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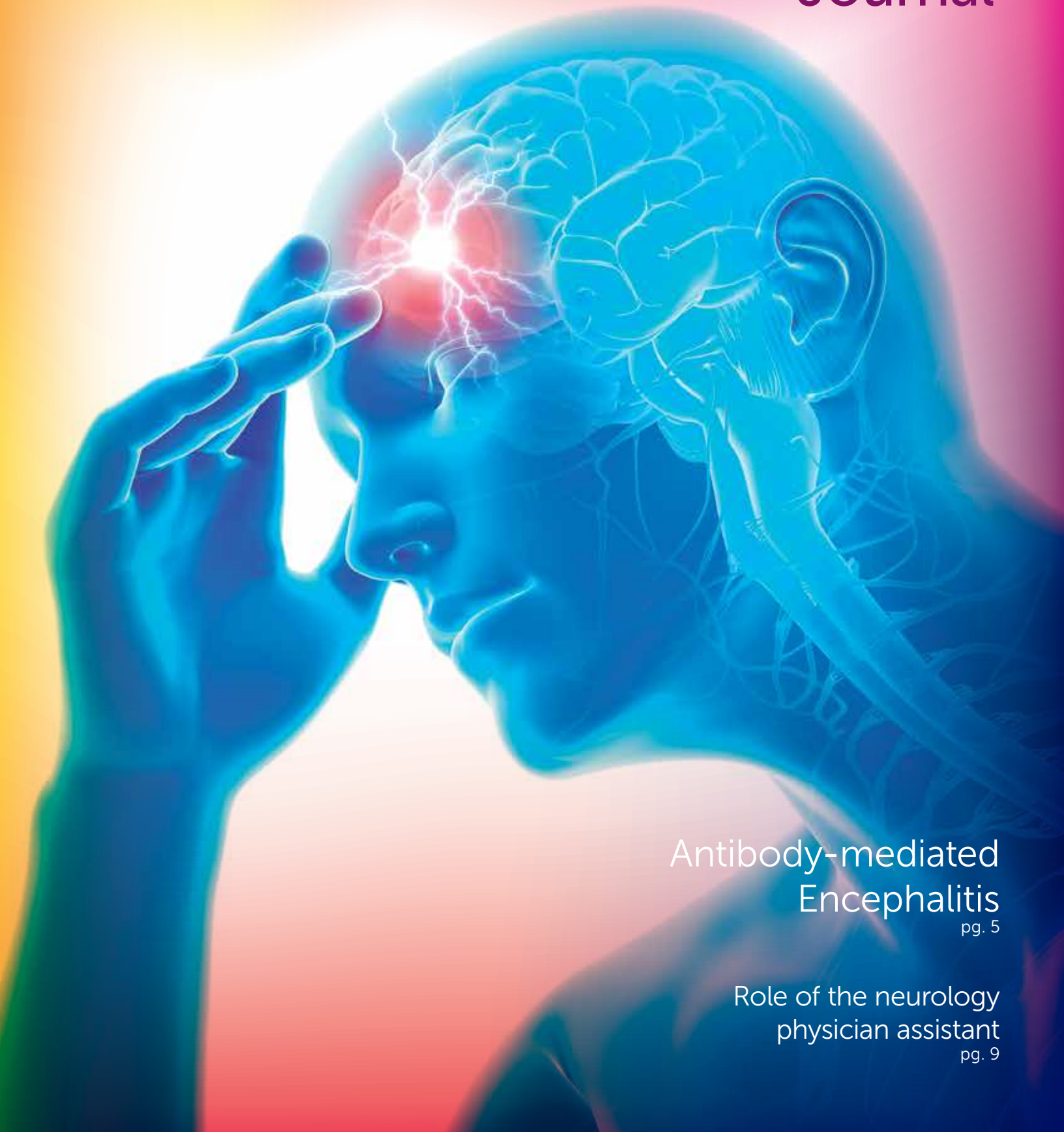
Neuroscience Journal



Antibody-mediated Encephalitis

pg. 5

Role of the neurology physician assistant

pg. 9

As physician co-leaders of Prisma Health–Midlands neuroscience service,

we share a vision to provide the most advanced neurology and neurological surgery treatments available to the residents of the South Carolina. We are excited to share this latest edition of our neuroscience journal featuring articles about antibody-mediated encephalitis and the important role of our neurology physician assistants.

