PRIMER

Antibody prevalence in epilepsy and response to immunotherapy in epilepsy scores: primer for "Predictive models in the diagnosis and treatment of autoimmune epilepsy"

Rishika Quick-Singh
Department of Biology, University of Minnesota Duluth

Abstract

It is only in recent years that epilepsy has been looked at as a symptom of autoimmune responses. Autoimmune epilepsy is very easily misdiagnosed, as the symptoms are often identical to epilepsy with a neurological origin. The purpose of this primer is to provide context to the importance of predictive models, specifically using Antibody Prevalence in Epilepsy (APE) scores and Response to Immunotherapy in Epilepsy (RITE) scores, in the diagnosis and treatment of autoimmune epilepsy. In the original research by Dubey et al. (2017a), APE scores were developed as a predictive model for antibody positivity, and this score was further refined into RITE scores to predict immunotherapy response. Among 1,736 total patients, those who received immunotherapy as a result of the RITE scoring system saw a decrease in seizure recurrence by more than 50%.

Keywords: epilepsy, autoimmune epilepsy, predictive models

INTRODUCTION

Epilepsy is a chronic disease that most notably produces seizures caused by abnormal electrical signals in the brain. It is the fourth most common neurological disorder of all ages and affects 150,000 people per year on average and 65 million people worldwide (Sirven and Shafer, 2014). The most common course of treatment is antiepileptic drugs (AEDs), but over one third of patients live with unpredictable seizures because their epilepsy disorder does not respond to these drugs (Quek et al., 2012). Sixty percent of diagnoses come from unknown **etiology** (Sirven and Shafer, 2014).These patients may be unable to drive, work, or lead normal lives due to frequent seizure outbursts. In addition, they are at risk for sudden unexpected death of someone with epilepsy (SUDEP), which affects 1 in 1000 adults every year (Sirven and Shafer, 2014).

Etiology: the cause or reason for a condition.

Epileptogenesis: the process by which the brain develops epilepsy.

Patients whose epilepsy is not responding to normal treatment may be tested for autoimmune origins. Autoimmune disorders are those in which a patient's immune system mistakes the body's cells as foreign and produces antibodies that attack its own tissue. Autoimmune disorders encompass a broad range of diseases and can be difficult to distinguish from diseases without autoimmune origins. One such disorder is autoimmune epilepsy. Identification and correct treatment of this disorder can drastically improve recovery, and even slow or reverse the course of **epileptogenesis**. Patients whose epilepsy is identified as having an autoimmune origin can be switched to an immunotherapy treatment plan (Quek et al., 2012).

Autoimmune diseases are fairly straightforward to diagnose by testing for the presence of antibodies. Anti-neuronal antibodies are present in the serum and cerebrospinal fluid (CSF) of patients with autoimmune neurological disorders. In the case of autoimmune

Corresponding Author:
Rishika Quick-Singh
quick112@umn.edu

epilepsy, specific anti-neuronal antibodies are present (Irani and Lang, 2008). It is up for debate whether the occurrence of these antibodies is causative or just correlated with autoimmune epilepsy (Palace and Lang, 2000). However, the presence of antibodies in serum and CSF is what allows medical professionals to diagnose neurological autoimmune diseases. Serum is extracted by doing a lumbar puncture or **spinal tap**. Past research linking the presence of **autoantibodies** with seizure occurrence suggested the need for a method for early recognition of autoimmune epilepsy (Suleiman et al., 2013). Dubey et al. 2017a developed a scoring system to be used as a predictive model for the diagnosis of autoimmune epilepsy, and refined this system further to assess potential response to immunotherapy.

Spinal tap: A procedure in which a needle is inserted into the spinal cord between two lumbar vertebrae and cerebrospinal fluid is extracted.

Autoantibodies: Antibodies that react to one's own cells or proteins.

Autonomic nervous system: Part of the peripheral nervous system that directs largely unconscious bodily functions such as breathing, digestion, and heart rate.

Facial dyskinesia: involuntary repetitive movements of the mouth and face.

METHODS

APE and RITE scores

APE scores are used in this study to assign points to various symptoms a patient may exhibit. Nine criteria are assessed and given points. These criteria are symptoms such as neuropsychiatric changes, **autonomic** dysfunction, or **facial dyskinesia**. When evaluated individually, these symptoms would not indicate an autoimmune diagnosis, but when analyzed together they make up a useful tool. Criteria are given one or two points, for a total of 15. If a patient is scored more than 4 points, an autoimmune diagnosis is given. The authors further refined APE scores to include response to immunotherapy and came up with a second measure, RITE scores. These use the same nine criteria as APE scores, with the addition of two more, for a total of 19 points. APE scores are useful in predicting the likelihood of autoimmune etiology, while RITE scores predict the likelihood of immune therapy response [Table 1 of Dubey et al. (2017a)].

