catatonic schizophrenia. These symptoms alternate with periods of agitation. Some patients develop bizarre and inappropriate behavior such as smiling, echophenomenal (both words and movement), or catalepsy-like symptoms.[11] Dissociative (paradoxical) responses to stimuli (unresponsive to painful stimuli, but resistant to eye opening) are often presented in patients, mimicking a psychogenic condition or malingering. Most patients later develop hyperkinetic abnormal movements, the majority of which are oro-lingual-facial dyskinesia; however, other types of movement may also be observed. During the same period, autonomic instability and hypoventilation also occur. The autonomic manifestations include hyperthermia, tachy-bradycardia, and labile blood pressure. Autonomic dysfunction leads to a prolonged cardiac pause and requires a temporary pacemaker. Hypoventilation can present alone or in association with autonomic instability, which necessitates respiratory support. This phenomenon often occurs during the period of hyperkinetic movement, or it can occur during early stages of symptoms. Within 4 weeks of symptom onset, most patients develop a similar spectrum of symptoms irrespective of their age.[14] The characteristics of classical anti-NMDAR encephalitis progression are summarized in Figure 1. However, the clinical presentation of patients with anti-NMDAR encephalitis varies depending on the individual patient. This review focuses on each symptom of anti-NMDAR encephalitis.

Prodromal symptoms

This viral-like illness usually presents 1-2 weeks before the development of psychiatric symptoms.[13] It is not known whether the symptoms are due to NMDAR dysfunction, the systemic immune response to autoimmune disease or secondary responses to a viral infection which later precipitate autoimmune disease.

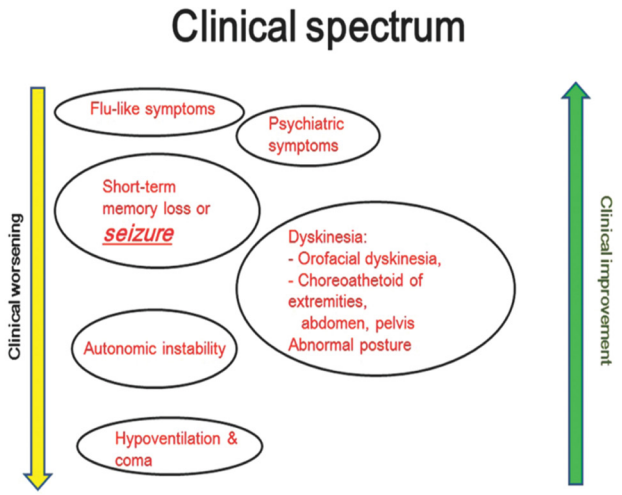

Figure 1: The spectrum of anti-N-methyl-D-aspartate receptor encephalitis showing the common sequence of symptoms with clinical worsening and improvement

Psychiatric symptoms

The psychiatric symptoms of anti-NMDAR encephalitis encompass a broad spectrum that includes anxiety, depression, agitation, abnormal behavior, delusion, hallucination, mania, and frank psychosis.[13] The symptoms usually present at the beginning of the disease, leading to medical attention (mostly by a psychiatrist). It is the most common initial manifestation in both sexes.[15] In younger children, parents may describe the symptoms as temper tantrums, behavioral changes, aggression, and progressive speech deterioration.[16] Staff phobia has also been reported in children or adolescents.[16] Overall, the psychiatric symptoms associated with the initial manifestation or during relapses are the same in both sexes and all ages.[17] Isolated psychiatric symptoms can be observed in up to 4% of patients (either at disease onset or during relapses).[17] These symptoms may be explained by reduced NMDAR synaptic content and disruption of receptor function in discrete regions of the brain. NMDARs are widely expressed throughout the entire brain, and, therefore, the density of receptor expression or the susceptibility of some regions (especially the frontostriatum or hippocampus) to autoantibodies may be the cause of the symptoms.[17]

Cognitive dysfunction

Cognitive dysfunction, especially short-term memory impairment, has been underestimated due to the predominance of psychiatric and speech problems that interfere with the cognitive assessment.[11] There is evidence that IgA antibody subtypes recognizing the NMDAR antibody might be present in patients with progressive cognitive decline.[18] However, a later study suggested that IgA subtypes against NMDAR can be found in the control population and are not related to the neurological disease.[19] The role of NMDAR-IgA remains uncertain.

Seizure

Seizures occur in approximately 70% of adults and are even more common in children.[14] They typically occur after a prodromal period and psychiatric symptoms in adults, but they may be the initial manifestation and occur with greater frequency in children and adult males.[15] This phenomenon may be explained by a reduced influence of hormonal factors or by a selection bias whereby women with initial psychiatric symptoms are more likely to be suspected of this disease compared to men. Up to 5% of patients with anti-NMDAR encephalitis have purely a seizure disorder without prominent neuropsychiatric involvement.[20] The seizure types

can present as generalized, focal, or complex partial seizures. Some cases may progress to status epilepticus or nonconvulsive status epilepticus. Most of these cases are refractory to treatment with standard antiepileptic drugs but may respond well to immunosuppressive drugs. One case report described nonconvulsive status epilepticus lasting for 6 months that was refractory to all immunomodulating therapies but showed marked improvement following removal of an ovarian tumor.[21] Seizures in anti-NMDAR encephalitic patients usually have an extratemporal origin.[20,22]

