Evidence for Autoimmunity in Paraneoplastic Disorders

Historically, paraneoplastic syndromes of the CNS were thought to result from neuronal degeneration and secondary inflammation, viral infection, or an immune-mediated mechanism; a preponderance of evidence now points toward the latter as causative (10). In particular, multiple clinical-immunologic relationships have been characterized in which a specific autoantibody occurs exclusively with a given clinical syndrome and (often) cancer type (Table 1) (10, 11); paraneoplastic autoantibodies are virtually never found in comparison subjects (15). The discovery of these antibodies has provided a laboratory method for screening of patients, as well as potential early detection of underlying malignancy (16). Autoantibodies can usually be found in both serum and CSF, although titers are frequently higher in CSF. In further support of immunologic pathogenesis of paraneoplastic disorders, many symptoms respond to immunotherapy, driving the ongoing search for unknown antibodies when no well-described antibodies are found in available screens.

The prevalence of paraneoplastic syndromes depends on the type of cancer, and it ranges from below 1% in breast and ovarian cancers to 3%–5% in small cell lung cancer and 20% in thymomas (7), although these numbers may be underestimations of the true prevalence rates.

Antibodies associated with paraneoplastic disorders that often include neuropsychiatric manifestations can be subcategorized on the basis of the cellular locations of the antigens they recognize (Table 1). One group of antibodies is directed against intracellular neuronal antigens. Their pathogenic activity is thought to be mediated by cytotoxic
PSYCHIATRIC MANIFESTATIONS OF PARANEOPLASTIC DISORDERS

FIGURE 1. Approach to Evaluation and Treatment of Suspected Paraneoplastic Disorder Involving the Central Nervous System

**Evaluation**
- **Suspected paraneoplastic disorder involving the CNS**
  Examples of indicators: acute change in behavior or mental status, atypical symptoms or demographic features, progressive course with conventional therapies

- **Brain MRI with and without contrast**
  Look for abnormalities in fluid-attenuated inversion recovery (FLAIR) or T2 sequences; consider EEG

- **Lumbar puncture**
  Screen for well-characterized paraneoplastic antibodies; also assess for inflammatory/autoimmune CSF markers: lymphocytic pleocytosis, high IgG index, oligoclonal bands with or without elevated protein

**Treatment**
- Treat cancer according to standard of care for primary cancer diagnosis
- Immunotherapy—consider intravenous methylprednisolone (1 g/day for 5–10 days), plasmapheresis (~5 exchanges in 10 days), and/or intravenous immunoglobulin (IV Ig: 0.4 g/kg body weight/day for 5 days); if poor response, consider pulses of cyclophosphamide (750 mg/m²) or rituximab (375 mg/m² weekly for 4 weeks).

* Increasingly it is appreciated that disorders once thought to be paraneoplastic in nature might in some instances be purely autoimmune and occur in the absence of any identifiable tumor, as is found in approximately 50% of the cases of N-methyl-D-aspartate (NMDA) receptor encephalitis.

* Given the relative rarity of these disorders, there is no standard of care with regard to immunotherapy. These guidelines are therefore based on clinical experience (7–9) rather than established care protocols.

T-cell immunity, rather than by the autoantibodies directly, and is characterized by infiltrates of oligoclonal T-cells in the CNS with deposits of paraneoplastic antibodies in T-cell-dense areas (17, 18). In fact, stereotyped T-cell responses have been demonstrated in response to paraneoplastic antigens, resulting in cell-mediated damage (19). That treatment aimed at the humoral immune response is largely ineffective further suggests that the antibodies themselves are not the primary pathogen, although they might still play a role in generating the abnormal immune response and are crucial for diagnosis (6). Another antibody group recognizes cell-surface antigens and appears to directly cause paraneoplastic syndrome symptoms, likely by disrupting normal synaptic transmission (7, 20). This group can occur with or without an associated cancer, and it includes antibodies recognizing voltage-gated potassium channels and ionotropic glutamate receptors. Syndromes that are directly related to antibody presence appear far more responsive to immunomodulation, although long-term behavioral sequelae and relapse can be significant (20–22).

