Chapter 13
Identifying and Managing Brain and Behavior Conditions

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Introduction

The central nervous system (CNS) controls cognition, affect, and behavior, and CNS disorders often present with psychiatric symptoms and have great psychosocial impact. Neuropsychiatry involves the comprehensive evaluation and management of children with complex neurobehavioral problems associated with a range of CNS disorders, including neurodegenerative diseases, developmental disorders, seizure disorders, stroke, brain tumors, and inflammatory and infectious CNS diseases, among others. This chapter will review several childhood CNS disorders and highlight the neuropsychiatric considerations in their presentation, assessment, and treatment.

Seizures

Vignette A

A 12-year-old girl presents to her pediatrician after her parents notice that, for the past 6 weeks, she has had unusual involuntary hand and body movements. At first, her right hand would occasionally clench a few times and then relax. Over the next few weeks, the muscles in her right arm would also jerk, and she would experience anxiety and fear before these movements. Her parents report that, after her arm movements, she would appear to "zone out" and not be herself for some time afterward.

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Table 13.1 Types of seizures

Generalized seizures: occurring throughout the cortex	Partial seizures: localized in one area of the brain
Tonic-clonic (grand mal): Sudden loss of consciousness, followed by a tonic phase with contraction of muscles and then a clonic phase with symmetric rhythmic contraction of the extremities	*Simple*: Consciousness is unaffected
Absence (petit mal): Brief alterations in consciousness with motionless staring	*Complex*: Consciousness is altered
Myoclonic: Brief and sudden muscle contractions	
Atonic (akinetic, "drop"): Sudden loss of muscle tone	

While in the office, her right hand and arm begin moving, and a few seconds later, her head and neck turn to the right. She then extends both arms, lets out a cry, and slumps down onto the floor. She then has symmetrical rhythmical movement of all her extremities for 30 s.

Epilepsy or seizure disorders are the most common childhood neurological disorder, affecting about 1% of children between birth and 17 years of age (Williams et al. 2016). Seizures are abnormal paroxysmal electrical discharges in the brain that result in changes in motor function, sensation, or consciousness and are further subclassified into various seizure types (Table 13.1)(Huffman et al. 2010).

The young girl in vignette A initially had simple partial seizures (hand movements without change in consciousness), which then progressed to complex partial seizures (arm movements with altered consciousness), which then progressed to a generalized seizure (tonic-clonic movements with loss of consciousness).

It can be challenging to differentiate neuropsychiatric phenomena that occur during (ictal), before or after (peri-ictal), or between (interictal) seizures from primary psychiatric symptoms. Broadly, seizure-related psychiatric symptoms often have abrupt onset and offset, occur with other stereotyped manifestations of seizures (i.e., automatisms), and are frequently short-lived (i.e., few minutes), with possibly altered consciousness, poor recall of the event, and almost always an abnormal electroencephalogram (EEG). When psychotic symptoms are present, they usually involve olfactory, gustatory, or tactile hallucinations. Primary psychiatric symptoms, in contrast, usually have a more gradual onset, absence of stereotyped movements, absence of altered consciousness or recall, and a normal EEG. When psychotic symptoms are present, they usually involve paranoia or auditory hallucinations (Huffman et al. 2010). Complex partial seizures, especially those with a temporal lobe focus, are commonly associated with neuropsychiatric phenomena including sensory, affective, perceptual, behavioral, or cognitive symptoms, such as the young girl's premonitory anxiety and fear. Complex partial seizures risk being missed as they often lack tonic-clonic activity, and the electroencephalogram (EEG) may even appear normal (Huffman et al. 2010).

Cortical insults, whether acute, as in concussion, infection, or bleeding, or chronic, as in intracranial tumors, poststroke cortical damage, or neurodegenerative

disease, can result in seizures. In the pediatric population, seizure disorders often co-occur with autism spectrum disorder, cerebral palsy, Down syndrome, intellectual disability (Jones et al. 2008), and syndromes involving cortical malformations, such as lissencephaly, Sturge-Weber syndrome, tuberous sclerosis, and focal cortical dysplasia (Wilfong 2016). Certain pediatric genetic and metabolic disorders are also associated with seizures and include the various epilepsy syndromes, such as Lennox-Gastaut syndrome, Landau-Kleffner syndrome, and juvenile myoclonic epilepsy (Wilfong 2016).

