmail.com (D. Dubey).

http://dx.doi.org/10.1016/j.seizure.2015.04.007
1059-1311/

diagnosed with autoimmune epilepsy. It contributes to the currently sparse literature characterizing autoimmune epilepsy and its management.

We hypothesized that that early diagnosis, as well as early treatment initiation, would lead to significant reduction in seizure frequency, as measured by responder rate (RR). Additionally we also hypothesized that the patients with underlying malignancy would respond less favorably to immunomodulatory therapy compared to those without cancer.

2. Methods

We conducted a retrospective chart review using data from two teaching hospitals primarily managing adult patients [Parkland Memorial Hospital (PMH) and UT Southwestern University Hospital (UTSW)]. Clinical data was collected from January 2008 through December 2013. Institutional Review Board approval and site clearance from both sites were obtained. Patients were screened by selecting charts with a primary diagnosis corresponding to the ICD-9 code of encephalitis (323.0, 323.9) during the hospital encounter. Cases included in the study were patients presenting with new onset electrographic seizure activity, plus at least two of the following: (1) CSF findings consistent with inflammation (elevated CSF protein >50 and/or lymphocytic pleocytosis), (2) brain MRI showing signal changes consistent with limbic encephalitis, (3) autoimmune/paraneoplastic antibodies in serum or CSF which have been associated with autoimmune encephalitis in previous studies (any neuronal nuclear/cytoplasmic antibody such as anti-Hu or anti-CRMP-5, any neuronal membrane antibody including anti-VGKC, anti-NMDA-R, anti-$GABA_B$-R, anti-ganglionic AChR, or anti-glutamic acid decarboxylase (GAD) antibody), (4) new onset seizure responding to immunomodulatory therapies. Cases were excluded if there was evidence of another identified cause of the patient's seizures: (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 thyroid peroxidase (TPO) antibodies (>100 IU/ml). Anti-TPO antibody was not included in the pre-specified inclusion criteria, due to lack of specificity of this antibody for autoimmune encephalopathy [12].

Collection of patient health information, including epidemiological and demographic variables [age, sex, race, location (county hospital or university hospital), clinical presentation, symptoms, duration of presentation to diagnosis, laboratory tests, cerebrospinal fluid (CSF) analysis, type of antibodies, electro-encephalography (EEG) findings, imaging (MRI), immunosuppressive therapies used, and neurological outcome] was performed by manual search of the electronic medical record system at both institutions (PMH and UTSW). A reduction of ≥50% seizure frequency was considered a favorable clinical outcome, and was termed the "Responder Rate" (RR).

Categorical variables were analyzed using Chi Square. Assessment of normative distribution of independent variables was performed by Shapiro–Wilk test of normality. Normative data was analyzed by independent t-test, and non-normative data was analyzed using Mann–Whitney *U* test. Due to multiple comparisons, Bonferroni correction was utilized; *p*-value of < 0.05 was considered statistically significant. Binomial logistic regression was utilized to adjust for baseline characteristics.

3. Results

34 patients with autoimmune epilepsy were identified. Table 1 summarizes demographics and results. Mean age of patients was 44.94 years and 64.7% (22) of the patients were males. 52.9% (18) cases came from the county hospital while 47.1% (16) came from the university hospital. Specific autoimmune antibodies were detected in 76.5% (26) of patients; anti-VGKc in 23.5% (8); anti-NMDA-R in 20.6% (7); anti-thyroid/TPO in 14.7% (5); anti-GAD in 11.8% (4); anti-$GABA_B$ in 5.9% (2). Nine patients (26.5%) included in the study had an underlying malignancy; 2 ovarian teratomas, 2 breast cancer, 1 adenocarcinoma of the lung, 1 small cell lung cancer, 1 testicular cancer, 1 papillary thyroid cancer and 1 thymoma. Median duration of symptom onset to EEG was 22 days (3–96 days), symptom onset to diagnosis was 32 days (5–393 days), symptom onset to brain MRI brain was 33 days (2–309 days), and symptom onset to immunomodulatory therapy initiation was 35 days (range 8–396 days). Median time to clinic follow-up after hospital discharge was 53.5 days (19–101 days). Electrographic seizures were documented in 64.7% (22) of patients in our institution, while the remainder of the patients had evidence of electrographic seizures at an outside hospital prior to transfer to our institution. Of the 34 patients included, 22 (64.7%) had unilateral and 4 (11.8%) had bilateral temporal lobe onset, while 8 (23.5%) had extra-temporal onset/multiple ictal foci. 29.4% (10) patients had only electrographic seizures, without clinical correlate; 44.1% (15) patients were discovered to have focal status epilepticus on vEEG monitoring. Interictal discharges were present in 79.4% (27) of cases. Median number of seizures during initial prolonged vEEG monitoring was 8 (range 0–48); median number of anti-seizure medications used was 2 (range 1–5). 70.6% (24) patients had MRI changes concerning for autoimmune encephalitis (Fig. 1).

63.3% (19) of patients had 50% reduction in seizure frequency (RR) 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. 94.1% (32) patients received immunomodulatory therapies, including high dose corticosteroids (96.8%), plasmapheresis (62.5%), and IVIG (34.4%). 9 (28.1%) patients received only high dose corticosteroids as immunomodulatory therapy for acute management of recurrent seizures, whereas the remaining patients received a combination of corticosteroids with plasmapheresis and/or IVIG [Corticosteroids + plasmapheresis: 12(35.3%), Corticosteroids + IVIG + plasmapheresis: 8 (25%), Corticosteroids + IVIG 3 (9.4%)]. Several patients also received additional immunomodulation in the form of chemotherapeutic agents, including rituximab (21.8%), mycophenolate (15.6%), cyclophosphamide (12.5%). There was no significant difference in RR at first clinic visit with use of different immunomodulatory regimens.

Among the two patients who did not receive immunomodulation, one patient was started on levtriacetam 500 mg BID with good seizure control; his evaluation was remarkable for CSF pleocytosis and FLAIR hyperintesity involving left medial temporal lobe, but no antibody was indentified. The second patient had anti-GAD antibody, and also showed significant improvement in seizure frequency following initiation of levtriacetam.

There was no significant difference in seizure reduction based on gender, race, age, hospital category (county or university hospital), presenting symptom (behavior change, memory loss, seizure, altered mental status, speech changes, or movement disorder), or type of antibody detected. But, patients without an underlying malignancy had a better RR ($p < 0.05$). Having antibodies directed against neuronal cell membrane antigens