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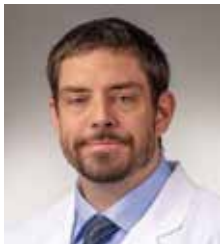
Welcome, new providers!



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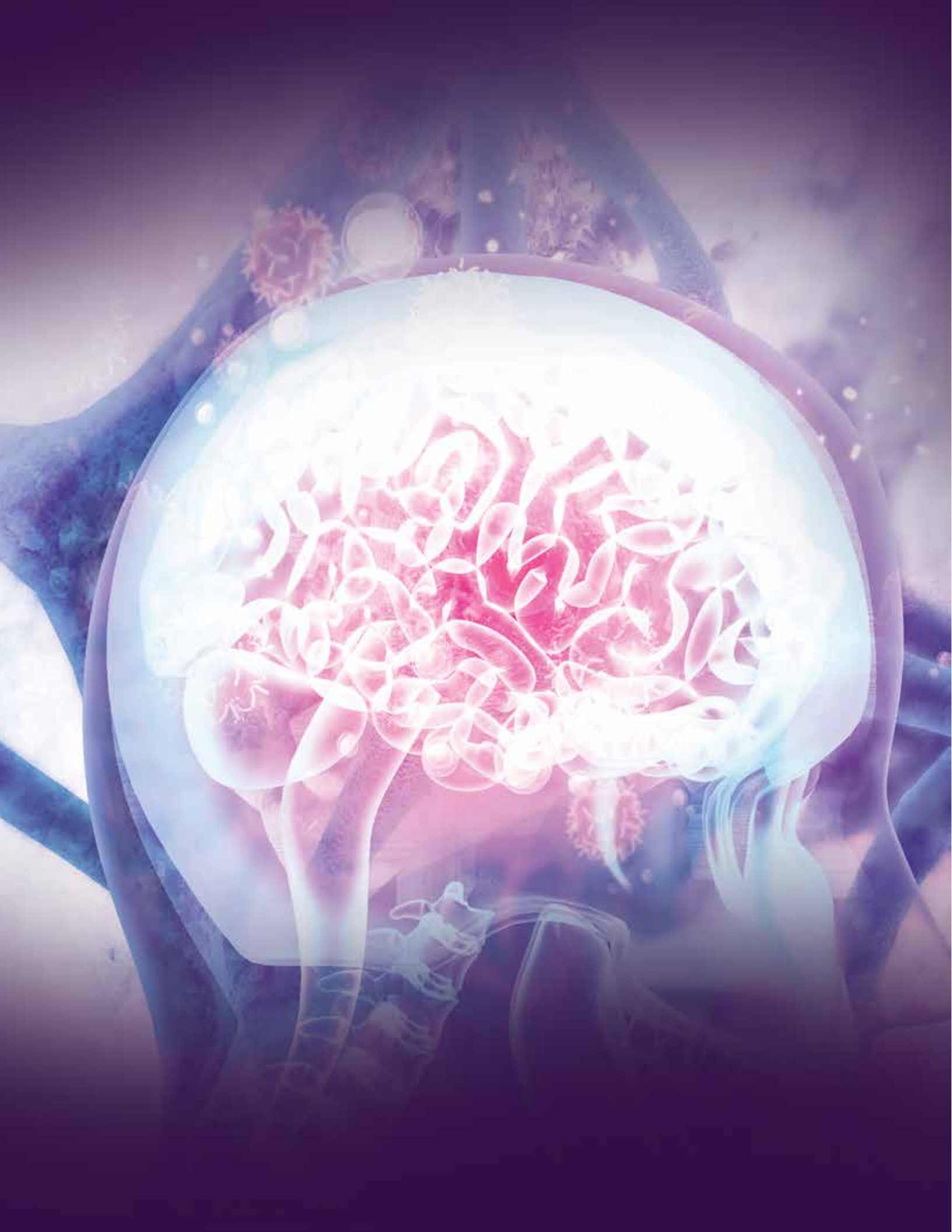

Antibody-mediated Encephalitis: A Window into the Past and Future

By Alex Mirzoev, MD, Palmetto Health-USC Neurology

What do *The Exorcist*, monstrous tumors and the New York Post have in common?