Psychiatric and behavioral comorbidities are estimated to affect 20–60% of children with chronic epilepsy and most commonly include attention-deficit/hyperactivity, depressive, and anxiety disorders and, less frequently, psychotic disorders (Jones et al. 2008). Behavioral issues include hyperactivity, inattention, and oppositional defiant and conduct problems and appear to be more prevalent in conditions with structural brain abnormalities (Jones et al. 2007). Psychiatric disorders are thought to develop from multiple factors, including the underlying neurobiological abnormalities preceding and consequent to the epilepsy, family and social stresses secondary to epilepsy, and medication-related effects (Jones et al. 2008).

Attention-deficit hyperactivity disorder (ADHD) is the most common comorbid psychiatric disorder, affecting an estimated 20–50% of children with epilepsy. Attention problems can be adversely influenced by epileptiform activity, irrespective of seizure type, cause, or severity; structural abnormalities; medication effects; and earlier age of seizure onset, which is associated with greater cognitive deficits (Williams et al. 2016; Jones et al. 2008). Medication management includes cautiously selecting appropriate antiepileptic drugs (AEDs), as some may worsen ADHD symptoms. For example, topiramate is associated with cognitive slowing and worsened concentration, while barbiturates are associated with inattention and hyperactivity (Jones et al. 2008). Because of the various risks involved with ADHD medications, ADHD treatment should maximize behavioral and parental interventions. ADHD treatment involving stimulant or alpha-adrenergic medication often raises concern for reducing seizure threshold, but the benefits of improved academic and behavioral performance may outweigh the minimal risk of increase in seizure frequency if families are adequately informed and patients are closely monitored (Williams et al. 2016). In children with comorbid epilepsy and ADHD, methylphenidate is largely effective, while amphetamines and atomoxetine are less effective. Alpha-adrenergic agents are less effective than stimulants but should be considered when stimulants are inefficacious or have intolerable side effects or when patients have comorbid emotional conditions. Other alternatives include tricyclic antidepressant and bupropion, but these medications present greater concerns about lowered seizure threshold and have not been studied with comorbid epilepsy in the pediatric population (Williams et al. 2016).

Vignette A Continued

The young girl is started on carbamazepine at 100 mg twice daily for treatment of the complex partial seizure disorder with secondary generalization. She responds well without further seizures. A few weeks later, she and her parents return to the pediatrician and report that she has been spending more time isolating herself in her room, is sad and tearful, has decreased energy and motivation, and recently revealed thoughts of wanting to die. Her pediatrician suspects that she is depressed, in part because of the recent diagnosis of a seizure disorder, and starts her on fluoxetine 10 mg daily. About 1 week after starting the fluoxetine, she presents to the hospital with nausea, vomiting, dizziness, and trouble with motor coordination. On testing, her serum carbamazepine level is found to be toxic.

Population-based studies suggest that depression and anxiety symptoms are more prevalent among children and adolescents with epilepsy than among the general population or among peers with other chronic medical conditions. Unfortunately, these symptoms are underdiagnosed and undertreated. Depressive symptom prevalence rates can range from 10% to 30%, and, while depressive symptoms often present as they do in the general population, they may also be temporally associated with seizures, which may often go unrecognized. Untreated depression in children and adolescents with epilepsy can have serious consequences, including psychosocial impairment and suicidality, which occurs at a higher rate than in the general population (Reilly et al. 2011). It is therefore important to carefully screen for and aggressively treat depression in youth with epilepsy. Temporal lobe foci, a negative attitude toward seizures, and a negative assessment of family relationships present a higher risk for depression, while seizure type does not. Study results are mixed as to whether frequency, severity, age of onset, degree of control, and family history of seizures are correlated (Reilly et al. 2011). AEDs, many with known behavioral side effects, can alter mood and anxiety when initiated as well as when discontinued, and multiple studies have found polytherapy to be associated with increased symptom severity (Reilly et al. 2011). Treatment of depression generally follows that of children who do not have epilepsy and emphasizes psychological therapies and pharmacological management if necessary. Psychotherapy can include group and individual cognitive behavioral therapy (CBT), interpersonal therapy, and family therapy (Reilly et al. 2011). Selective serotonin reuptake inhibitors (SSRIs) are first-line antidepressants as they have fewer adverse effects, are less likely to lower the seizure threshold, and have minimal overdose risk (Reilly et al. 2011). Tricyclic antidepressants and monoamine oxidase inhibitors are not recommended due to risk of lowering the seizure threshold, cardiac side effects, and risk in overdose. Bupropion immediate release (IR) is not recommended due to risk of lowering the seizure threshold and risk of seizure in overdose (Bujoreanu et al. 2011). It is important to monitor for interactions between AEDs and antidepressants. For example, SSRIs such as fluoxetine may inhibit certain CYP450 enzymes and raise AED levels, while some AEDs such as carbamazepine induce CYP450 enzymes and reduce the levels and efficacy of certain SSRIs (Jones et al. 2008). In our case, the young girl's

depressive symptoms and suicidality may represent a reaction to her chronic illness, an endogenous depression, or a side effect of her anticonvulsant, carbamazepine. In addition, fluoxetine inhibits certain CYP450 enzymes and thereby decreases metabolism of carbamazepine. The increased serum concentrations, in turn, produce toxic side effects. In our case, there may be a need to change the anticonvulsant regimen.

