Autoimmune Encephalitis in the context of rare neuroimmune disorders

You can view this presentation at: youtu.be/qzil-MJOvgU

Dr. Tammy Smith: [00:00:05] I want to thank the SRNA for inviting me to speak to all of you about this important topic today and thank all of you who are attending for your interest in learning more about autoimmune encephalitis. I know you've already heard some excellent talks today about ADEM, acute flaccid myelitis, transverse myelitis, MOGAD, and NMOSD from leaders in the field of autoimmune neurology. We're going to switch gears now and talk about a rare neuroimmune disorder that the SRNA has not traditionally focused on, but I hope to convince you of its importance. The field of autoimmune neurology has developed over the past 15 to 20 years and it's a really exciting time to be more involved in this work as new markers of disease are discovered every year allowing us to provide clarity to patients who are seeking a diagnosis and develop better treatments going forward. Prior to 2007, the year NMDA receptor encephalitis was initially described, there were very few articles on the National Institutes of Health PubMed website regarding autoimmune encephalitis. Since then, the field has grown exponentially. During the time we have today, I will discuss the definition of autoimmune encephalitis, review how rare it is and then discuss ongoing work to better understand this diagnosis and how to treat it going forward. Encephalitis is a descriptive term simply defined as brain inflammation.

[00:01:38] This inflammation can be due to many causes. Classically encephalitis was thought to be caused primarily by infections, most often viruses such as the herpes virus, West Nile virus, or VZV, the virus that causes chickenpox and shingles. However, over the past 20 years, it's become increasingly recognized that some forms of encephalitis can be caused by a misdirected attack from a patient's immune system against their own brain. This leads to the condition we call autoimmune encephalitis. So how rare is this rare neuroimmune disorder? It's estimated that the overall annual incidence of encephalitis due to all causes is about 5 to 8 cases per 100,000 persons. So how many of these cases are due to autoimmune causes? The California encephalitis project was established in 1998 to study the epidemiology of encephalitis and to identify its causes. When NMDA receptor encephalitis was described in 2007, this group started looking at the incidence of NMDA receptor encephalitis compared to viral encephalitis in their population. In 2012, they published their work that showed that in people under 30 years of age NMDA receptor encephalitis, one specific form of autoimmune encephalitis was the single most common cause of encephalitis occurring more often than in encephalitis due to enterovirus, herpes virus, varicella virus or West Nile virus. This brought some real attention to the importance of considering autoimmune encephalitis on the differential when patients present with symptoms of encephalitis.

[00:03:29] In 2018, a group from the Mayo Clinic looked at the prevalence and incidence of encephalitis in the Minnesota County where their hospital is based. They looked at two-time points, one was 1995 to 2005 before many of the antibodies responsible for autoimmune encephalitis were characterized and the other was 2006 to 2015, a time when new antibodies were being discovered at a rapid rate. While the incident rate of infectious encephalitis remains stable between these two time periods, the rate of autoimmune encephalitis tripled. Increasing awareness of this diagnosis has been important as early testing for antibodies can lead to appropriate treatment and improved outcomes. Symptoms of autoimmune encephalitis can be similar to infectious encephalitis however, in autoimmune encephalitis, the progression of symptoms is often less acute, happening over weeks to a month or two rather than rapidly progressing over hours to days as it does when an infection is causing the symptoms. Sometimes this more insidious onset leads families and clinicians to think that the patient is experiencing a new psychiatric disease rather than being affected by an autoimmune process.

[00:04:52] In many cases, I have seen patients were brought to the emergency room by family due to concerns about new and unusual behaviors only to be sent home when no acute cause for these symptoms was recognized only after worsening often to the point of having a seizure where patients brought back to the hospital and ultimately diagnosed. This type of back and forth can lead patients and their families to feel frustrated with the health care system. Improving our ability to diagnose these disorders is important. The diagnosis of autoimmune encephalitis is a clinical one based on the interpretation of a variety of findings including the history of the disease and the patient's medical history, physical exam findings, MRI results, cerebral spinal fluid studies EEG, and investigation of possible alternative causes while finding a specific anti-neural antibody in a patient with clinical history supporting a diagnosis of autoimmune encephalitis is helpful. It is not required. There are several reasons why this is the case.

[00:06:02] One reason is that we are finding new antibodies which cause unique autoimmune encephalitis syndromes every year. It's possible that a patient will meet the criteria for autoimmune encephalitis, but they harbor as yet unclassified anti-neural anti-antibody. If the clinical picture fits the diagnosis and reasonable alternatives have been ruled out, they should be treated as if they have autoimmune encephalitis and reevaluated for treatment responsiveness. So, what causes these self-reactive antibodies to develop? Some forms of autoimmune encephalitis are associated with specific kinds of cancer. In these cases, the tumor cells have been shown to express proteins which are similar or identical to proteins found in the nervous system. When tumor cells die, Dendritic cells take up these proteins and bring them to lymph nodes where they are displayed to be in T-cells parts of the adaptive immune response. These cells then develop responses such as antibodies and receptors which specifically recognize and target cells expressing these proteins. It's thought that this response can lead to your own immune system fighting off cancer. There are specific cancer therapies that are designed to promote this very process. However, when these responses are misdirected against proteins in the nervous system, they can cause encephalitis. Not all patients with autoimmune encephalitis have tumors.