The most commonly observed (90%) electroencephalogram (EEG) pattern typically shows diffuse slowing or predominantly anterior slowing, but these phenomena do not correlate with the clinical and MRI findings.[13,16,23] One-third (34%) of patients exhibited focal slowing. One case series described a unique EEG pattern of "extreme delta brush" in 30% of the patients in early stages of the disease. This pattern suggests the occurrence of more severe disease (a more prolonged hospitalization).[23]

Abnormal movement

Abnormal movement (mostly hyperkinetic movement) has been described in up to 80% of patients during the course of the disease and may be the initial manifestation in some patients, especially in the pediatric group.[14] However, abnormal movement usually follows psychiatric symptoms or seizure. Some of these symptoms may be difficult to differentiate from seizure clinically, but the EEG does not reveal electrographic seizure during an episode.[24] These abnormal movements do not respond to anti-epileptic or dopamine receptor antagonist drugs. Abnormal movements can alert clinicians to investigate autoimmune processes in cases of suspected viral encephalitis, which do not typically present this feature.[25,26]

Various forms of abnormal movement have been described in anti-NMDAR encephalitis. The majority of these movements are complex uni- or bilateral stereotypic movements, in particular, orofacial dyskinesia.[14,27] The spectrum of abnormal movements includes chorea, choreoathetosis, facial/limb myorhythmia, facial-limb-truncal dystonia, myoclonus, tremor, opsoclonus-myoclonus or ataxia, and opisthotonus.[14,27-29] The distinct abnormal movements observed in anti-NMDAR encephalitis may be due to a dissociated state, in which movement disorder may persist during unconsciousness.[28] This feature may be difficult to differentiate from frontal lobe seizure, but an EEG might provide helpful information.[28] One patient can develop more than one characteristic of abnormal movement during the course of the disease. MR spectroscopy of the basal ganglia and thalamus may show a reduction of the N-acetylaspartate/creatine (Cr) ratio in patients during involuntary movements.[30]

DIAGNOSTIC EVALUATIONS

The CSF profile in cases of anti-NMDAR encephalitis typically shows pleocytosis and mild protein elevations. The normal CSF profile does not exclude immune-mediated disease. The brain MRI may be normal in up to 50% of cases.[13] The EEG typically shows diffuse slow or rhythmic activity. The EEG of anti-NMDAR encephalopathy is characterized by an extreme delta brush, which can be found in up to 30% of cases.[23] For specific antibody testing, it is recommended that both CSF and serum be assessed. In the majority of immune-mediated limbic encephalitis including anti-NMDAR encephalitis, the CSF is more sensitive than the serum, excluding cases of VGKC-complex autoantibody (Lgi1 and Caspr2), in which the serum may be more sensitive than the CSF.[13,31] The NMDAR-IgG can be demonstrated by the presence of immunologic reactivity to mouse brain tissue (especially in the hippocampus area and the granular layer of the cerebellum) or NMDAR-transfected cells [Figure 2]. The antibody titer is higher in the CSF compared to the serum in patients with a poor outcome or the presence of teratoma, and titer changes in the CSF are more likely to be related to clinical relapses than to changes in the serum.[32]

Because ovarian teratoma is found in up to 40% of cases of anti-NMDAR encephalopathy, it is recommended that these patients be screened for this condition. If the initial workup is negative for ovarian teratoma,

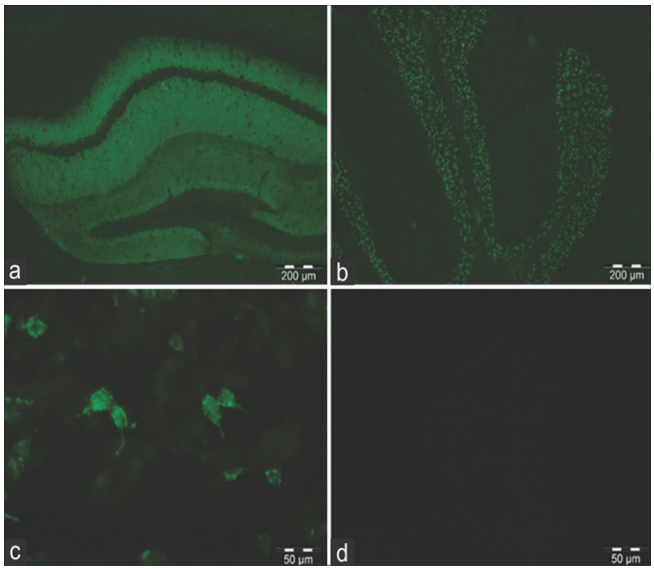

Figure 2: Immunohistochemistry of mouse brain sections showing binding of the N-methyl-D-aspartate receptor (NMDAR)-IgG to the hippocampus. (a) and granular layer of the cerebellum; (b) HEK293 cells expressing NMDAR (GluN1); (c) show antibodies binding to the cell membrane; (d) no reactivity is seen with normal cerebrospinal fluid