**Clinical Consideration of Limbic Encephalitis**

Limbic encephalitis is one of the best-appreciated causes of rapid behavioral dysfunction in association with neurological symptoms, and its clinical manifestations warrant specific discussion. Causes of limbic encephalitis include systemic autoimmune disease, viral disorders, and paraneoplastic disorders (Figure 2). The term “limbic encephalitis” was first used in 1968 to describe patients with memory dysfunction in association with bronchogenic carcinoma (4). Pathology revealed inflammatory and degenerative changes in temporal gray matter in the limbic area of the patients (hippocampus, amygdala, cingulate gyrus). Clinically, the classic syndrome evolves over
days to weeks and includes psychiatric changes such as irritability, depression, hallucinations, personality disturbances, and cognitive changes, e.g., short-term memory loss that may progress to dementia. In addition, patients may experience sleep disturbances, confusion, and/or seizures. The CSF often shows a mild lymphocytic pleocytosis (6, 11, 12), and magnetic resonance imaging (MRI) may demonstrate uni- or bilateral medial temporal lobe hyper-intensities on fluid-attenuated inversion recovery (FLAIR) and $T_2$-weighted images with progressive hippocampal gyrus volume loss upon repeat imaging (Figure 3) (23).

Reflecting the variable psychiatric presentation of limbic encephalitis, patients have been described with myriad symptoms, ranging from delusional thought content and paranoid ideation to obsessive-compulsive behavior (24, 25). Although “limbic encephalitis” or “psychiatric manifestations” are often used as blanket generalizations to describe the behavioral features of these patients, detailed case studies yield a rich characterization of the neuropsychiatric symptoms. In the following sections, we discuss specific autoantibody syndromes and their psychiatric manifestations, some but not all of which fall into the category of limbic encephalitis. This overview of paraneoplastic disorders is organized according to antigen location.

**Syndromes Associated With Intracellular Antigens**

These antigens include anti-Hu antibodies, anti-Ma antibodies, antibodies against collapsin response mediator protein type 5 (CRMP5) and CV2, and rare autoantibodies with intracellular targets.

**Anti-Hu Antibodies**

The most common known paraneoplastic neurological syndrome is associated with anti-Hu antibodies, which recognize a family of RNA-binding proteins involved in normal neuronal development (26). Anti-Hu encephalitis usually manifests as classic limbic encephalomyelitis occurring with small cell lung cancer (8, 27, 28). Limbic encephalomyelitis entails a wide spectrum of neurological dysfunction, including limbic encephalitis, sensory neuropathy, motor neuron abnormalities, and cerebellar ataxia (8, 16, 27, 28). Patients with anti-Hu antibodies are often in their 50s or 60s with a long history of smoking and complaints of painful sensory neuropathy with recent confusion and amnesia (8, 16, 28, 29). Depression appears as the next most cited symptom, although less prevalent, followed by rare reports of hallucinations (1, 16, 28). Overall, patients with small cell lung cancer and limbic encephalitis fair poorly, with a median survival of about 1 year and a 3-year survival rate of approximately 20% (8, 28). Treatment of the tumor along with immunotherapy for the T-cell response (e.g., cyclophosphamide) can result in symptom stabilization, although not often improvement, and early intervention (within weeks of symptom onset) generally yields better results (8, 30).

**Anti-Ma Antibodies**

A decade ago, an autoantibody syndrome associated with testicular germ cell tumors and paraneoplastic limbic encephalitis was described (31). Antibodies recognize the onconeuronal antigen Ma2, whose cellular localization and structural motifs suggest roles in mRNA processing or biogenesis (32). In contrast to anti-Hu antibodies, isolated
anti-Ma2 antibodies are usually seen in young men with CNS-specific disturbances—most often limbic encephalitis along with hypothalamic and/or brainstem encephalitis (2, 6, 9). A review of all published patient reports reveals common traits within this population: severe short-term memory deficits stand out as the most common feature, with a few reports of confusion or disorientation (9, 31–34). Symptoms frequently occur with other overt neurological deficits, such as visual dysfunction (diplopia, gaze abnormalities, nystagmus), gait disturbances, and hypokinesia (9, 33). Affective changes (specifically depression and irritability) as well as hallucinations are mentioned in some individual patient descriptions, but these symptoms seem relatively rare (9, 33).

