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Predictors of neural-specific autoantibodies and immunotherapy response in patients with cognitive dysfunction

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ABSTRACT

Recognition of autoimmunity as a cause of encephalopathy has increased. Recent studies have validated the use of Antibody-Prevalence-in-Epilepsy (APE) and Responsive-to-immunotherapy-in-Epilepsy (RITE) scores in the evaluation and management of autoimmune-epilepsy. We aim to assess the utility of these models for patients with cognitive dysfunction. Among the evaluated patients, 17% had antibodies universally associated with autoimmune-encephalopathy. NMDA-R-IgG and LGI1-IgG were the most common antibody specificities. Antibody-Prevalence-in-Epilepsy-and-Encephalopathy (APE^2) score ≥ 4 was 99% sensitive and 93% specific for neural-specific-antibodies. Responsive-to-immunotherapy-in-Epilepsy-and-Encephalopathy ($RITE^2$) score ≥ 7 had 96% sensitivity and 86% specificity for favorable initial immunotherapy response. Application of these models may optimize autoantibody evaluations and immunotherapeutic trials.

1. Introduction

Recent studies have revealed that autoimmunity was under-estimated in the past as a cause of encephalopathy or epilepsy (Granerod et al., 2010; Dubey et al., 2017a,b; Dubey et al., 2018a,b). The apparent increasing incident rates of autoimmune encephalitis in recent decades is partly due to increased detection of neural-specific autoantibodies (Dalmau et al., 2008; Gable et al., 2012; Linnoila et al., 2014; Dubey et al., 2018a,b). With timely immunotherapy, there is potential for significant clinical improvement (Titulaer et al., 2013; Toledano et al., 2014; Dubey et al., 2015a,b; Thompson et al., 2018). This realization has increased the frequency of neural autoantibody evaluations and immunotherapy trials (Lang and Prüss, 2017; McCracken et al., 2017). However, over-utilization of these resources are both an economic and a clinical concern. In this regard objective scoring systems derived from variables shown to have significant association with autoimmunity may guide clinical decision making and patient care. Ideally, clinical assessment and standard evaluations for encephalopathy (CSF and MRI brain) would be the foremost considerations before pursuing more specialized investigations. If an autoimmune etiology is suspected, a model predicting likelihood of therapeutic response might justify early immunotherapy and, in some instances, may offer prognostic insight and be of counselling value for patient or caregiver.

Scores for Antibody Prevalence in Epilepsy (APE) and Response to Immunotherapy in Epilepsy (RITE) were derived from analysis of retrospective studies (Table 1) (Dubey et al., 2017a,b). They included clinical variables that were identified to be significantly associated with neural autoantibody positivity or favorable immunotherapy outcome (Dubey et al., 2015a,b). These scores were validated to have a high accuracy in predicting the presence of antibodies and clinical outcomes (responder rate) among patients with epilepsy (Dubey et al., 2017a,b). However, only a subset of patients with autoimmune encephalopathy have co-existing epilepsy (Flanagan et al., 2010; Graus et al., 2016; McKeon, 2016; Dalmau et al., 2017; Tobin and Pittock, 2017). Additionally, even among patients with epilepsy, encephalopathy or cognitive disability contributes to a significant morbidity (Quek et al., 2012; Irani et al., 2013; Toledano et al., 2014). In this study, we aim to validate these scoring systems among patients with encephalopathy or cognitive decline for prediction of neural-specific autoantibody positivity, and response to immunotherapy in terms of neurological and cognitive disability.

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Table 1
Components of the APE^2 score (1A) and RITE^2 score (1B). RITE^2 score included all the components of APE^2 score and 2 additional variables: initiation of immunotherapy within 6 months of symptom onset and plasma membrane-specific autoantibody detected (1B). The assigned APE^2 and RITE^2 scores are the sum of values for all components.