Anxiety symptoms are also common in children and adolescents with epilepsy. As with depression, it is helpful to identify symptoms temporally related to seizures. Some anxiety symptoms may arise from fear of having a seizure while away from parents and may resemble separation anxiety. It is also important to differentiate panic attacks from complex partial seizures. Management includes psychotherapy and medications such as SSRIs. AEDs should be carefully evaluated, as some have been associated with anxiety as a side effect, while others may induce anxiety upon discontinuation (Reilly et al. 2011).

Bipolar spectrum disorder is often a diagnostic challenge. This diagnosis excludes causation by another medical illness such as epilepsy and is difficult to differentiate from mood changes that may be seizure related. Medication management using AED monotherapy for epilepsy and bipolar disorder is appropriate (Bujoreanu et al. 2011).

Seizure-related psychotic symptoms are categorized based on their relationship to the seizure itself: ictal, postictal, or interictal psychosis. Postictal psychosis is the most common, may occur after a prolonged seizure or cluster of seizures, can last several days, and usually resolves spontaneously. Children experiencing seizure-related psychosis – unlike psychosis from primary psychotic disorders – generally cannot recall the content of the hallucinations (Jones et al. 2008; Bujoreanu et al. 2011). Medication management should include assessing AEDs for potential risk of precipitating psychotic symptoms and assessing antipsychotic medications for risk of interactions with AEDs and for risk of lowering seizure threshold. Clozapine and chlorpromazine are generally avoided due to greater risk – compared to other antipsychotics – of lowering seizure threshold. Clinicians should also carefully consider the longer-term metabolic risk of second-generation antipsychotics (Jones et al. 2008, Bujoreanu et al. 2011).

Stroke

Vignette B

A 9-year-old African-American boy presents to the emergency room 30 min after having a 2-min seizure that was witnessed by his parents, who found that he was subsequently unable to speak or move his right arm or leg. On exam, he is drooling from the right side of his mouth, and his right arm and leg are flaccid and immobile. He has hyperactive deep tendon reflexes and a positive Babinski sign on the right. His medical history is notable for sickle cell anemia. Two days ago, he was seen in

the emergency room because of a headache accompanied by right-sided facial weakness that was diagnosed as a complicated migraine after negative imaging and resolution of symptoms within an hour.

Pediatric stroke or cerebral vascular accidents (CVAs) are neurological injuries secondary to cerebral blood vessel occlusion or rupture that result in compromised function of brain areas and that are classified into ischemic and hemorrhagic subtypes. Ischemic strokes are secondary to arterial occlusion or, less commonly, occlusion of cerebral veins or sinuses, while hemorrhagic strokes are secondary to bleeding from cerebral artery rupture or to bleeding in an ischemic area. They are generally rare events. Ischemic and hemorrhagic CVAs have an incidence of 1.2–13 cases per 100,000 children below age 18 years (Tsze and Valente 2011). In western counties, arterial ischemic stroke (AIS) accounts for about half of all strokes in children (Tsze and Valente 2011) and is notable for a higher incidence – 1 per 4000 live births – during the perinatal and neonatal period (Jeong et al. 2015). Stroke is more common in boys than girls and in black children than children of other ethnicities, even after accounting for sickle cell disease as a risk factor (Tsze and Valente 2011).

Ischemic stroke usually presents as a focal neurological deficit, and the acute onset of any focal neurological deficit in children should be managed as a stroke until proven otherwise. Common focal manifestations include hemiplegia, occurring in up to 94% of cases, as well as diplopia, dysarthria, vertigo, and ataxia. Hemorrhagic strokes commonly present as headaches and altered level of consciousness and are more commonly associated with vomiting than ischemic strokes (Jeong et al. 2015). At the onset of the stroke, seizures of various types occur in up to 50% of children experiencing either type of stroke (Tsze and Valente 2011). Stroke presentation often varies based on age. Younger children demonstrate more non-specific symptoms, such as seizures, irritability, lethargy, sleep changes, poor feeding, vomiting, or sepsis-like features, and are less likely to have focal deficits, while older children, like adults, demonstrate more specific neurological deficits, such as hemiparesis and language and speech difficulties. Specific types of stroke can also present differently in each age group. Venous sinus thrombosis and subarachnoid hemorrhage in infants can present with bulging fontanelles while in older children can present with signs of increased intracranial pressure (ICP) and meningismus (Tsze and Valente 2011). In vignette B, the boy has several presenting symptoms that raise concern for a left-sided stroke: acute-onset neurological deficits (aphasia, right hemiparesis, and right lower facial weakness) and a seizure at the time of onset of neurological deficits. In addition, he has individual risk factors of male gender, African-American ethnicity, and sickle cell disease.