Interestingly, there appears to be a specific connection between anti-Ma2 antibodies and sleep dysregulation of hypothalamic origin (35, 36). As many as one-third of patients have shown excessive daytime sleepiness in addition to other symptoms (9). Generally, patients with narcolepsy are thought to have abnormally low levels of the neuropeptide hormone hypocretin (37, 38). While anti-Ma2 antibodies are not a cause of idiopathic narcolepsy, hypocretin CSF levels have been demonstrated to be low in patients with anti-Ma2 limbic encephalitis (36). One case study (35) describes a 69-year-old man with a 3-month history of progressively severe hypersomnia, memory loss, diplopia, gait unsteadiness, short episodes of fear, and apathy. Further investigation revealed REM sleep behavior disorder, low levels of hypocretin-1, and anti-Ma2 antibodies in CSF and serum.

In a few instances, anti-Ma2 limbic encephalitis has been manifested as a pure psychiatric disturbance, such as a sense of unexplained fear, “nervous breakdowns” and panic attacks, or loss of self-confidence (2, 9). One case describes a 39-year-old previously healthy man who developed obsessive-compulsive behaviors (25). He first had obsessive thoughts of a water leak in his home and began checking equipment over 10 times each day. Within 6 months, he developed additional compulsions and was diagnosed with obsessive-compulsive disorder (OCD) (39). He was ultimately found to have a testicular teratoma and anti-Ma2 antibodies, which the authors suggest as causative, given data indicating involvement of limbic regions in OCD (39).

In comparison to patients with paraneoplastic disorders mediated by other intracellular antibodies, those with isolated anti-Ma2 antibodies may respond well to treatment of the tumor and immunotherapy. While 30%–50% of patients ultimately deteriorate neurologically (the death rate is approximately 15%), one-third experience neurological improvement and 20%–40% stabilize (32, 33). The association of testicular cancer and anti-Ma2 limbic encephalitis in men younger than 50 years is so strong that studies suggest consideration of orchiectomy or testicular irradiation even if a tumor cannot be found (34). In one study, six patients with risk factors for testicular neoplasm and neurological deterioration underwent orchiectomy.
for questionable ultrasound findings in the absence of an identifiable tumor; all were found to have preinvasive malignant cells in orchietomy specimens (34).

**Anti-CRMP5 and Anti-CV2 Antibodies**

Anti-CRMP5 and -CV2 antibodies have been found most commonly in patients with small cell lung cancer but also thymoma and, less frequently, other tumors (40). CRMP localizes to neuronal cell bodies and axons in the mammalian CNS, and it is known to be involved in axon guidance and possibly synapse function (41). Both anti-CRMP5 and anti-CV2 antibodies recognize the CRMP5 antigen, and the presence of these antibodies may accompany anti-Hu antibodies in patients with small cell lung cancer (2). Patients with anti-CV2/CRMP5 have a wide spectrum of neurological symptoms, most notably chorea characterized by involuntary movements often involving the face (42). Optic neuropathy and abnormalities of olfaction and taste are remarkable for their unusually high frequencies in paraneoplastic conditions with these antibodies (40).

Anti-CV2/CRMP5 antibodies are often associated (30%–40% of patients) with various cognitive deficits and limbic encephalitis (40, 42). One of the largest studies of this patient group (40) reported subacute dementia as the most frequent symptom of limbic encephalitis, but it also described rare instances of personality change, depression, confusion, and psychosis. Remarkably, paraneoplastic involvement of striatal and basal ganglia circuitry that results in striatal encephalitis with choreic movements can also affect nonmotor circuitry in the same regions. Cases of patients with manic mood, memory deficits with spatial/temporal disorientation, and obsessive-compulsive behavior have been reported. Nuti et al. (43) described a patient with chorea and progressive neuropsychological deterioration characterized by memory dysfunction and constructional apraxia, with a score of 17 out of 30 on the Mini-Mental State Examination (MMSE), who eventually received a diagnosis of non-Hodgkin’s T-cell lymphoma. Muehlschlegel et al. (44) reported a 69-year-old woman who developed irrational and argumentative behavior, followed by obsessive-compulsive-like behaviors. Four weeks later she experienced choreic movements and an unsteady gait. The patient deteriorated neurologically, and CV2 antibodies were reported several days after her death.