Tests for Antibody Presence

A variety of tests are used in this research to assay serum and cerebrospinal fluid, each used to find different antibodies specific to each test:

Immunofluorescence Assay (IFA)

This laboratory technique causes the sample to become fluorescent if the antigen is present. In Dubey et al. (2017a), indirect IFAs were used, but direct IFAs are also a form of the test. In direct IFAs, an antibody marked with fluorescence directly binds to the antigen and allows for detection. In indirect IFAs, a primary antibody binds to the desired antigen. A second antibody marked with fluorescence recognizes the primary antibody, thereby allowing detection (Hagen, 1993).

Radioimmunoprecipitation Assay (RIA)

In this technique, antibodies are immobilized using resin or magnetic beads as support. It is an extremely sensitive test and is used to detect antigens present at less than 0.001 micrograms/ml. The standard curve plots the amount of unbound antigen to the amount of bound antigen over time (Six and Kasel, 1978). In patients with an autoimmune disorder, the bound antigen will be higher than the unbound.

Enzyme Linked Immunosorbent Assay (ELISA)

With the ELISA technique, a sample being tested for autoantibodies is added to a plastic surface laced with antigens. If present, the autoantibodies will bind and stick to the antigens. Secondary antibodies covalently attached to a marker such as an enzyme or fluorescent tag are then added. If the primary antibody is present, it will bind to the

antigen. The secondary antibody will bind to the primary antibody and can be detected through the marker (Hagen et al., 1998).

Immunotherapy

In this paper, the term immunotherapy is used hand in hand with APE scores. Immunotherapy is most commonly used in treating cancer, but is successful in treating other types of immune disorders as well. Treatment revolves around targeting the autoimmune response a patient is exhibiting and shutting it down, including stimulating the patient's own immune system to attack cells (Institute, 2017). One might infer that immunotherapy "response" refers to reduction of seizures.

RESULTS

Before this manuscript, there was a recognition that a scoring system was needed for diagnosing autoimmune epilepsy (Dubey et al., 2017b). Earlier work by this same group described the APE scoring system and applied it in a clinical setting. However, the usefulness of the APE score as a predictor was unknown. This primer focuses on this group's next step in this research, in which APE and RITE scores were analyzed (Dubey et al, 2017a).

They found these scores to have significant promise as predictors in autoimmune epilepsy diagnosis and treatment. APE scores had a high sensitivity, however a low specificity, meaning the score did well at showing autoimmune etiology, but not at confirming if a patient did not have the disorder. APE scores were very good at diagnosing autoimmune epilepsy. Among those that tested positive for CNS-specific antibodies, 97.7% of patients received an APE score over 4 (Figure 1). The comparison study between antibody-positive and antibody-negative cases found that the average APE score was higher among those who tested positive for CNS-specific antibodies (Table 1). Validating the use of APE scores for diagnoses, 92.5% (37 out of 40) of those who responded to immunotherapy had APE