Retrospective studies suggest that more than a third of children with arterial strokes had preceding transient ischemic attacks (TIAs), which are brief episodes of neurovascular compromise with symptom resolution within 24 hours and which are often undiagnosed (Tsze and Valente 2011). Misdiagnosis of strokes is also frequent, given that many other diseases can mimic a stroke: complex migraines, which can cause focal, quickly resolving neurological symptoms; metabolic abnormalities, such as hypoglycemia; intracranial neoplasms; infections such as meningitis and herpes simplex encephalitis; and even somatic symptom disorders.

Partial seizures can result in transient postictal hemiparesis (Todd's paralysis), but if the duration of the deficit is greater than the duration of the seizure, stroke should be considered. Rarer mimics include alternating hemiplegia and metabolic disorders such as MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke) (Tsze and Valente 2011). In retrospect, the vignette B patient's previously diagnosed complex migraine (focal right-sided facial weakness, without neuroimaging abnormalities and with quick resolution) was likely a TIA. His second presentation clearly warranted another stroke investigation because of additional focal deficits and duration (30 min) greater than seizure length (2 min).

The International Pediatric Stroke Study (IPSS) and other stroke studies identify the following major etiologies: cardiac, hematologic, infectious, vascular, syndromic and metabolic, vasculitic, oncologic, traumatic, and drug-related (Jeong et al. 2015). A patient's risk factors can vary by geography, ethnicity, age at presentation, and availability of medical resources to survive other illnesses that can increase stroke risk. For example, hemoglobinopathies, including sickle cell disease, are a common cause of stroke in children of Mediterranean and African heritage; moyamoya disease (involving blocked arteries in the base of the brain and tiny artery tangles formed to compensate for the blockage) is a relatively more common cause of stroke in children of Japanese heritage; and coagulation disorders are a relatively more common cause of stroke in children of European heritage (Jeong et al. 2015; Lynch and Han 2005).

Management of pediatric stroke is based on small nonrandomized trials, case series, consensus or individual expert opinions, or adult stroke studies. Generally, children with stroke require immediate attention, stabilization through supportive care, and treatment of acute complications such as infection, seizures, increased ICP, and increased blood pressure. If possible, they should be transferred to an institution with pediatric neurovascular expertise (Lynch and Han 2005). Further treatment depends on the stroke type and etiology and can involve acute surgical and medical management such as surgical evacuation, shunt placement, embolization, thrombolytic agent administration, and short- and long-term anticoagulation.

Pediatric ischemic stroke leads to significant morbidity and mortality: 10–25% of children die from the stroke; up to 25% experience recurrence; and up to 66% experience persistent neurological deficits or sequelae, including motor problems, epilepsy, cognitive and learning disorders, or developmental problems (Tsze and Valente 2011). Poorer outcomes are associated with decreased consciousness and seizures during presentation, presence of an underlying causative disease, middle cerebral artery origin, and infarction volumes greater than 10% of intracranial volumes (Lynch and Han 2005).

Pediatric hemorrhagic stroke also leads to significant morbidity and mortality: 25% of children die from the stroke; about 30% experience seizures or cognitive or motor problems; and about 40% of children are neurologically normal (Lynch and Han 2005). Predictors of poorer outcomes and death include age less than 3 years, decreased consciousness on presentation, infratentorial location, and underlying blood disorder or vascular malformation. The highest risk of recurrent hemorrhagic stroke is within the first year and usually in children who do not receive intervention

for underlying vascular anomalies; hence, aggressive treatment involving embolization or surgical excision is usually pursued (Lynch and Han 2005).