For decades, it was known that serum autoantibodies could cross the blood-brain barrier and lead to neurological symptoms (e.g., Hashimoto encephalopathy, sarcoid leptomeningitis, Sjogren's neuropathy, etc.)[1]. Moreover, the association of neuromuscular junction diseases with particular tumors is well established (thymomas in myasthenia gravis and small-cell lung cancer in Lambert-Eaton syndrome)[2]. These are called paraneoplastic syndromes, since the neoplasm secretes pathological antibodies with distant effects or leads to an autoimmune response in different organ systems.

However, the entire landscape of medicine changed when in the mid-2000s, Dr. Dalmau and colleagues studied patients with severe psychiatric symptoms, refractory to medical treatment. Some patients also exhibited neurological symptoms from dyskinesias to refractory status epilepticus. They discovered clustering of antibodies to the NMDA receptor in the hippocampi of these patients, which explained their hallucinations, delusions, cognitive impairment and seizures. The condition was named anti-NMDA encephalitis[3].

Interestingly, some patients' antibodies could be traced to ovarian teratomas (and were therefore, paraneoplastic). Derived from immature sperm cells or ova, these tumors grow multiple differentiated tissue, leading to combinations of skin, hair, bone (including teeth and nails), muscle, eyes and/or neural tissue. It is the latter that produces the antibodies and tricks the immune system into attacking the brain itself, instead of the ectopic (foreign) tissue (Figure 1 on Page 6). A terrifying imposter tumor indeed.

Since then, several other new antibodies and syndromes from known antibodies and tumors have been described. Outside of seizures and psychosis refractory to their respective medications, new

FIGURE 1 - Ovarian teratoma, the imposter tumor.

and pathognomonic movement disorders have been discovered, such as faciobrachial dystonia, opsoclonus-myoclonus, and severe stiffness with startling[4].

There is a scene in *The Exorcist*, wherein a demon-possessed girl crab-walks. Interestingly, there are rare reports of dystonia resembling crab-walking. Given that seizures alone were regarded as supernatural, one can only wonder if throughout history, observing seizures, hyperreligiosity, hallucinations and such disturbing movements led to witch trials and exorcisms.

In March 2009, an aspiring journalist for the New York Post named Susannah Cahalan began suffering from extreme mood swings, severe fatigue and seizures, all despite treatment. After a monthlong hospitalization at NYU, she was ultimately diagnosed with anti-NMDA encephalitis and treated accordingly[5]. Continuing her career as a journalist, she produced a biography and has become the most prominent and influential spokesperson for these syndromes. (I recommend her memoirs to patients and their caregivers with these conditions.)

Currently, there is a division between tumor-specific ("onconeural"), intracellular, cell-surface and non-neuron specific antibodies (Figure 2). This division has practical implications, as intracellular antibody syndromes will not respond to plasma exchange and onconeural syndromes will only improve with tumor resection.

Back in 2009, Susannah Cahalan required a brain biopsy for correct diagnosis. Ten years later, both serum and CSF (cerebrospinal fluid) samples can be sent to Mayo Clinic or the University of Pennsylvania for a comprehensive analysis of all the known antibody-mediated encephalitides (antibody panels). Though costly, this pales in comparison to the typical prolonged critical care hospitalization (median stay of 49 days)[6] and the fatal consequences if left untreated. These panels are analyzed within 10 days, but the logistics of external testing still lead to a 2–3 week delay in results.

Given the diagnostic difficulty – be it this lag in results or ambiguous symptoms – the Antibody Prevalence in Epilepsy/Encephalopathy (APE) score was created (Figure 3 on Page 8)[6]. Now in its second version, it provides faster and cheaper assessments (clinical, radiological and preliminary CSF studies) to initiate empirical treatment (i.e., without prior knowledge of the exact antibody).

In fact, treatment is where the horror stories take a positive turn. Immunomodulation with high-dose IV corticosteroids, plasma exchange and IVIg is the key to improvement, recovery and remission, though each therapy has limitations and side effects. Since multiple rounds are necessary, other immunosuppression (e.g., rituximab, mycophenolate, etc.) is used to avoid the adverse effects of long-term

FIGURE 2[1]

A: Onconeural antibodies
B: Cell surface antibodies
C: Antibody comparisons

FIGURE 2A Onconeural antibodies

Antibody	Cancer type
ANNA-1/Hu	Lung
ANNA-2/Ri	Breast
ANNA-3	Lung
PCA-1/Yo	Ovarian, breast
PCA-2	Lung
PCA-Tr/DNER	Hodgkin lymphoma
CRMP-5/CV-2	Thymoma
Amphiphysin	Breast
Ma-1, Ma-2	Testicular, breast
Sox-1/AGNA	Lung (LEMS)
Zic4	Lung

