Chapter 7
Psychiatric Presentation of Brain Inflammation

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Abstract Autoimmune encephalitis associated with antibodies targeting neural cell surface antigens have emerged in the past 10 years as a major cause of encephalitis. Those associated with antibodies against the N-methyl-D-aspartate receptor (NMDAR) is the most frequent. This newly recognized disease is characterized by a stereotyped clinical phenotype. The clinical course usually begins in the majority of cases by psychiatric symptoms, sometimes preceded by prodromal symptoms. The psychiatric stage is usually followed by severe fluctuations in consciousness with neurologic involvement with cognitive impairment, speech impairment, movement disorders, seizures, and behavioral problems. Typically the disease affects young women, and an ovarian teratoma is frequently associated, but cases have been reported in children, in men, and in patients without tumors. The treatment consists of early immunotherapy and, if necessary, tumor removal. The outcome is good in many cases if the treatment is started early, but severe sequelae or death is possible. The management of psychiatric symptoms can be difficult.

Keywords Encephalitis • Autoimmune • Antibody • Neural cell surface antigen • N-Methyl-D-aspartate receptor • Psychosis • Seizures • Limbic encephalitis • Dystonia • Teratoma • Paraneoplastic

Introduction

The first central nervous system (CNS) conditions associated with the presence of autoantibodies have been recognized in the 1980s [1]. The onconeural antibodies (Ab), which target neuronal epitopes within the cytoplasm or the nucleus, were described in patients with peripheral and CNS syndromes associated with cancer (paraneoplastic syndromes) [2]. The antibodies include anti-Hu, anti-Yo, and many

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others, which are used as biological diagnostic markers [2, 3]. The pathogenic roles of these Ab have been questioned, as their targets are intracellular proteins and because immunotherapy is rarely useful in these cases [3, 4]. It is considered, nowadays, that T cell cytotoxicity plays a more important role than Ab in the lesions that occurs in these encephalopathies [3, 4]. In the past 15 years, several CNS disorders, with encephalopathy, have been characterized by their association to Ab that bind to membrane-associated epitopes on neuronal cells [4, 5]. These disorders are frequently not associated with cancer, and immunotherapy could be effective, suggesting that these Ab are pathogenic. Table 7.1 summarizes the main CNS disorders associated with Ab targeting neuronal cell surface antigens [5]. The most frequent clinical syndrome seen during these disorders is limbic encephalopathy (LE) which

Table 7.1 Encephalitis and other disorders associated with antibodies targeting neuronal cell surface antigens [5]

Antigen	Clinical data	Sex/age	Tumor	Outcome
NMDAR	Psychiatric symptoms, memory and language deficits, seizures, movement disorders, autonomic instability, and decreased level of consciousness	80 % female	Teratoma (40–50 %)	Good outcome with timely immunotherapy (and tumor removal if required)
		Median age 21 (12–85)		Sequelae 25 %
LGI1 (VGKC complex[a])	LE	65 % male	Rare	Good response to immunotherapy but absent or poor response with AED in faciobrachial dystonic seizures
	Faciobrachial dystonic seizures	Median age 60 (30–80)		
CASPR2 (VGKC complex[a])	Neuromyotonia, LE, Morvan syndrome, ataxia	85 % male	Thymomas, SCLC	Good outcome, but can be complicated by tumor
		Median age 60 (46–77)	(uncommon)	
AMPAR	LE	90 % female	SCLC, thymoma, or breast cancer (70 %)	50 % of relapses, even in the absence of tumor
	Prominent psychiatric manifestations	Median age 60 (38–78)		
	Sometimes isolated neuropsychiatric phenotype			
GABAbR	LE, seizures	50 % female	SCLC (50 %)	Good outcome; relapses are rare
		Median age 62 (24–75)		
GlyR	Progressive encephalomyelitis, rigidity, and myoclonus	60% male	Thymoma, Hodgkin lymphoma (rare)	Good outcomes
		Median age 46 (1–70)		Relapses possible
	Stiff person syndrome			

[a]Rare reports of pure psychiatric phenotype associated with VGKC complex antibodies (no target identified)

is an inflammation of the limbic system, including the hippocampus, thalamus, hypothalamus, and amygdala [6]. LE is characterized by subacute development of short-term memory loss, behavioral change, and epileptic seizures. Magnetic resonance imaging (MRI) typically shows signal abnormalities on T2/FLAIR sequences in these regions. Cerebrospinal fluid is usually inflammatory [6]. Psychiatric manifestations have been described in newly identified autoimmune encephalopathies and are the main features of encephalitis associated with anti-N-methyl-D-aspartate receptor (NMDAR) Ab [4, 5, 7–9]. Autoimmune encephalitis associated with other Ab usually rarely includes psychiatric symptoms [10]. Pure psychiatric forms have been reported in encephalitis associated with anti-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) or with anti-voltage-gated potassium channels (VGKC) complex Ab [10]. However, LE is the usual presentation of encephalitis with anti-AMPAR Abs and those with anti-leucine-rich, gliomainactivated1 (LGI1) (part of VGKC complex) [5], although patients with anti-contactin-associated protein-like 2 (Caspr2) antibodies (also part of VGKC complex) have neuromyotonia or LE or both (Morvan syndrome) [11]. Confusion and paranoia have also been reported in cases of encephalitis with anti- γ-aminobutyric acid receptor (GABAbR) [10] which are usually presenting with LE. Psychiatric symptoms could also occur but rarely during viral encephalitis with enterovirus, herpes simplex virus 1, varicella-zoster virus, or West Nile virus [12]. We will focus this review on anti-NMDAR autoimmune encephalitis.