Outcomes are less clear for patients with anti-CV2/CRMP5 antibodies than for those with anti-Hu and -Ma2 antibodies. One study described improvement of chorea with tumor treatment, immunotherapy, and antipsychotics, with about 50% of the patients surviving 4–42 months after the onset of chorea (42). Because many patients have psychiatric changes and chorea, differentiating this disorder from Huntington’s disease or Wilson’s disease (through family history, time line of symptoms, CSF inflammatory markers, and copper metabolism studies) is important given the distinct approach to treatment and potential underlying tumor.

Aside from the syndromes described in the preceding sections, other antibodies recognizing intracellular antigens have been identified in patients with paraneoplastic disorders and psychiatric symptoms. Two of these reports involve protein kinases as targets. Sabater and colleagues (45) described a 61-year-old man with a 2-week history of confusion, personality changes, and short-term memory deficits, subsequently diagnosed with small cell lung cancer. Ultimately, an antibody against BR serine/threonine kinase 2 (BRSK2)—a close homologue of the SAD1 kinase in *Caenorhabditis elegans*, known to be crucial for proper synapse formation—was discovered (46). Similarly, Tuzun et al. (47) reported two male patients in their early 70s with rapidly progressive confusion and memory deficits. One also had delusional thoughts with agitation and aggressive behavior, while the other experienced personality changes and difficulty recognizing faces. Both patients experienced progressive deterioration to dementia that was unaffected by immunotherapy. An autoantibody against adenylate kinase 5, thought to have a role in neuronal energy transfer and RNA/DNA synthesis (48), was identified; no cancer was detected in either patient.

**Rare Autoantibodies With Intracellular Targets**

* Axial MRI fluid-attenuated inversion recovery (FLAIR) sequence demonstrates bilateral medial temporal hyperintensities, primarily involving the left hippocampus (arrows).

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syndrome, but it was also described in a woman with small cell lung cancer with memory deficits and an MMSE score of 23 out of 30 (49). She went on to develop agitation, hallucinations, and generalized convulsions but improved significantly following tumor treatment. Antoine and colleagues (50) also described a patient with small cell lung cancer harboring antiamphiphysin antibodies who became abnormally anxious and depressed and then, as her condition deteriorated, developed olfactory and auditory hallucinations and anterograde memory loss. Finally, antibodies recognizing the antigen Ri—commonly associated with brainstem or cerebellar syndromes (51)—were identified in a patient with carcinoid tumor and striking neuropsychological symptoms (52).

**Syndromes Associated With Cell-Surface Antigens**

This group of antigens includes antibodies against voltage-gated potassium channels, antibodies against the N-methyl-D-aspartate (NMDA) type of glutamate receptors, antibodies against α-amino-3-hydroxy-5-methyl-4-isoxazolopropionic acid (AMPA) receptors, and antibodies against γ-aminobutyric acid type B (GABAB) receptors.

**Antibodies Against Voltage-Gated Potassium Channels**

These antibodies are usually associated with nonparaneoplastic limbic encephalitis, but they can occur in the context of an underlying tumor (20% with small cell lung cancer or thymoma) (21, 53). The disorder typically affects middle-aged or older patients, who develop severe verbal and visual memory deficits and confusion or disorientation (21, 22, 54). Seizures are common, but CSF pleocytosis is rare in syndromes with antibodies against voltage-gated potassium channels, which is not the case in classic limbic encephalitis (21, 53).

A survey of case descriptions of patients with voltage-gated potassium channel antibodies illustrates more diffuse psychiatric disturbances than occur in classic limbic encephalitis (described earlier). Behavioral changes are frequent and often include apathy and irritability (21, 22). These symptoms may occur concurrently with signs of autonomic dysfunction, such as excess sweating and salivation (21, 22). Visual hallucinations have also been described (22, 54), although this symptom is rare in comparison to memory dysfunction. In addition, associations between this syndrome and hyponatremia (21, 22), hypothermia (54), and REM sleep behavior disorder (55) have been reported. Despite the clinical variability in presentation, review of the literature highlights memory impairment as a core finding.

