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Review

Paraneoplastic epilepsy

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ABSTRACT

Epilepsy can be a manifestation of paraneoplastic syndromes which are the consequence of an immune reaction to neuronal elements driven by an underlying malignancy affecting other organs and tissues. The antibodies commonly found in paraneoplastic encephalitis can be divided into two main groups depending on the target antigen: 1) antibodies against neuronal cell surface antigens, such as against neurotransmitter (N-methyl-D-aspartate (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), gamma-aminobutyric acid (GABA)) receptors, ion channels (voltage-gated potassium channel (VGKC)), and channel-complex proteins (leucine rich, glioma inactivated-1 glycoprotein (LGI1) and contactin-associated protein-2 (CASPR2)) and 2) antibodies against intracellular neuronal antigens (Hu/antineuronal nuclear antibody-1 (ANNA-1), Ma2/Ta, glutamate decarboxylase 65 (GAD65), less frequently to CV2/collapsin response mediator protein 5 (CRMP5)). In this review, we provide a comprehensive survey of the current literature on paraneoplastic epilepsy indexed by the associated onconeuronal antibodies. While a range of seizure types can be seen with paraneoplastic syndromes, temporal lobe epilepsy is the most common because of the association with limbic encephalitis. Early treatment of the paraneoplastic syndrome with immune modulation/suppression may prevent the more serious potential consequences of paraneoplastic epilepsy.

1. Introduction

A small percentage of patients with epilepsy have an immune reaction driven by an underlying malignancy as the etiology of their seizure disorder. While this is an uncommon explanation for seizures, it is an important one for epileptologists, neurooncologists, general neurologists, and general oncologists to recognize. As opposed to other epilepsy etiologies, the differential diagnoses, treatments, and prognosis differ significantly. We will review the clinical, neurophysiological, and neuroradiological characteristics of paraneoplastic epilepsy, as well as the underlying pathophysiology and management of paraneoplastic epilepsy syndromes.

Epilepsy is one of the most frequent neurological conditions, affecting 1% of the population [1]. Population-based studies revealed that patients with autoimmune disease constitute 17.5% of patients with epilepsy [2–4]. There has been an increased recognition of paraneoplastic neurological syndromes (PNS) involving the limbic system or cerebral cortex as an underlying etiology of seizures [5]. As one of the main symptoms of paraneoplastic encephalitis (PE), seizures can occur as the initial presentation or at in a later stage of the disease. Twenty-seven percent (23/84) of late onset temporal lobe epilepsy, in a series of 84 patients, were due to limbic encephalitis (LE), and within this group, 26% (6/23) of them had paraneoplastic limbic encephalitis (PLE) [3]. The neuropathology is thought to be a consequence of an immune reaction to neuronal elements driven by the underlying malignancy. It is important to recognize that a negative antibody or lack of detection of underlying tumor on initial screening does not rule out paraneoplastic etiology in a patient presenting with typical PNS symptoms and epilepsy [6]. In the last ten years, a dramatic increase in new neural and glial-specific antibodies and their target antigens has been found [7–9]. Early recognition of a paraneoplastic etiology for epilepsy can lead to earlier treatment with immunotherapy and the control of the underlying malignancy. This, in turn, may facilitate better seizure control in these patients with typically refractory epilepsy.

Abbreviations: AEDs, antiepileptic drugs; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ANNA, antineuronal nuclear antibody; ADLTE, autosomal dominant lateral temporal epilepsy; ADPEAF, autosomal dominant partial epilepsy characterized by auditory features; CRMP, collapsin response mediator protein; CASPR2, contactin-associated protein-2; EPC, epilepsia partialis continua; EDB, extreme delta brush; FBDS, faciobrachial dystonic seizures; FLAIR, fluid-attenuated inversion recovery; FDG-PET, ^{18}F-fluorodeoxyglucose positron emission tomography; GABA, gamma-aminobutyric acid; GAD, glutamate decarboxylase; LGI, leucine rich, glioma inactivated glycoprotein; LE, limbic encephalitis; NMDA, N-methyl-D-aspartate; PE, paraneoplastic encephalitis; PLE, paraneoplastic limbic encephalitis; PNS, paraneoplastic neurological syndromes; PLEDs, periodic lateralized epileptiform discharges; SCLC, small-cell lung cancer; SE, status epilepticus; VGKC, voltage-gated potassium channel.