Anti-NMDAR Autoimmune Encephalitis

The first cases of encephalitis associated with Ab directed toward neuronal cell surface antigens were two cases of LE associated with anti-VGKC Ab [13], which was later attributed to anti-LGI1 [14]. Anti-NMDAR GluR ∈2 subunit autoantibodies were, first, detected in patients with Rasmussen encephalitis [15]. Two years later, the cases of four patients with severe paraneoplastic encephalitis, affecting young women with ovarian teratomas, were described [16]. The clinical syndrome associated acute psychiatric symptoms, seizures, memory impairment, hypoventilation, and decreased level of consciousness. The same group described other cases associated with Ab to unknown antigens (a subgroup of neuropil antigens) predominantly expressed in the cell membrane of hippocampal neurons [17]. The demonstration of the association of these encephalitic cases with anti-NMDAR antibodies was published in 2007 [18]. Since these seminal observations, many cases have been reported, including men, women, and children, and frequently without evidence of cancer [4, 5, 19, 20].

Glutamatergic neurotransmission is mediated via several receptors including the ionotropic NMDAR and plays a critical role in the modulation of synaptic plasticity, mood, pain transmission and regulation, cognitive processes, and motricity [21]. The hyperactivation of NMDAR could mediate acute neuronal death and is thought to play a role in chronic neurodegenerative diseases like Alzheimer's disease and

amyotrophic lateral sclerosis [21]. In contrast, severe hypofunction of NMDAR is able to produce a clinical syndrome similar to schizophrenic exacerbation [22]. It has been observed that anesthetic drugs acting on NMDAR such as phencyclidine and ketamine may induce schizophrenia-like symptoms [21, 22]. Indeed, increasing evidence suggests the implication of NMDAR dysfunction in the pathogenesis of schizophrenia and, in particular, in negative and cognitive symptoms [23]. Several polymorphisms of genes controlling the NMDA receptor's pathway have been found associated with increase susceptibility for schizophrenia [23].

Encephalitis associated with anti-NMDAR Ab is a recently recognized entity and its prevalence is largely unknown. From 2005 to 2011, Dalmau and co-workers [19] identified 419 cases. Several studies attempted to measure the frequency of anti-NMDAR Ab in different populations of patients with encephalitis: from 1 % of patients with encephalitis of unknown etiology admitted to the intensive care unit of one center [24] to 4 % in a multicenter prospective study of patients with encephalitis made in England during 2 years [25] and in a prospective cohort in California [26]. In the California Encephalitis Project, who included patients aged <30 years, anti-NMDAR encephalitis was identified .4 times as frequently as herpes simplex virus-1, West Nile virus, or varicella-zoster virus [26]. It appears that NMDAR Ab-associated encephalitis is not rare and this diagnosis has to be considered in patients presenting with psychiatric symptoms [9, 10].

Clinical Presentation

Several studies have established the clinical syndrome associated with anti-NMDAR Ab [20, 27–30].

The disease was initially described exclusively in female patients, but it could also occur in less than 10 % of cases, in male patients [29, 30]. The age at onset varies considerably, and cases have been reported in children [30], adults, and geriatric patients, but the mean age is in the second decade [20, 29]. In a majority of patients (up to 86 % of cases), the disease is preceded by prodromal symptoms: headache, fever, nausea, vomiting, diarrhea, or upper respiratory tract symptoms. These symptoms last from a few days (median 5) to 2 weeks before the onset of the psychiatric symptoms [19, 20, 17, 28, 29]. The psychiatric presentation is, by far, the most frequent, occurring in nearly 80 % of cases [9, 10, 19, 29]. These symptoms include anxiety, insomnia, fear, delusions, perceptual disturbances, hyperreligiosity, disorganized thoughts and behaviors, agitation, and paranoid ideation. Also possible are social withdrawal and stereotypical behavior [9, 10]. In children, the disease presents with behavioral or personality change, and sleep dysfunction, hyperactivity, and hypersexuality are seen [9, 10, 20, 30]. The psychiatric symptoms usually last from 1 to 3 weeks.

Due to this usual psychiatric presentation, many patients are seen initially by psychiatrists.