Childhood stroke results in significant long-term cognitive, language, and psychiatric impairment, likely due to underlying neural network damage that impairs already developed skills and thwarts the development of emerging skills (Greenham et al. 2017). It is difficult, because of stroke heterogeneity, to identify risk factors associated with poor outcomes. Little association has been found between outcomes and age at stroke or lesion location. On the other hand, poststroke epilepsy and greater neurological deficits appear associated with poorer cognitive and psychosocial outcomes (Greenham et al. 2017; O'Keeffe et al. 2014). Arterial ischemic stroke has been associated with deficits in intelligence, memory, language, processing speed, and executive function, which involves attention, cognitive flexibility, and planning (Lynch and Han 2005; O'Keeffe et al. 2014). Children with ischemic stroke are reported to have poststroke psychiatric and behavioral issues, including ADHD, anxiety disorders, mood disorders, personality changes (Lynch and Han 2005), and externalizing behaviors such as aggression, hyperactivity, and emotional lability (Greenham et al. 2017). Hemorrhagic stroke has been associated with deficits in intelligence, memory, speech and language, learning, and behavior (Lynch and Han 2005). One element of interest is the debate around the role of neuronal plasticity in children with stroke. Some studies associate younger age with poorer functional outcome and more severe neurological disability, while others suggest some support for a theory of early brain plasticity, with better outcomes in children between age 1 and 6 years (O'Keeffe et al. 2014).

In both vignettes presented thus far, a combined neurology-psychiatry service could be very effective in following up the patients, in addressing long-term rehabilitative needs, and in supportively screening for and intervening upon any behavioral symptoms that may emerge – either from the previous neurological insult or from the neurological condition's psychosocial impact on the patient and the family. In the next several sections, we present other neurological conditions that are potentially associated with behavioral sequela and that may be optimally managed through a collaboration between neurology and consultation-liaison psychiatry.

Brain Tumors

CNS tumors are the second most common pediatric cancer, making up about 20% of all pediatric cancers and having a 5-year survival rate approaching 60–70% for primary malignant tumors (Shah et al. 2015). Treatment regimens are tailored to tumor histology and generally involve a combination of surgery, radiation, and chemotherapy. Children may experience both acute and chronic cognitive, psychiatric, and behavioral changes from the direct effects of tumors, from cell-destroying treatments given to a developing brain, from medication side effects such as corticosteroids, and from other posttreatment complications such as endocrine disorders, secondary malignancies, strokes, seizures, moyamoya disease, and motor

dysfunction. Factors affecting cognitive and psychiatric outcomes include tumor type, location, size, and presence of metastases; patient age, sex, prior neurodevelopmental state, and psychological adjustment; family socioeconomic status, values, and adjustment; and various aspects of treatment including involvement of intracranial surgery, chemotherapy, and cranial radiation of a certain field and at a certain dose (Turner et al. 2009). Studies of long-term psychiatric sequelae in children are limited, but studies of adult survivors of pediatric brain cancer suggest that rates of depression, anxiety, suicidal ideation, psychotic disorders, and other behavioral problems are higher in the survivor population than the normal adult population. Female sex, astrocytomas, and glial tumors are associated with psychiatric side effects of treatment; craniospinal radiotherapy is associated with depression, anxiety, and schizophrenia; surgical treatment is associated with suicidality; and cerebellar vermis damage is associated with behavioral abnormalities (Shah et al. 2015).

Posterior fossa tumors, which include astrocytomas, medulloblastomas, and ependymomas, account for up to 60% of all pediatric brain tumors and often present with symptoms of hydrocephalus and raised ICP. These symptoms may include nausea, vomiting, lethargy, and irritability. Tumor-related damage to the cerebellum and other brain structures, hydrocephalus, damage related to treatment (resection, chemotherapy, or radiotherapy), endocrine complications, or tumor recurrence (Lassaletta et al. 2015) may impact cognitive and neuropsychiatric outcomes. Cerebellar damage is linked to decreased intellectual function; impairment in executive function, spatial cognition, attention, and working memory; personality changes; linguistic difficulties; and behavioral disturbances ranging from irritability to autism-like behaviors. Posterior fossa syndrome (cerebellar mutism syndrome) can occur 1–2 days after resection in up to one third of children following damage to the cerebellum and involves reduced or entirely absent speech, dysarthria, emotional lability, personality/behavioral change, disinhibition or inappropriate behavior, and apathy. While symptoms tend to improve with time, up to two thirds of these patients might have speech and language dysfunction 1 year later (Lassaletta et al. 2015).