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2. Clinical presentation and diagnosis

The classic symptoms of PLE are short-term memory loss, confusion, seizures, and psychiatric disturbances [10]. When seizures are the initial symptom, they often rapidly develop and occur in high frequency. Complex partial seizures and generalized seizures, at times with convulsive or nonconvulsive status epilepticus, are all reported. The cooccurrence of movement disorder with seizure is a characteristic feature of several paraneoplastic syndromes. Each antibody is associated with a specific type of movement disorder: GAD65 antibody-positive patients are typically associated with stiff person syndrome; patients with anti-NMDA receptor encephalitis often present with orobuccolingual dyskinesias; and parkinsonian features are usually observed in patients with anti-Ma2 and anti-CRMP5 antibody-positive PE [11–15]. Epilepsia partialis continua (EPC), a clinical syndrome with spontaneous regular or irregular clonic muscular twitching affecting a limited part of the body occurring for a minimum of 1 h, has been frequently reported in anti-Hu seropositive paraneoplastic encephalomyelitis [16–20]. Temporal lobe epilepsy is the most common seizure type because of the association with PLE. When patients present with focal motor or sensory seizures, extratemporal involvement is suggested. Status epilepticus (SE) is a prolonged seizure or multiple seizures with incomplete return to baseline with an incidence of 10–41 per 100,000 of the general population [21]. The incidence of SE in paraneoplastic syndrome is low but often resistant to conventional antiepileptic drug (AED) treatment. In a series of 100 patients with anti-N-methyl-D-aspartate (anti-NMDA) receptor encephalitis, SE occurred in 6% of the patients [22]. It has recently been suggested that SE, especially nonconvulsive SE, could be misdiagnosed as confusional states, and the frequency might be underestimated in patients with cancer [23].

Paraneoplastic epilepsy can be associated with any cancer. The most common association is with small cell lung cancer (SCLC) (40%), a malignancy in which almost all onconeuronal antibodies have been detected [24,25]. The second most common cancer is germ-cell tumors of the testes (20%) in which anti-Ma is the most common associated antibody. Other cancers commonly associated with onconeural antibodies are breast cancer (8%), Hodgkin's lymphoma, thymoma (anticollapsin response mediator protein 5 (anti-CRMP5)), and immature teratoma (anti-NMDA receptor antibody) [12,26]. Seizures or other neurological symptoms could occur 3–6 months to 4–5 years before the diagnosis of tumor [26–28]. Paraneoplastic antibodies should be screened in clinically relevant patients in both serum and CSF because 15% of patients have only positive CSF titers. If a paraneoplastic antibody has been identified, the type of antibody could provide a guide for subsequent screening for a tumor [11,29].

It is important to have a high index of suspicion, as early recognition of autoimmune/paraneoplastic epilepsy is of the utmost importance, since prompt initiation of treatment is associated with better outcomes [30–33]. Syndromic manifestations of limbic or extralimbic encephalitis are not always present, and new-onset epilepsy may be the sole presenting manifestation [30]. Also, as previously stated, the failure to detect an autoantibody does not rule out the diagnosis as some patients have been found to still respond to immunosuppression [30,33]. To continue to make the diagnosis more complicated, several studies have confirmed the presence of voltage-gated potassium channel (VGKC) antibodies and GAD65 antibodies in around 10% of adults with longstanding epilepsies [34–36].