Antibodies recognizing voltage-gated potassium channels are well known to underlie the neurological abnormalities in Isaacs and Morvan syndromes, characterized by neuromyotonia, hypersalivation, hyperhidrosis, and insomnia (21). Although some of the clinical symptoms of Isaacs and Morvan syndromes exist in encephalitis caused by antibodies against voltage-gated potassium channels, the predilection for limbic areas is not well understood. Perhaps antibodies in these distinct disorders are subtly different and target peripherally, rather than centrally, expressed potassium channel subtypes (21, 56). It is also not known how antibodies against voltage-gated potassium channels result in memory deficits, although modulation of neuronal excitability likely plays a role (22) and a knockout animal model lacking one of the channels expressed in the hippocampus does display memory impairment (57).

A significant distinction between limbic encephalitis caused by antibodies against voltage-gated potassium channels and limbic encephalitis due to other causes is the rapid response to immunotherapy. About 80% of patients improve neurologically and radiologically following prompt (within 2 months) treatment with high-dose steroids, intravenous immunoglobulins, or plasma exchange (21, 22); neuropsychological improvements have been noted but are less robust. While most patients show a large degree of cognitive and behavioral recovery, the majority still experience short-term memory deficits, although less serious than at symptom onset (21, 22). Given the prognostic outcome with immunotherapy, prompt recognition and diagnosis of this syndrome is crucial, a fact emphasized by work demonstrating relatively poor improvement with more prolonged symptoms (greater than 9 months) prior to treatment (21).

**Anti-NMDA Receptor Antibodies**

Perhaps the most intriguing disorder with regard to psychiatric symptoms is the autoimmune syndrome involving the NMDA-type glutamate receptor. NMDA receptors are ionotropic glutamate receptors with well-known roles in synaptic transmission and plasticity (58), as well as in neuropsychiatric disease (59). Antibodies in this syndrome recognize the NR1 subunit (Figure 4), which normally combines with various NR2 subunits (A–D) to form heteromers with distinct properties (59). Although the antibody was only identified in the last few years, about 200 patients have now been described with this disorder, and nearly 75% were seen by a psychiatrist or initially admitted to a psychiatric unit (7). Because of the constellation of symptoms, patients were often misdiagnosed with acute psychosis, malingering, or drug abuse (60).

In many ways, the anti-NMDA receptor encephalitis is unique from the other syndromes discussed in this review. Rather than having predominant symptoms of memory changes or disorientation, patients are typically young women (75%) or children (40% younger than 18 years) with prominent psychiatric symptoms, including anxiety and agitation, bizarre behavior, delusional and/or paranoid thoughts, and visual or auditory hallucinations (see clinical vignettes) (7, 61, 62). Recent work has focused specifically on the presentation of anti-NMDA receptor encephalitis in the pediatric population (as young as 23 months old), finding initial symptoms such as temper tantrums,
tumor is a positive prognostic factor in this syndrome, as patients with tumor removal within 4 months of neuropsychiatric changes fared better than all other patients (7).

The posthospitalization course in this patient population merits specific discussion. Of patients that ultimately make a full recovery or are left with only mild deficits, most (85%) have significant psychiatric abnormalities at discharge, including poor attention and planning, impulsivity, and behavioral disinhibition; approximately 25% experience sleep dysfunction (7). Recovery is often slow, and it takes many months for patients to return to their baseline behavioral and cognitive status. In addition, 15 out of 100 patients had instances of relapse of encephalitis in one study, and most experienced a persistent amnesia for the entire illness (7). The clinical picture and scientific results in this syndrome suggest that the antibody itself is pathogenic, as antibody titers correlate with disease severity (63) and antibody activity results in a reversible decrease in synaptic NMDA receptors (7). In addition, many drugs that modulate NMDA receptors are known to cause a similar constellation of symptoms, such as psychotic behavior (64), dystonia (65), and autonomic dysfunction (66), while over the past several decades NMDA receptor hypofunction has received increasing scrutiny as a putative mechanism of schizophrenia (67).

Anti-AMPAR Antibodies

A recently discovered paraneoplastic disorder associated with limbic encephalitis is characterized by antibod-
ies against subunits of the AMPA-type glutamate receptor (20). The AMPA receptor mediates the majority of fast glutamatergic neurotransmission in the brain and plays a role in molecular mechanisms of learning and memory (68). In this syndrome, subunits GluR1 and GluR2 are specifically targeted, resulting in the internalization and redistribution of AMPA receptors away from the synapse; the effect is reversible upon removal of antibody-containing CSF from neurons (20). Animal models with similar mistracking of AMPA receptors have abnormalities in behavioral paradigms of learning and memory, as well as emotional disturbances (69).

