Anti–N-Methyl-D-Aspartate Receptor Encephalitis in Children and Adolescents

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ABSTRACT

Anti–N-methyl-D-aspartate receptor (NMDAR) encephalitis is an autoimmune disease that is becoming increasingly recognized in the pediatric population. It may be the most common cause of treatable autoimmune encephalitis. The majority of cases of anti-NMDAR encephalitis are idiopathic in etiology, but a significant minority can be attributed to a paraneoplastic origin. Children with anti-NMDAR encephalitis initially present with a prodrome of neuropsychiatric symptoms, often with orofacial dyskinesias followed by progressively worsening seizures, agitation, and spasticity, which may result in severe neurologic deficits and even death. Definitive diagnosis requires detection of NMDAR antibodies in the cerebrospinal fluid. Optimal outcomes are associated with prompt removal of the tumor in paraneoplastic cases, as well as aggressive immunosuppressive therapy. Early detection is essential for increasing the chances for a good outcome. Close follow-up is required to screen for relapse and later onset tumor presentation. The nurse practitioner plays a major role in the research, screening, diagnosis, treatment, follow-up, and rehabilitation of a child or adolescent with anti-NMDAR encephalitis. J Pediatr Health Care. (2016) *30*, 347-358.

KEY WORDS

Anti–N-methyl-D-aspartate receptor, anti-NMDA, NMDA, NMDAR, encephalitis

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Diana is a 14-year-old previously healthy girl who presented with behavioral changes and difficulty speaking. One week earlier, she reported upper respiratory symptoms and a headache. As the week progressed, Diana's parents noted that she appeared increasingly confused. Diana was admitted to the pediatric neurology unit, at which time her dysarthria worsened and progressed to vocal automatisms and echolalia. Her affect was flat, and she was regularly found staring off into space. She appeared to have audiovisual hallucinations, but because of her limited language abilities, the hallucinations were difficult to confirm.

After a few days in the hospital, Diana began having generalized tonic-clonic seizures. Her seizures became increasingly difficult to identify as she began to exhibit dyskinetic movements, frequently choreoathetoid in nature, as well as sympathetic storms characterized by tachycardia, hypertension, and extreme agitation with whole-body shaking. She was often found twisted and contorted in rigid, dystonic postures. Diana was empirically diagnosed with anti–N-methyl-D-aspartate receptor (NMDAR) encephalitis and immunomodulatory therapy was promptly instituted, concurrent with evaluation for an occult paraneoplastic etiology. She underwent a diagnostic lumbar puncture, which confirmed the presumed diagnosis.

BACKGROUND

A paraneoplastic neurologic syndrome is a condition that affects any level of the nervous system and is indirectly caused by cancer (Leypoldt & Wandinger, 2014). Many different types of paraneoplastic neurologic syndromes exist that cause devastating, oftentimes irreversible, and even lethal neurologic symptoms (Zaborowski, Spaczynski, Nowak-Markwitz, & Michalak, 2015). In many cases, these syndromes are thought to be autoimmune and can occur in the absence of cancer, in which case they are called nonparaneoplastic neurologic

syndromes. Anti-NMDAR encephalitis is a type of neurologic syndrome that can be paraneoplastic or nonparaneoplastic in nature. It has only recently been discovered, and as a result of new diagnostic testing, the number of identified cases is on the rise. Symptoms of anti-NMDAR encephalitis arise as a result of autoimmune antibodies binding to the NMDA receptor on certain neuronal cell surfaces (Leypoldt & Wandinger, 2014). It is becoming much more recognized in children and young adults (Nijmeijer, Bontemps, Naeiji, & Coutinho, 2014).

Anti-NMDAR encephalitis was first defined in 2005 when Dr. Joseph Dalmau studied the neurologic clinical presentation of four female patients with ovarian teratomas (Dalmau et al., 2007). Although anti-NMDAR encephalitis is often categorized as a paraneoplastic syndrome, more frequently it is nonparaneoplastic in nature, particularly in the pediatric population (Lazar-Molnar & Tebo, 2015). The purpose of this article is to review what is currently known about anti-NMDAR encephalitis in the pediatric population, as well as current and future implications for nurse practitioners (NPs) regarding the identification and management of children with the disease. Table 1 contains the definitions of terms.

OVERVIEW OF PARANEOPLASTIC NEUROLOGIC SYNDROMES

In paraneoplastic neurologic syndromes, many tumors, particularly those of neuroectodermal lineage, may express central or peripheral nervous system antigens. Autoimmune antibodies react to those tumor antigens, causing an immune-mediated response by the central, peripheral, or autonomic nervous system (Dalmau & Rosenfeld, 2008; Leypoldt & Wandinger, 2014). The antibodies can be found in the cerebrospinal fluid (CSF) and/or serum of the affected patient (Dalmau & Rosenfeld, 2008; Darnell & Posner, 2003; Leypoldt & Wandinger, 2014; Panzer & Dalmau, 2011). Paraneoplastic syndromes can result in damage to almost any organ or tissue remote from the site of the tumor (Darnell & Posner, 2003).

TABLE 1. Definitions of terms

Term	Definition
Choreoathetoid	Involuntary, purposeless, and uncontrollable movements characteristic of chorea, which is spasmodic movement, and athetosis, which is slow movement (Merriam-Webster, 2005)
Echolalia	Pathologic repetition of what is heard, as if to echo (Merriam-Webster, 2005)
Hyperintensities	White matter changes visible on magnetic resonance imaging scans of the brain (Pressman, 2014)
Intrathecal	Occurring within or administered into the area below the arachnoid membrane in the brain or spinal cord (Merriam-Webster, 2005)
Teratoma	A tumor composed of a mixture of heterogeneous tissues (Merriam-Webster, 2005)
Oophorectomy	Surgical removal of one or both ovaries (Merriam-Webster, 2005)
Pleocytosis	Abnormal increase in the number of white cells in the cerebrospinal fluid (Merriam-Webster, 2005)

Paradoxically, some studies have suggested that patients with paraneoplastic neurologic syndromes have better prognoses and outcomes than do patients with the same tumors that are not associated with neurologic disorders (Darnell & Posner, 2003; Zaborowski et al., 2015). This is the case with anti-NMDAR encephalitis. One hypothesis for this phenomenon is that a naturally occurring antitumor response may be induced by the paraneoplastic process (Zaborowski et al., 2015). Another possibility is that the presence of overt neurologic symptoms may prompt a more thorough diagnostic workup of this otherwise occult malignancy, allowing the cancer to be detected earlier (Darnell & Posner, 2003). Tumors that are able to secrete autoantibodies may be fundamentally different. Their synthetic capability suggests that they may be more differentiated and thus manifest a less aggressive course of disease.

Approximately 1% of all malignancies are associated with paraneoplastic neurologic syndromes, and approximately 10% of those malignancies are ovarian tumors (Zaborowski et al., 2015). Ovarian tumors are the most commonly found tumors associated with anti-NMDAR encephalitis in children (Panzer & Dalmau, 2011). Suspicion for a diagnosis of a paraneoplastic neurologic syndrome, such as anti-NMDAR encephalitis, raises the likelihood of a probable neoplasm and should lead to a thorough investigation for an underlying tumor.

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OVERVIEW OF ANTI-NMDAR ENCEPHALITIS

Epidemiology

Anti-NMDAR encephalitis may be the most common cause of autoimmune encephalitis in children (Cohen & Wong-Kisiel, 2014; Titulaer et al., 2013). It is more prevalent in females (Lin et al., 2014; Tachibana