Craniopharyngiomas are rare, benign, slow-growing tumors that are typically located in the sellar and/or suprasellar region and have high survival rates greater than 90%. The tumor frequently invades critical neurovascular structures such as the frontal lobes, cranial nerves, hypothalamus, and pituitary and often results in vision loss, panhypopituitarism, and diabetes insipidus. Given the location, complete resection is often infeasible; therefore, treatment usually involves adjunctive radiation therapy, which is associated with a high risk of tumor recurrence. Factors thought to negatively impact outcome include degree of hypothalamic involvement; hormonal manifestations, including diabetes insipidus and low growth hormone; hydrocephalus; younger age at onset; time since treatment; tumor size; retrochiasmatic location; recurrence; repeated surgeries; and frontal lobe dysfunction from surgical and radiation treatments. Intelligence, attention, and verbal memory are relatively preserved, but there are often deficits in executive function and spatial working memory and notable social-behavioral difficulties, including depression, anxiety, emotional dysregulation, impulsivity, and aggressiveness. Social functioning

is often greatly impacted; difficulties may include social isolation and self-perceived unattractive appearance as a result of hormonal disorders (Zada et al. 2013).

Radiotherapy is often an integral part of treatment of brain tumors, especially when the tumor location or type limits efficacy of resection or chemotherapy, but it has both acute and chronic cognitive and behavioral effects. Cranial radiation in children is associated with declines in intelligence, memory, attention, and cognitive processing; behavioral and language disturbances; and hypothalamic-pituitary deficiency. Contributing factors are thought to be radiation-induced focal necrosis and white matter changes (demyelination and reactive gliosis), and, consequently, greater injury is seen with higher radiation doses, larger radiation field, increased time from radiotherapy, and younger age at treatment. Radiation necrosis of cerebral arteries can result in small cerebral strokes, which can result in further cognitive impact and other neuropsychiatric sequelae seen in strokes (Lassaletta et al. 2015; Nejad et al. 2010).

Chemotherapy can also contribute to neurocognitive decline, although it appears to be less severe than that secondary to radiation therapy and may involve specific areas in attention, visual processing, and visual-motor functioning. Some chemotherapy agents are known to be neurotoxic. Methotrexate can result in a short-term delirium as well as white matter injury and associated cognitive impairments (Roddy and Mueller 2016; Kaufman 2007).

Other medications that are used in pediatric cancer treatment and that are associated with mental status changes include AEDs; antiemetics, which may precipitate dystonia and Parkinsonian side effects through dopamine blockade; and antihistamines, opioids, benzodiazepines, and sedative-hypnotics, which are frequently used for pain, pruritus, anxiety, and insomnia but which can result in delirium. Corticosteroids are also well-known to induce insomnia, irritability, mood lability, and psychosis. Psychosis is usually managed symptomatically with antipsychotics (Nejad et al. 2010).

In a cohort of survivors of childhood brain tumor or acute lymphocytic leukemia (ALL), methylphenidate has been used to improve attention/concentration, social functioning, and academic performance (Lassaletta et al. 2015). A small pilot study utilizing donepezil in survivors of childhood brain tumors found improvement in memory and executive function (Roddy and Mueller 2016).

Hydrocephalus

Pediatric hydrocephalus is one of the most common birth defects and involves excessive cerebrospinal fluid that leads to ventricular enlargement, displacement of adjacent brain structures, and increased ICP (Lacy et al. 2012). The most common etiologies are myelomeningocele and associated Chiari malformation, aqueductal stenosis, intraventricular hemorrhage, and Dandy-Walker syndrome. Hydrocephalus may also be a complication of meningitis, traumatic brain injury, tumors, and

infectious diseases (Martini 2010). Management is primarily through surgical shunting procedures to relieve elevated ICP (Lacy et al. 2012).

Hydrocephalus within the first year of life exerts pressure and alters blood flow in the cortex and other brain structures, impacts neuronal development across gray and white matter regions and developing circuits, and ultimately impacts the development of cognitive processes (Lacy et al. 2008). Children with hydrocephalus show deficits in verbal and nonverbal intellectual functioning (Lacy et al. 2008) and in executive functioning, including planning, working memory, and attention (Lacy et al. 2012). They also have a higher prevalence of behavioral and emotional challenges, including difficulties with self-regulation and emotional control (Lacy et al. 2012), anxiety, and somatic symptoms such as headache and stomachache (Lindquist et al. 2006).

Hydrocephalus with concurrent learning disabilities appears to strongly increase the risk of behavioral difficulties, disruptive behavior, and anxiety. Comorbid cerebral palsy and epilepsy further increase the risk of behavioral issues. Notably, the prevalence of autism among children with hydrocephalus is much higher than in the normal population. Furthermore, the prevalence of autism is up to five times higher in children with comorbid epilepsy or cerebral palsy compared to children with only hydrocephalus. (Lindquist et al. 2006). Shunt failure may present with signs of ICP. The signs may include headache, vomiting, lethargy, and papilledema or vague signs such as behavior change and decreased school performance (Martini 2010).