Neurological symptoms are as frequent as psychiatric symptoms but are frequently underestimated [19]. Typically they followed psychiatric symptoms. These neurological symptoms are mainly cognitive impairment with short-term memory loss and speech problems [29]. Progressive decline in speech and language, including alogia, echolalia, perseveration, mumbling, and mutism, is characteristic [19, 29]. Seizures are present in a large majority of patients, frequently generalized tonic-clonic seizures, but sometimes partial motor or complex and other types are seen [19, 29]. Although seizures can been seen at all stages of the illness, the frequency of the seizures usually decreases as the disease evolves. In children, the first symptom to be recognized is often nonpsychiatric—e.g., seizures, status epilepticus, dystonia, verbal reduction, or mutism [30].

Dyskinesis (especially orofacial), dystonic posturing, and choreic-like movements of the limbs and spastic rigidity occur also very frequently but predominate usually in a second stage of the disease when the psychiatric symptoms decreased and are followed by decreased responsiveness, global alterations in consciousness sometimes progressing to a catatonic-like state with mutism and eyes open, or sometimes to a stage of agitation. During this second stage, autonomic symptoms (hyperthermia, urinary incontinence, cardiac arrhythmia, hypo- or hypertension, and central hypoventilation) are common and can require intubation or pacemakers [19, 29].

Spontaneous neurological improvement has been reported but appears to be slow and inconstant.

Paucisymptomatic cases have been reported, associated with only seizures [31] or dystonia [32].

Diagnostic

Magnetic resonance imaging could show signal hyperintensity on T2/FLAIR sequences in the cerebral cortex, mainly the medial temporal lobe and less frequently in cerebellar or brainstem regions or basal ganglia [29]. Cortical or meningeal contrast enhancement is possible but rare. The MRI abnormalities are not specific and could be absent in about 50 % of cases. Brain atrophy could occur in untreated cases [19].

Electroencephalograms (EEG) are abnormal in more than 90 % of cases showing nonspecific, slow, and disorganized activity, and paroxysmal activities are detected in about 20 % of cases [29]. Video-EEG could be helpful [30].

Cerebrospinal fluid (CSF) analysis is essential for diagnosis. At onset, the CSF is abnormal in 80 % of patients and becomes abnormal later in the disease in most other patients. Lymphocytic pleocytosis is common. Oligoclonal bands are positive in 60 % of cases [19, 20]. The detection of NMDAR Ab in the CSF and in sera is essential for the diagnosis. Ab are identified in CSF in 100 % of cases and in sera in 85 % [33]. Ab titers in CSF and serum were higher in patients with poor outcome or teratoma than in patients with good outcome or no tumor. Over time there was a

decrease of Ab titers regardless of outcome, and after recovery, the majority of samples remains positive. However, relapses were associated with an increase in titer more often in CSF than in serum [33].

Anti-NMDAR antibodies could be detected by indirect immunofluorescence on cryopreserved sections or primary cell cultures of the rodent brain or in vitro enzyme-linked immunosorbent assay examination or using a cell-based immunoassay of culture cells (i.e., HEK cells) transfected with the complementary DNA (cDNA) representing the single or assembled NR1–NR2 subunits [20]. The cell assay is more specific.

Brain biopsies are not helpful, showing normal or nonspecific findings, including perivascular inflammation with B and T cell infiltrates and microglial activation [19].

The differential diagnosis includes viral encephalitis, acute psychosis, and mania eventually with psychotic features, drug abuse, and neuroleptic malignant syndrome.

Association with Tumors and Gender

The first reported cases were all women presenting with teratoma [16]. In later reports it appears that the disease occurs in 80 % of women and is being more frequently recognized in younger teenagers and children [30]. In a large series of 100 cases, tumors were diagnosed in 58 cases and included 53 teratomas in women, one immature teratoma of the testis and one small-cell lung cancer in two men [29]. The detection of an underlying tumor is dependent of age, sex, and ethnic background. Analysis of 400 patients confirms that tumors are less likely to be found in younger patients and that teratomas are found in more than half of women older than 18 years. Black women are more likely to have an underlying ovarian teratoma than are patients of other ethnic groups [19].

The screening procedures for ovarian teratomas include MRI, CT scan, and ultrasound. Serological tumor markers are not helpful. Exploratory laparoscopies and blind oophorectomies have been helpful in some cases [19].

Outcomes and Treatments

Immunotherapy and tumor resection are the two main aspects of the management of anti-NMDAR Ab encephalitis. Although no controlled trial has been done, there is some evidence of the efficacy of these treatments. Retrospective studies reported 4 % of mortality and a good recovery, complete or with mild sequelae in 75 % of patients, but all other patients remain severely disabled [29, 30]. Immunotherapy includes corticosteroids and intravenous immunoglobulin or plasma exchange, but they work best when an underlying tumor has been removed

[11, 19, 29]. In the absence of tumors, a second-line immunotherapy is frequently needed with mycophenolate mofetil or azathioprine [29].

Management of psychiatric symptoms is complex and not standardized [9]. It has been suggested initiating treatment with quetiapine in patients with psychotic symptoms and agitation or Thorazine in patients who refuse oral medications [9]. High-potency antipsychotics must be avoided. Valproic acid could be helpful in patients with mood symptoms, emotional lability, and/or mania [9].

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