1A: Antibody prevalence in epilepsy and encephalopathy (APE^2 score)	Value	1B: Response to immunotherapy in epilepsy and encephalopathy score (RITE^2 score)	Value
New onset, rapidly progressive mental status changes that developed over 1–6 weeks or new onset seizure activity (within one year of evaluation)	(+1)	New onset, rapidly progressive mental status changes that developed over 1–6 weeks or new onset seizure activity (within one year of evaluation)	(+1)
Neuropsychiatric changes; agitation, aggressiveness, emotional lability	(+1)	Neuropsychiatric changes; agitation, aggressiveness, emotional labiality	(+1)
Autonomic dysfunction [sustained atrial tachycardia or bradycardia, orthostatic hypotension (≥20 mmHg fall in systolic pressure or ≥ 10 mmHg fall in diastolic pressure within three minutes of quiet standing), hyperhidrosis, persistently labile blood pressure, ventricular tachycardia, cardiac asystole or gastrointestinal dysmotility][a]	(+1)	Autonomic dysfunction [sustained atrial tachycardia or bradycardia, orthostatic hypotension (≥ 20 mmHg fall in systolic pressure or ≥ 10 mmHg fall in diastolic pressure within three minutes of quiet standing), hyperhidrosis, persistently labile blood pressure, ventricular tachycardia, cardiac asystole or gastrointestinal dysmotility][a]	(+1)
Viral prodrome (rhinorrhea, sore throat, low grade fever) to be scored in the absence of underlying systemic malignancy within 5 years of neurological symptom onset	(+2)	Viral prodrome (rhinorrhea, sore throat, low grade fever) only to be scored in the absence of underlying malignancy within 5 years of neurological symptom onset	(+2)
Faciobrachial dystonic seizures[c]	(+3)	Faciobrachial dystonic seizures[c]	(+3)
Facial dyskinesias, to be scored in the absence of faciobrachial dystonic seizures	(+2)	Facial dyskinesias, to be scored in the absence of faciobrachial dystonic seizures	(+2)
Seizure refractory to at least to two anti-seizure medications	(+2)	Seizure refractory to at least to two anti-seizure medications	(+2)
CSF findings consistent with inflammation[b] (elevated CSF protein > 50 mg/dL and/or lymphocytic pleocytosis > 5 cells/mcL, if the total number of CSF RBC is < 1000 cells/mcL)	(+2)	CSF findings consistent with inflammation[b] (elevated CSF protein > 50 mg/dL and/or lymphocytic pleocytosis > 5 cells/mcL, if the total number of CSF RBC is < 1000 cells/mcL)	(+2)
Brain MRI suggesting encephalitis[b] (T2/FLAIR hyperintensity restricted to one or both medial temporal lobes, or multifocal in grey matter, white matter, or both compatible with demyelination or inflammation)[c]	(+2)	Brain MRI suggesting encephalitis[b] (T2/FLAIR hyperintensity restricted to one or both medial temporal lobes, or multifocal in grey matter, white matter, or both compatible with demyelination or inflammation)[c]	(+2)
Systemic cancer diagnosed within 5 years of neurological symptom onset[c] (excluding cutaneous squamous cell carcinoma, basal cell carcinoma, brain tumor, cancer with brain metastasis)	(+2)	Systemic cancer diagnosed within 5 years of neurological symptom onset[c] (excluding cutaneous squamous cell carcinoma, basal cell carcinoma, brain tumor, cancer with brain metastasis)	(+2)
	Total (max: 18)	Immunotherapy initiated within 6 months of symptom onset	(+2)
		Neural plasma membrane autoantibody detected (NMDAR, $GABA_AR$, $GABA_BR$, AMPAR, DPPX, mGluR1, mGluR2, mGluR5, LGI1, IgLON5, CASPR2 or MOG)	(+2)
			Total (max: 22)

(AMPAR: amino-3-hydroxy-5-methyl-4-isoxazolepropionic, ANNA-1: Anti-neuronal nuclear antibody-1, ANNA-2: Anti-neuronal nuclear antibody-2, ANNA-3: Anti-neuronal nuclear antibody-3, CASPR-2: Contactin Associated Protein 2, CRMP5: Collapsin response-mediator protein-5, DPPX: dipeptidyl-peptidase-like protein 6, FLAIR: fluid attenuated inversion recovery, GAD65: Glutamic Acid Decarboxylase-65, GABABR: γ-aminobutyric acid-B receptor, GFAP α: Glial fibrillary acidic protein, LGI1: leucine-rich glioma-inactivated protein-1, MOG: myelin oligodendrocyte glycoprotein, NMDAR: *N*-methyl D-Aspartate Receptor, PCA-1: Purkinje cell cytoplasmic antibody type 1, PCA-2: Purkinje cell cytoplasmic antibody type 2).

[a] Scored only if no history of autonomic dysfunction prior to onset of suspected autoimmune syndrome and the autonomic dysfunction not attributable to medications, hypovolemia, plasmapheresis or infection.

[b] Patients scored zero if MRI brain or CSF analysis not performed.

[c] Modifications since the initial version of APE and RITE score.

2. Methods

2.1. Data collection

The study was approved by the institutional review board of Mayo Clinic. We reviewed records of patients with diagnoses of altered consciousness level, short term memory loss, or cognitive or neuropsychiatric dysfunction, for whom serological evaluation for autoimmune encephalitis, autoimmune dementia or autoimmune epilepsy had been ordered (serum and/or CSF) between July 1, 2014 and June 30, 2016 (Fig. 1). Patients presenting with seizures without sustained cognitive changes beyond 24 h were not included. Similarly, patients with ataxia or dysautonomia without cognitive dysfunction also were excluded (Fig. 1). Demographic and clinical data including etiology of cognitive dysfunction or encephalopathy, autoantibody specificity and titer, cancer by history or subsequently found, and results of magnetic resonance imaging (MRI) and positron emission tomography (PET) scan were collected. For patients who received immunotherapy, the initial agents and interval from symptom onset to starting therapy were noted.

2.2. Modifications

Antibody prevalence in epilepsy and encephalopathy (APE^2) scores were computed with three modifications since the initial version (APE score): 1) MRI brain criteria included additional abnormalities recognized as consistent with encephalitis per autoimmune encephalitis diagnostic criteria (T2 or fluid-attenuated inversion recovery [FLAIR] hyperintensity largely restricted to one or both medial temporal lobes, or multifocal involving grey matter, white matter, or both compatible with demyelination or inflammation) (Graus et al., 2016). 2) only cancers diagnosed within 5 years of seizure and/or cognitive dysfunction onset were scored (Graus et al., 2004). 3) score for faciobrachial dystonic seizure (FBDS) was increased (FBDS is a pathognomic feature (Irani et al., 2011) and an independent predictor of leucine rich glioma-inactivated protein 1 (LGI1) IgG positivity (Dubey et al., 2017a,b)). These modifications in the scoring system improved the specificity for prediction of neural autoantibody positivity from 78% to 84% among patients with epilepsy, without sensitivity loss (98%) (Dubey et al., 2017a,b). Response to immunotherapy in epilepsy and encephalopathy (RITE^2) included additional points for neural-specific cell surface autoantibodies and interval of < 6 months from seizure onset to starting immunotherapy (Dubey et al., 2016; Dubey et al., 2017a,b).

2.3. Antibody evaluation

Serum and CSF specimens were screened by standardized mouse