FIGURE 2B: Cell surface antibodies

Antibody	Syndromes
AChR	Myasthenia gravis (a1) Autoimmune autonomic syndromes (ganglionic a3) Chronic focal encephalitis (a7)
AMPA-R	Limbic encephalitis Autoimmune epilepsy
AQP4	Demyelinating disease
Caspr2	Neuromyotonia, dysautonomia, epilepsy
DPPX	Encephalopathy, epilepsy
GABA-R (A and B subtypes)	Limbic encephalitis Autoimmune epilepsy
Glutamate-R	Progressive cerebellar degeneration (metabotropic R1) Chronic focal encephalitis (R3) Opsoclonus-myoclonus (D2)
IgLON5	Sleep disorders, bulbar palsy, gait difficulty ("early PSP")
Glycine-R	Stiff-person syndrome Progressive encephalomyelitis, rigidity and myoclonus
LG1	Limbic encephalitis Autoimmune epilepsy (FBD)
MOG	Demyelinating disease
NMDA-R	Limbic encephalitis Autoimmune epilepsy
Septin-5	Cerebellar ataxia, oscillopsia
VGCC	Progressive cerebellar degeneration Lambert-Eaton myasthenia

FIGURE 2C: Antibody comparisons

	Onconeural	Surface	Non-neuron specific
Location	Intracellular	Cell membrane	Intracellular
Cancer risk	High	Moderate	Low
Immune mechanism	Cell-mediated	Direct antibody	Direct antibody
Antibody characteristics	Insensitive but specific	Sensitive, less specific	Less sensitive, less specific
Multiple antibodies	Frequent	Rare	Rare
Treatment	Tumor removal	Immunotherapy	Immunotherapy

FIGURE 3: APE2 score[7]

Antibody prevalence in epilepsy and encephalopathy score (APE2 score)	
New onset, rapidly progressive mental status changes that developed over 1–6 weeks or new-onset seizure activity	(+1)
Neuropsychiatric changes; agitation, aggressiveness, emotional liability	(+1)
Autonomic dysfunction	(+1)
Viral prodrome only to be scored in the absence of underlying malignancy within 5 years of neurological symptom onset	(+2)
Faciobrachial dystonic movements	(+3)
Facial dyskinesias, to be scored in the absence of faciobrachial dystonic seizures	(+2)
Seizure refractory to at least to two anti-seizure medications	(+2)
CSF findings consistent with inflammation	(+2)
Brain MRI suggesting encephalitis (T2/FLAIR hyperintensity restricted to one or both medial temporal lobes, or multifocal in gray matter, white matter, or both compatible with demyelineation or inflammation)	(+2)
Systemic cancer diagnosed within 5 years of neurological symptom onset (excluding cutaneous squamous cell carcinoma, basal cell carcinoma, brain tumor, cancer with brain metastasis)	(+2)
	Max: 18

corticosteroid use or the high costs of regular plasma exchange. Seizures usually resolve within months. Tumor identification and removal lends to remarkably high rates of recovery.

My own experience has paralleled the meteoric rise in the field of autoimmune encephalitis. My first encounter was as a medical student in March 2013 during the OB/GYN rotation. The service was consulted to remove an ovarian "cyst" in a young female with subacute anxiety, seizures and psychosis. Despite my best efforts in presenting the available research to the gynecologists, the awareness was not there (and who listens to medical students anyway?). When the confirmatory antibodies resulted one month later, the patient was transferred to a larger academic center, promptly underwent a salpingo-oopherectomy (removal of ovaries) and eventually recovered.

During my neurology residency 2016–19, the department managed over a dozen cases, which is high for only 3 years in a catchment area of less than a million (but maybe my alma mater is astute at diagnosis?). In the first three weeks at Palmetto Health-USC Medical Group, I had already managed two cases.

These conditions both provide objective insight into ancient traditions (e.g., demonic possession) and into future developments. Neurologists can now lead a team of psychiatrists, oncologists and intensivists in saving people from severe epilepsy, lifelong psychiatric institutionalization and coincidentally, discovering tumors at earlier stages. This extraordinary ability comes with two responsibilities: early detection for best outcomes and contributing to the growing body of data.