Of the 10 described patients with anti-AMPA receptor limbic encephalitis, nine were women, and the median age was 60 years. Almost all had isolated limbic symptoms: subacute memory loss (less than 8 weeks) and confusion (20). The other most common symptom was agitation and/or aggressive behavior, which was reported in one-half of the patients (another had “behavioral changes” not otherwise specified (70)). Seven of the 10 patients had an associated tumor of the breast or lung or thymoma. All living patients with an identified neoplasm received cancer treatment, and nine patients received immunotherapy. Every patient receiving immunotherapy responded well, with reduced cognitive and behavioral symptoms (20).

One of the most striking features of anti-AMPA receptor limbic encephalitis is the tendency to relapse despite treatment. Seven patients in the preceding series experienced relapsing symptoms, with deficits of short-term memory and persistent behavioral problems, such as aggression, in all but one patient, who had mild persistent depression and apathy (20). All relapse cases occurred in the absence of tumor or tumor recurrence, suggesting that a persistent autoimmune disorder had been triggered. Taken together, these results demonstrate a remarkable similarity between the clinical picture and the behavior one would predict on the basis of AMPA receptor function in animal models.

**Anti-GABA\_b Receptor Antibodies**

Paraneoplastic limbic encephalitis can also result from antibodies recognizing receptors involved in inhibitory neurotransmission. Anti-GABA\_b receptor antibodies have been identified in association with small cell lung cancer, with patients exhibiting seizures, confusion, and severe memory abnormalities (71). Such observations underscore how imbalances in excitation and inhibition can manifest with neurocognitive dysfunction (72).

**Disorders With Potential Paraneoplastic Etiologies**

In light of how quickly the field of paraneoplastic biology has progressed over the past decade, it is likely that other, as-yet-undefined paraneoplastic disorders exist. Almost certainly, the discovery of new autoantibodies will occur and help define groups of patients with specific symptoms but no clear underlying mechanism. In the following sections we discuss three examples of psychiatric and cognitive syndromes or symptoms hypothesized to have a humoral component independent of the existing cancer itself.

**Opsoclonus-Myoclonus-Ataxia and Neuroblastoma in Children**

Opsoclonus, myoclonus, and ataxia are characteristic findings in patients with underlying neuroblastoma, occurring almost exclusively in children (73). The symptoms are found in 2%–3% of children with neuroblastoma, although approximately 50% of children experiencing this triad of symptoms are found to have a neuroblastoma (11,
and 30% have both symptoms. It is noteworthy that psychosomatic patients experience depression, 50% have anxiety, and 50% have anxiety. Austin (80) found that approximately 70% of pancreatic cancer patients experience depression, 50% have anxiety, and 50% have anxiety. Since that time, numerous studies have demonstrated that depression often occurs before clinical diagnosis and prognosis is poor because of central hypoventilation (76); the cognitive and psychiatric abnormalities that persist despite tumor treatment (73). Symptoms include obesity and hyperphagia, hypersomnia and/or reversal of sleep-wake cycles, abnormalities in thermoregulation, and central hypoventilation (76). In addition, two groups have reported a total of seven children with neural crest tumors, with personality and behavioral changes in all but one (75, 74). Mood or personality changes include lability of affect with episodic aggressive behavior, outbursts of euphoria and laughing, and impaired concentration. While treatment aimed at symptoms of typical hypothalamic syndrome is sometimes effective, prognosis is poor because of central hypoventilation (76); the cognitive and psychiatric abnormalities persist regardless of treatment (11, 75).