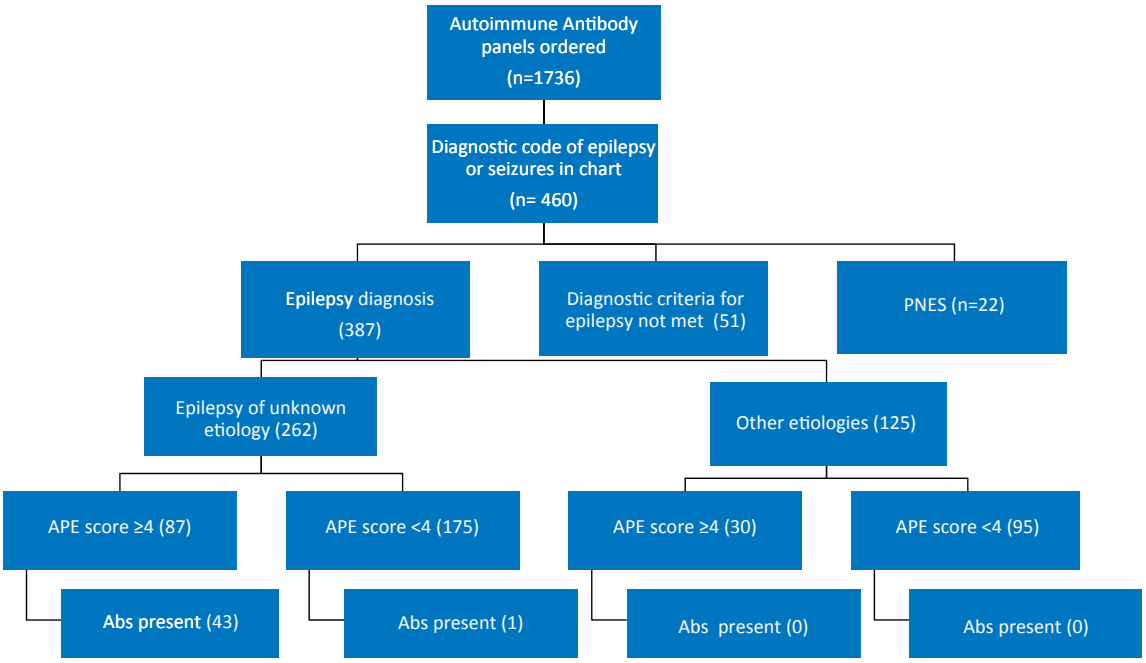

Figure 1: Distribution of epilepsy cases based on neural antibodies present and APE score results. Serum and CSF antibodies (Abs) were only present in patients with a diagnosis of epilepsy from unknown etiology. 97.7% of antibody-positive cases were found in patients with APE scores ≥ 4. PNES: psychogenic nonepileptic seizures. Adapted from Figure 1 of Dubey et al., 2017a.

Table 1: Comparison of antibody-positive and antibody-negative cases*

Variables	Antibody-positive cases (n=44)	Antibody-negative cases (n=343)
Median APE score	6	2
APE score ≥ 4	97.7%	21.1%

*Modified from Table 2 from Dubey et al., 2017a.

scores greater than or equal to four, and responded with at least a 50% reduction in seizure frequency.

RITE scores include all the criteria of APE scores, with the addition of two more. Points were given to patients who received immunotherapy within 6 months of having an epileptic seizure, and for patients whose cerebrospinal fluid analysis were positive for neural plasma membrane autoantibodies. RITE scores were successful at predicting immunotherapy response. They analyzed 77 patients that received immunotherapy. Out of 40 patients who responded to the treatment, 87.5% of patients had a RITE score at or above seven (Table 2). Therefore, RITE scores are good tool for suggesting who should continue immunotherapy.

DISCUSSION

The development of these scoring systems allows doctors to hasten immunotherapy or alter a patient's treatment in other ways to better match their diagnosis. In this paper, the author's also make the point that many autoimmune disorders are chronic, and while many patients see a lessening or disappearance of their symptoms, others may struggle with their disorder daily. Not only is this taxing physically but can be monetarily draining as insurance premiums rise with different treatments. RITE scores may be able to encourage insurance companies to reimburse medical costs by showing the likelihood of immunotherapy success. This paper shows APE and RITE scores to be useful predictive models for the diagnosis and treatment of autoimmune epilepsy. Both patients and doctors will benefit from this research and the use of this scoring system (Dubey et al, 2017a).

Although this is a strong paper, there are several places that need more explanation. Despite the criteria for APE and RITE scores being largely the same, the authors discuss them as being medically distinct. More context is needed for how the addition of only two extra criteria (initiation of immunotherapy within 6 months of symptom onset and detected neural plasma membrane auto-antibody) make RITE scores so distinct from APE scores that the two can be used for separate predictions, especially as the APE score correlates better with response to immunotherapy (92.5% vs 87.5%). Additionally, it is not explained how the point system was created or why a cut off of 4 points was used. As another example, the authors of this paper frequently talk about immunotherapy, but offer no explanations for what this treatment entails, nor what a response to immunotherapy means in this context.

Table 2: Comparison of responders and nonresponders following a trial of immunotherapy*

Variables	Responders (n=40)	Nonresponders (n=37)
Median APE score	6	4
APE score ≥ 4	92.5%	54.1%
Median RITE score	9	4
RITE score ≥ 7	87.5%	16.2%

*Modified from Table 3 from Dubey et al., 2017a.

ACKNOWLEDGEMENTS

I would like to thank Dr. Jennifer Liang, Haley Ersfeld, and Patrick Fehrenbach for assisting me with my writing and their continued support throughout this semester. Their assistance has been incredible, and this manuscript could not have been written without their help. I would also like to thank the University of Minnesota Provost's office and Center for Educational Innovation for providing a Experiments in Learning Innovation Grant through which software used in the production of this manuscript was provided.

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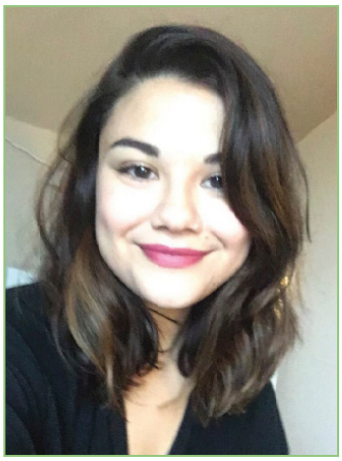

Author Biography: Rishika is a senior majoring in Biology at the University of Minnesota Duluth. She is currently involved in the plant physiology lab as an undergraduate researcher studying variations in wood anatomy. Her future goals are to attend graduate school for neuroscience and pursue research in that field. Her hobbies include running, baking, and spending time with friends and family.