[00:07:39] Some cases of autoimmune encephalitis have been associated with preceding viral infections such as the herpes simplex virus. In these cases, it's thought that the immune response to the viral infection in the brain leads to self-reactive immune cells causing autoimmune encephalitis. In many cases, no viral infection or tumor is found. Some genetic variations have also been shown to predispose to some forms of autoimmune encephalitis, but this is likely a complex process with many factors and more research is being done to better understand how anti-neural antibodies develop. I've mentioned a few times that anti-neural antibodies are a relatively new discovery because the immune system has such a powerful ability to generate many millions of different antibodies targeting different proteins. Finding the antibodies causing neurologic disease can be like finding a needle in a haystack. One strategy which allows us to identify new antibodies is using tissue-based Immunofluorescent Assays or IFAs. To do this, we dissect tissue from rodent brains

and place thin slices of this tissue onto microscope slides. We can then add samples of patient serum or cerebrospinal fluid and look to see if there is anything in these patient samples that sticks to the tissue using fluorescent-labeled antibodies. Depending on the protein that these patients' samples bind to, we will see different patterns of fluorescence when we look at these tissues under the microscope. This type of strategy tells us there is something in the patient sample that finds to neural tissue.

[00:09:23] However, more specific tests need to be done to determine the actual target of these antibodies. The target proteins and autoimmune encephalitis are cell surface proteins involved in neuronal signaling and synaptic plasticity. Antibodies binding to these proteins disrupt their function leading to the varied clinical syndromes we see. Let's look at two of the most common types of autoimmune encephalitis and compare and contrast their findings. NMDA receptor encephalitis is the poster child for autoimmune encephalitis and the most common form that we identify. It occurs much more often in young women than in other age groups and many people have heard of this because Susannah Cahalan, a reporter, wrote a book about her experience with an NMDA receptor encephalitis called Brain on Fire. Behavior changes in NMDA receptor encephalitis often develop early and can range from irritability and anxiety to frank psychosis. Many people go on to develop seizures, abnormal facial movements, and dysfunction of the autonomic nervous system. In about 30% of cases, a tumor called the teratoma is found. In most cases, no cancer is found.

[00:10:48] In some patients, NMDA receptor encephalitis has developed after herpes encephalitis. In contrast to NMDA receptor encephalitis, LGI1 encephalitis occurs more often in older men. It's also associated with behavior changes, but these are more likely to include apathy, disinhibition, and amnesia. In addition, seizures are a much more prominent early symptom of LGI1 encephalitis. The classic type of seizure in LGI1 diseases is called faciobrachial dystonic seizure, which can occur hundreds of times a day. These can progress to other forms of epilepsy. Autonomic dysfunction can occur in LGI1 as well, though it is less common than an NMDA receptor disease. While LGI1 encephalitis has been associated with some forms of cancer, this is much less common and found in only 13% of patients. I discussed two specific antibodies associated with particular forms of autoimmune encephalitis but would like to point out that there are well over a dozen characterized neural antibodies which have been reported in the past decade or so. Most general neurologists have only heard of a few of these, so I don't think it's helpful to bore you with the details of each of these syndromes.

[00:12:11] However, it's important to know that many of these syndromes have unique qualities which help to clinically distinguish them, much like the distinctions we just discussed between NMDA receptor and LGI1 encephalitis. Research in this field will need to include understanding the mechanisms by which each of these antibodies causes disease, improving diagnosis, and developing targeted treatments to improve lives. Currently, there are no FDA-approved therapies to treat autoimmune encephalitis. However, expert consensus dictates early treatment with high-dose IV steroids as well as either plasma exchange which removes antibodies from the blood, or IVIG which crowds out pathogenic antibodies with normal antibodies from blood donors. If the tumor is found, tumor removal is important to achieving a good outcome. If an inadequate clinical response is achieved with first first-line therapy, second-line immunosuppressive agents such as Rituximab or Cyclophosphamide may be used. Recovery rates and the degree of residual deficit vary based on the type of autoimmune encephalitis but generally occur over months to years. Relapse rates also vary based on the type of autoimmune encephalitis and the appropriate duration for immunotherapy remains unclear and an active area of investigation. Conducting clinical trials in rare diseases can be challenging as many of you know.

[00:13:51] However, clinical trials provide an opportunity for us to develop the highest level of evidence to guide treatment decisions for patients. The extinguished trial to determine the role of a monoclonal antibody targeting CD 19 positive cells, started enrolling patients this spring. Another clinical trial to determine the role of a monoclonal antibody targeting the Neonatal Fc receptor in patients with LGI1 encephalitis started

enrolling last fall. Additional clinical trials and autoimmune encephalitis are anticipated to begin in the near future. Hopefully, preliminary data in these studies will be out in the next year and will have additional evidence to guide treatment decisions going forward. While autoimmune encephalitis may be relatively rare, it is an important clinical syndrome to recognize and treat. In addition, understanding how antibodies interacting with the brain can cause symptoms such as the psychosis caused by anti-NMDA receptor antibodies may help us better understand the causes of more common psychiatric diseases such as Schizophrenia and depression. Rare diseases provide us with an opportunity to better understand how our bodies work and a chance to more broadly apply that understanding to human health. I want to thank all of you for the time you've committed to better understanding rare neuroimmune diseases and for being active members of your community. Communities like this one are critical for sharing information and providing support to patients and their families. Please feel free to reach out to me directly over email if you have any questions. Thank you for your time.