Hypothalamic Syndrome in Children With Neural Crest Tumors

Although even more rare than opsoclonus-myoclonus in the setting of neuroblastoma, idiopathic hypothalamic syndrome has been reported by a few groups in children with neural crest cell tumors, and this suggests a paraneoplastic etiology (75, 76). Symptoms include obesity and hyperphagia, hypersomnia and/or reversal of sleep-wake cycles, abnormalities in thermoregulation, and central hypoventilation (76). In addition, two groups have reported a total of seven children with neural crest tumors, with personality and behavioral changes in all but one (75, 76). Mood or personality changes include lability of affect with episodic aggressive behavior, outbursts of euphoria and laughing, and impaired concentration. While treatment aimed at symptoms of typical hypothalamic syndrome is sometimes effective, prognosis is poor because of central hypoventilation (76); the cognitive and psychiatric abnormalities persist regardless of treatment (11, 75).

Pancreatic Cancer and Alterations in Mood

The knowledge that changes of mood in patients with pancreatic cancer are more prevalent than in other gastrointestinal cancers dates back to the 1920s, with observations that depression, anxiety, and an impending sense of doom may often precede or accompany the diagnosis (77, 78). Since that time, numerous studies have demonstrated that depression often occurs before clinical diagnosis and that even in later stages of disease, mood disorders are more pronounced in patients with pancreatic cancer than in those with other abdominal tumors (79–81). Green and Austin (80) found that approximately 70% of pancreatic cancer patients experience depression, 50% have anxiety, and 30% have both symptoms. It is noteworthy that psychiatric symptoms preceded the initial physical complaint (and the cancer diagnosis) one-third of the time. Panic attacks or manic episodes have also been reported as behavioral predecessors to diagnosis (82, 83). While this body of research is intriguing, more work must be done to address whether the change in mood symptoms is caused by dysregulation of neuroendocrine signaling, as opposed to an autoimmune basis.

Conclusions and Future Directions

Paraneoplastic syndromes are a heterogeneous group of disorders affecting the peripheral or central nervous system with tremendous variability in clinical presentation. Those affecting the CNS often result in impaired neuropsychiatric functions and, to differing degrees, may involve consciousness, cognition, behavior, mood, and perception. The link between specific symptoms and individual autoantibodies accentuates that it is important for clinicians to recognize paraneoplastic disorders (Table 1, Figure 1). This fact is highlighted by the treatable nature of many of these syndromes and the role of early detection in improved outcomes of many cancers. In addition, recent work has demonstrated a generalized increased risk in cancer diagnosis in the first months following first-time admission to a psychiatric hospital (84). This review summarizes the current knowledge of psychiatric symptoms associated with paraneoplastic disorders and is intended to raise awareness that psychiatrists might have a significant role in the diagnostic process (Figure 1). Although psychiatric symptoms are often coupled with cognitive dysfunction, the literature is replete with cases of isolated psychiatric changes in patients later determined to have an underlying neoplasm and limbic encephalitis. Thus, these syndromes must be incorporated into the differential diagnosis of the psychiatrist who encounters a patient with unusual and complex behavioral changes (Figure 2).

Despite a much greater understanding of clinical symptoms and the course of paraneoplastic disorders today than even 10 years ago, the psychiatric characterizations of these syndromes remain relatively cursory. Future work should strive to offer a more rigorous and standardized examination of the behavioral disturbances. The possibility exists that particular combinations and temporal characteristics of psychiatric symptoms might herald oncoming severe neurological disturbances and guide the potential diagnosis. Although this idea has been recognized in the past (13, 14), psychiatry continues to play a small role in the characterization of these disorders.

Finally, although relatively rare, paraneoplastic disorders offer a means to further our understanding of general psychiatric illnesses. A neuroimmunologic basis for psychiatric disease has long been hypothesized (85), and paraneoplastic disorders provide specific examples of how autoantibodies can affect neuronal function. In addition,
many of these syndromes open a window onto how disturbance of specific neurotransmitter or intracellular signaling systems within particular neural circuits can affect behavior (7, 20, 45, 47). Researchers might aim to harness identified autoantibodies to explore how NMDA receptor signaling and trafficking, for example, relate to psychosis (7) or how proteins with known roles in neuronal development function in the mature brain (40, 41, 44–46). Recent work in the neurosciences demonstrates how targeted disruption of circuit function can dramatically improve understanding of complex behaviors (86, 87). Elucidation of why certain autoantibody syndromes affect only particular areas of the brain might provide yet another tool for studying the neurobiology of psychiatric disorders.

References

53. KAYSER, KOHLER, AND DALMAU