3. Neurophysiological characteristics

Neurophysiologic findings in paraneoplastic epilepsy are usually nonspecific. The most common EEG findings are generalized slowing and/or focal slowing. Epileptiform abnormalities are observed in less than 50% of patients and could be unitemporal or bitemporal spike/sharp waves or periodic lateralized epileptiform discharges (PLEDs) [11]. Extratemporal EEG abnormalities suggestive of extratemporal involvement are relatively common in anti-Hu-associated encephalitis [17]. Rhythmic delta can be the presentation of nonconvulsive SE, which has been reported in multiple cases of anti-NMDA receptor encephalitis [37,38]. Interestingly, patients with anti-NMDA receptor encephalitis show a highly characteristic electrographic pattern, described as “extreme delta brush” (EDB). It consists of generalized delta slowing with superimposed bursts of rhythmic 20- to 30-Hz beta frequency activity “riding” on each delta wave, resembling waveforms seen in premature infants [39]. This pattern was found in 7/23 (30.4%) of the patients in one study, and the presence of EDB is associated with a more prolonged hospitalization. The presence of EDB on EEG has been reported in earlier diagnosis of NMDA receptor encephalitis and initiation of treatment, although specificity is uncertain [40].

4. Treatment and prognosis

Paraneoplastic epilepsy is usually poorly responsive to AEDs. Almost all patients require more than two conventional AEDs. Agents frequently employed include the following: benzodiazepines, levetiracetam, lacosamide, phenobarbital, phenytoin, topiramate, and valproate [41]. The newer AEDs, such as oxcarbazepine, levetiracetam, and lacosamide, may be superior to the older generation because of less drug–drug interaction and better tolerability [32,33]. The lack of drug–drug interactions and limited myelosuppressive or hepatotoxic side effects are important considerations in patients who will be receiving chemotherapies and targeted therapies. Patients with SE are often difficult to treat and may require pharmacologically induced coma [42]. Early identification of paraneoplastic antibodies is essential in the management of this patient population as this leads to earlier treatment of the underlying malignancy [43]. Patients who received early tumor treatment have better outcomes and fewer neurological relapses than the rest of the patients [44,45]. Despite the lack of formal evidence, a rational therapeutic approach has been successfully applied in numerous paraneoplastic and autoimmune disorders [30]. The first-line acute treatment often targets reduction of the immune response and cytoreduction of the tumor burden. A range of immunosuppressive approaches has been employed including steroids, immunoglobulins, plasmapheresis, and immune cell-targeted approaches. Steroid regimens have included IV methylprednisolone 0.5–1 g/day for three to five consecutive days (chronic pulse treatment or prednisolone treatment requires individualization); intravenous immunoglobulin (IVIG) 0.4 g/kg/day for three to five consecutive days, potentially followed by monthly single day pulse treatment; and plasmapheresis [46]. Intravenous immunoglobulin is often used in diabetes mellitus and children given the perceived favorable side effect profile compared with corticosteroids [30]. Plasmapheresis is generally reserved for either critically ill patients or when corticosteroids or IV IG is poorly tolerated [30].

Second-line treatments are often implemented if there is no improvement in about 10 days after first-line treatment [29]. Second-line treatments include rituximab (375 mg/m^2 weekly for four weeks) and/or cyclophosphamide (750 mg/m^2 every month until signs of clinical improvement) [47]. Rituximab is a monoclonal antibody targeting CD20 and induces a rapid depletion of CD20-positive B-cells. Since T-cells are unaffected, rituximab is relatively safe in terms of infectious complications and is generally well tolerated [48]. Rituximab remains in serum for several months after completion of treatment, thus plasmapheresis should be avoided once the treatment is started. Recently, it has been demonstrated that rituximab as a second-line therapy for autoimmune limbic encephalitis results in more favorable outcomes regardless of the antibody status [49].

Dalmau et al. defined PE treatment failure as no sustained improvement within four weeks of initiation of immunotherapy or tumor removal and defined relapse as new onset or worsening of symptoms at least 2 months after improvement or stabilization [25]. In general, patients with PE associated with antibodies against neuronal cell surface antigens respond to immunotherapy better and have a better prognosis