Spina Bifida

Spina bifida is a congenital neural tube defect and includes three main types:

1. Spina bifida occulta, in which some vertebrae are not completely closed, but the spinal cord and meninges are maintained without any neurological compromise.
2. Meningocele, in which the meninges herniate between incomplete vertebrae, but the spinal cord and, hence, neurological function is generally not affected.
3. Spina bifida myelomeningocele (SBM), the most severe form, in which the meninges, spinal cord, and nerve roots protrude through the spine and in which there is altered spinal function and brain development.

Common cerebral changes in SBM include cortical malformations of the posterior cortex and white matter, midbrain, cerebellum, and corpus callosum and hydrocephalus (Vinck et al. 2009). Spinal lesions, depending on location, may result in differing levels of motor functioning, ranging from ambulating with assistance to needing a wheelchair, and may also affect urological functioning (Martini 2010).

Cognitive abilities in children with SBM can range from normal to more severe impairment. In children with SBM and hydrocephalus, intellectual functioning is generally in the average to low average range, and there are often deficits in visual perception, motor skills, and memory. Also, despite often good verbal skills, there

may be more subtle difficulties with verbal memory, speech fluency and articulation, executive functioning, and attention (Vinck et al. 2009).

Systemic Lupus Erythematosus

Vignette C

A 12-year-old girl of Asian Indian heritage is brought by her parents to her pediatrician because of mood and behavioral changes. For the past 3 months, parents have noted increased anxiety and depression, which they attributed to their daughter struggling to keep up with classwork. In the past month, her mood and behavior have worsened, with irritability, unprovoked anger outbursts, and physical aggressiveness. Yesterday, she reported being afraid of a threatening black figure in her room despite knowing that there was nothing present. Her pediatrician elicits that she has also experienced headache, increased fatigue, muscle aches/pains, joint stiffness, and decreased appetite. On exam, the pediatrician notes a light purplish rash across the bridge of her nose, swollen joints, and newly diagnosed hypertension.

The patient is admitted to the local hospital. Brain MRI shows multiple lesions in both cerebral hemispheres, and immunological testing shows positive antinuclear antibody and anti-double-stranded DNA (anti-ds DNA) antibodies.

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that affects multiple organ systems and that has varied symptom presentations and degrees of severity, ranging from rash and joint pain to life-threatening organ failure. Prevalence is about 3–8 per 100,000 children (Benseler and Silverman 2007). There is a higher prevalence in females and in Hispanic, African, North American First Nation, and Southeast and South Asian populations (Soybilgic 2015). The average age of onset is 13 years. The etiology is unknown but thought to be multifactorial with genetic, hormonal, and environmental components (Soybilgic 2015). Childhood-onset SLE, in comparison to adult-onset SLE, demonstrates greater disease activity at presentation and over time (Kohut et al. 2013).

Neuropsychiatric SLE (NPSLE) manifestations are classified by the American College of Rheumatology into 19 separate clinical syndromes (Table 13.2), covering CNS and peripheral nervous system manifestations as well as neurological and psychiatric symptoms. In the pediatric SLE population, prevalence of NPSLE symptoms is estimated at 22–95% (Ferraria et al. 2013), with about 70% of children having one or more symptoms within 1 year of SLE onset (Benseler and Silverman 2007). The etiology likely involves autoantibody-mediated CNS damage involving inflammation and neuronal cell death (Levy et al. 2009). It appears to be more aggressive and early-onset in children compared to in adults and results in higher rates of organ damage (Ferraria et al. 2013).

NPSLE should be considered in the differential diagnosis for new-onset severe neurologic or psychiatric disease in a child or adolescent (Soybilgic 2015).

Table 13.2 Neuropsychiatric lupus syndromes

Central nervous system
Headaches
Seizure disorders
Cerebrovascular disease
Demylinating syndrome
Myelopathy
Movement disorder
Aseptic meningitis
Cognitive dysfunction
Acute confusional state
Mood disorder
Anxiety disorder
Psychosis
Peripheral nervous system
Mononeuropathy, single/multiplex
Polyneuropathy
Cranial neuropathy
Acute inflammatory demyelinating polyneuropathy
Plexopathy
Mysasthenia gravis

Adapted from The American College of Rheumatology

Depression and anxiety (which were the presenting symptoms in vignette C) may result from direct CNS effects of the disease, from the impact of another NPSLE symptom (i.e., neurocognitive impairment and poor academic performance), from effects on other systems (i.e., pulmonary hypertension and fatigue), from complications of treatment (i.e., corticosteroids and mood effects), or from stress from having a chronic illness with various clinical sequelae (i.e., facial skin rashes, weight gain from steroid treatment, etc.) (Kohut et al. 2013).