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Role of the neurology physician assistant

By Alex Vezzetti, MSPAS, PA-C, Palmetto Health-USC Neurology

Pictured left to right: Khalil Ali, MD; Jasdeep Dhindsa, MD; Alex Vezzetti, PA-C

The national shortage of neurology providers is well known[1]. With an aging population with growing neurological needs, the demand for neurology physicians greatly exceeds the supply – a 16% shortage is expected by 2025. Even in states with an adequate number of neurologists, there are often rural areas with limited access to neurologists.

The supply of advanced practice providers (APPs), however, has steadily increased over the years, leading to incorporation of physician assistants (PAs) and nurse practitioners (NPs) in various health care fields. Although APPs are well-established providers in various specialties, including neurosurgery, the field of neurology has been slow to integrate both PAs and NPs. In 2018, only 0.8% of practicing physician assistants and 1.7% of nurse practitioners worked in neurology[2]. With the concurrent physician shortage and the increasing supply of APPs, the number of PAs and NPs working in neurology is expected to grow.

According to the National Center for Health Workforce report in 2017, the demand for PAs in neurology is expected to grow by 16%[3]. Here at Palmetto Health-USC Neurology, the ever-increasing patient load indicated a need for more providers. To solve this problem, the Palmetto-Health USC Neurology group incorporated the APP model within

Pictured left to right: Rachel Mascari, medical student; Alex Vezzetti, PA-C; Souvik Sen, MD, MS, MPH

their practice. Now, as the first PA working with Palmetto Health-USC Neurology, I have had many people ask me: How exactly does a PA function in neurology?

PAs serve in both the inpatient and outpatient setting, working to evaluate and manage patients, prescribe medications, order and interpret tests, and review imaging. While the scope of practice for each PA differs, supervising physicians are not generally required to see each of the PA's patients, granting time for these physician to more appropriately use their time. PAs are also certified to perform an array of procedures without direct physician supervision. In addition to the set tasks that all PAs can perform, PAs in South Carolina are certified to perform a multitude of other procedures, including interrogating and programming neurostimulators (including deep brain stimulators and vagus nerve stimulators) and Baclofen pumps, performing punch biopsies for small fiber neuropathy, and using telemedicine.

Additional skills can be added to a PA's certified procedures upon proper training, such as administering intravenous thrombolytics, lumbar punctures and Botox for migraine, spasticity, and dystonia. Much like physicians, PAs can specialize in one or two disease processes or practice general neurology. In addition to these duties, PAs can design and partake in clinical research and trials, as well as serve as reviewers of medical journals.

The ultimate goal of integrating PAs and NPs into health care systems, especially neurology, is to use a team-based approach to improve access to providers and enhance the quality of care for patients with neurological diseases. While they cannot replace neurologists, APPs can provide a collaboration beneficial to both the neurologist and patient.

With an APP, the neurologist's role in patient care can be revised. APPs can undertake straightforward cases, granting neurologists more time to devote

to complex cases. Furthermore, allowing APPs to assume responsibility for patients can decrease the burnout rate among neurologists. APPs can follow up with established patients or begin seeing a caseload of new patients of their own.

APPs can function simultaneously in inpatient and outpatient settings, allowing for a reduced burden on physicians in both clinical scenarios. Counseling, patient and family education, patient advocacy, and resource management also fall under an APP's scope of practice, allowing for further patient care independent of physicians. Ultimately, this functionality allows for enhanced patient care with decreased wait times and a lower cost of care, along with improved workplace satisfaction for providers.

As health care culture shifts to a team-based approach to patient management, APPs will become more prominent throughout neurology. The American Academy of Neurology has recognized that APPs are an integral part of neurological health care teams and has developed resources to further identify best practices for APPs[4]. The integration of APPs in neurology offers many advantages, such as providing a pathway to serve more patients without loss of care and offsetting the patient load burden on physicians.

It is said that "the journey of a thousand miles starts with a single step." This year, the first step of integrating APPs into the Prisma Health-USC Neurology team has been taken. While many other steps are to come, this substantial change will have great ramifications in the future for patients and providers within our care team.

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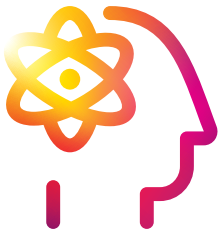

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