no response within several days, one can advance to intravenous immunoglobulin (IVIg) or plasma exchange, and then to immunosuppression with either rituximab or cyclophosphamide. Approximately 30% of patients with anti-Ma2-associated encephalitis respond to treatment of the tumor (usually a germ cell neoplasm of the testis) and immunotherapy.

ENCEPHALITIDES WITH ANTIBODIES TO CELL-SURFACE OR SYNAPTIC PROTEINS (TABLE 122-3)

These disorders are important for three reasons: (1) they can occur with and without tumor association, (2) some syndromes predominate in young individuals and children, and (3) despite the severity of the symptoms patients usually respond to treatment of the tumor, if found, and immunotherapy (e.g., glucocorticoids, IVIg, plasma exchange, rituximab, or cyclophosphamide).

Encephalitis with N*-methyl-*D*-aspartate (NMDA) receptor antibodies* (Fig. 122-1) usually occurs in young women and children, but men and older patients of both sexes can be affected. The disorder has a characteristic pattern of symptom progression that includes a prodrome resembling a viral process, followed in a few days by the onset of severe psychiatric symptoms, memory loss, seizures, decreased level of consciousness, abnormal movements (orofacial, limb, and trunk dyskinesias, dystonic postures), autonomic instability, and frequent hypoventilation. Monosymptomatic episodes, such as pure psychosis, occur in 4% of the patients. Clinical relapses occur in 12–24% of patients (12% during the first 2 years after initial presentation). Most patients have intrathecal synthesis of antibodies, likely by infiltrating plasma cells in brain and meninges **(Fig. 122-4*A*)**. The syndrome is often misdiagnosed as a viral or idiopathic encephalitis, neuroleptic malignant syndrome, or encephalitis lethargica, and many patients are initially evaluated by psychiatrists with the suspicion of acute psychosis. The detection of an associated teratoma is dependent on age and gender: 46% of female patients 12 years or older have uni- or bilateral ovarian teratomas, whereas less than 7% of girls younger than 12 have a teratoma **(Fig. 122-4*B*)**. In male patients, the detection of a tumor is rare. Patients older than 45 years are more frequently male; about 20% of these patients have tumors (e.g., cancer of the breast, ovary, or lung).

Encephalitis with leucine-rich glioma-inactivated 1 (LGI1) antibodies predominates in patients older than 50 years (65% male) and frequently presents with memory loss and seizures (limbic encephalopathy), along with hyponatremia and sleep dysfunction. In a small number of patients, the encephalitis is preceded by or occurs with myoclonic-like movements called faciobrachial dystonic or tonic seizures. Less than 10% of patients have thymoma.

Encephalitis with contactin-associated protein-like 2 (Caspr2) antibodies predominates in patients older than 50 years and is associated with Morvan's syndrome (encephalitis, insomnia, confusion, hallucinations, autonomic dysfunction, and neuromyotonia) and, less frequently, with limbic encephalitis, neuromyotonia, and neuropathic pain. About 30–40% of patients have thymoma.

Encephalitis with γ-aminobutyric acid type B ($GABA_B$) receptor antibodies is usually associated with limbic encephalitis and seizures. In rare instances, patients develop cerebellar symptoms and opsoclonus. Fifty percent of patients have SCLC or a neuroendocrine tumor of the lung. Patients may have additional antibodies to glutamic acid decarboxylase (GAD), which are of unclear significance. Other antibodies to nonneuronal proteins are often found in these patients as well as in patients with α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor antibodies, indicating a general tendency to autoimmunity.

Encephalitis with GABAA receptor antibodies may affect children and adults. When antibodies are present at high titer in serum and CSF, the disorder associates with prominent seizures and status epilepticus, often requiring pharmacologically induced coma. Low titer antibodies in serum are often associated with other autoimmune conditions, and the spectrum of symptoms is wider, including encephalitis, seizures, opsoclonus, or stiff-person syndrome. Most patients do not have an underlying tumor, but some may have thymoma.

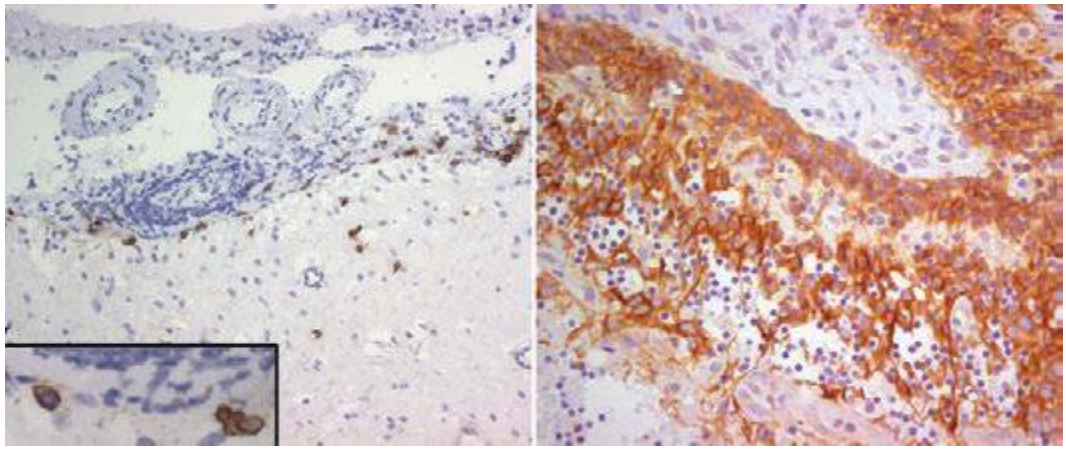
Encephalitis with AMPA receptor antibodies affects middle-aged women, who develop acute limbic dysfunction or, less frequently, prominent psychiatric symptoms; 70% of the patients have an underlying tumor in the lung, breast, or thymus. Neurologic relapses may occur; these also respond to immunotherapy and are not necessarily associated with tumor recurrence.

Encephalitis with glycine receptor (GlyR) antibodies has been described in adults with progressive encephalomyelitis with rigidity and myoclonus (PERM) and stiff-person spectrum of symptoms (with or without GAD antibodies). The disorder usually occurs without tumor association, although some patients have lung cancer, thymoma, or Hodgkin's lymphoma.

Encephalitis with dipeptidyl-peptidase-like protein-6 (or DPPX) antibodies results in symptoms of CNS hyperexcitability including agitation, hallucinations, paranoid delusions, tremor, myoclonus, nystagmus, seizures, and sometimes hyperekplexia. Some patients develop progressive encephalomyelitis with rigidity and myoclonus. Diarrhea, other gastrointestinal symptoms, and substantial loss of weight often suggest the presence of an underlying tumor, but no tumor association has been identified. The disorder responds to immunotherapy.

PARANEOPLASTIC CEREBELLAR DEGENERATION

This disorder is often preceded by a prodrome that may include dizziness, oscillopsia, blurry or double vision, nausea, and vomiting. A few



A ***B***

FIGURE 122-4 Pathologic findings in anti–*N*-methyl-D-aspartate (NMDA) receptor encephalitis. Infiltrates of plasma cells (brown cells; stained for CD138) in the meninges and brain of a patient (***A***); the inset is a magnification of some plasma cells. (***B***) Neurons and neuronal processes in the teratoma of a patient (brown cells; stained with MAP2); these neurons express NMDA receptors (not shown). *(From E Martinez-Hernandez et al: Neurology 77:589, 2011, with permission.)*