NPSLE psychiatric manifestations include mood disorders, anxiety disorders, acute confusional states, psychosis, and potentially neurocognitive dysfunction (Benseler and Silverman 2007). In Sibbitt el al.'s study (2002), the most common pediatric neuropsychiatric manifestations were mood disorders (57%), cognitive dysfunction (55%), acute confusional states (35%), and psychosis (12%). Neurocognitive impairment can occur without other SLE disease symptoms or other NPSLE manifestations; is seen in nearly 50–65% of the pediatric SLE population; and involves difficulties in complex problem-solving, working and verbal memory, processing speed, attention, visuospatial learning, and visuomotor integration (Levy et al. 2009).

Depression impacts approximately 15–55% of the pediatric SLE population (Knight et al. 2014). Unlike adult SLE, pediatric SLE does not appear to be a significant risk factor for primary depression. Because physical symptoms of

depression, such as fatigue, sleep disturbances, and poor appetite, often overlap with SLE symptoms, it is helpful for the clinician evaluating a child with SLE for possible depression to screen carefully for affective mood symptoms, such as negative mood and poor self-esteem. Notably, among pediatric patients with SLE, up to 34% report suicidal ideation (Knight et al. 2014), and 15–20% experience anxiety. Among patients with pediatric NPSLE, 12–40% have psychotic symptoms, which classically involve visual hallucinations and sometimes auditory or tactile hallucinations. Unlike in primary psychotic disorders, insight is usually preserved (Benseler and Silverman 2007). Mania and bipolar disorder are relatively uncommon in pediatric SLE (Benseler and Silverman 2007).

Treatment of pediatric SLE varies depending on the nature of the underlying process (i.e., inflammatory or thrombotic) and is focused on minimizing organ damage, reducing the duration and severity of flares, and symptomatically managing sequelae. NPSLE management lacks specific protocols, but for significant CNS disease, immunosuppressive therapy usually involves corticosteroids alone or in combination with other agents such as azathioprine, mycophenolate mofetil, or cyclophosphamide. In refractory or life-threatening cases, plasma exchange, intravenous immunoglobulin, and rituximab have been used (Soybilgic 2015). Treatment for affective and psychotic manifestations includes antidepressants and antipsychotics (Soybilgic 2015). For children, psychological support and educational interventions to maximize function are also helpful (Levy et al. 2009). Overall, greater than 90% of patients survive, and 80–95% enter remission (Soybilgic 2015). However, pediatric NPSLE patients who manifested seizures or cerebrovascular disease or who had severe disease activity are at risk for long-term sequelae, including persistent seizures or persistent cognitive impairment (Benseler and Silverman 2007; Soybilgic 2015).

Encephalitis and Meningitis

Meningitis, an inflammation of the meninges, and encephalitis, an inflammation of the brain parenchyma, can result in both acute and chronic neuropsychiatric symptoms. The most common causes of meningitis and encephalitis are bacterial, viral, fungal, or parasitic infections and noninfectious etiologies such as autoimmune diseases, malignancies, and medication side effects (Parmar and Ibrahim 2012). Acute presentations can include delirium, psychosis, mania, depression, anxiety, agitation, catatonia, or other behavioral changes (Nejad et al. 2010). Long-term cognitive and behavioral changes can vary depending on the cause, severity, length of illness, and success of treatment.

Congenital infections can have long-term brain effects depending on fetal age at the time of infection. Insults in the first or second trimesters often result in CNS malformations such as microcephaly, while later infections often result in destructive lesions such as aqueductal stenosis, hydrocephalus, calcifications, demyelination, and atrophy (Parmar and Ibrahim 2012).

Bacterial meningitis is a serious and often fatal infection in many parts of the world despite antibiotic treatment and relative availability of preventative vaccines. The risk of mortality or developing neurocognitive and behavioral complications is related to age, causative pathogen, severity of illness at time of presentation, and time of initiation of antibiotic therapy. About half of long-term survivors experience some sequelae, which include cognitive delay with low IQ and intellectual disability, learning disabilities, speech and language deficits, hearing and vision loss, emotional and behavioral including ADHD-like symptoms, motor delay/impairment, and seizures (Chandran et al. 2011; Ramakrishnan et al. 2009). Tuberculosis meningitis often presents with delirium (Nejad et al. 2010), and its complications include hydrocephalus and seizures. Prognosis is related to early diagnosis and treatment, and long-term deficits include visual and hearing loss and cognitive impairment (Wood 2012). Treatment relies on antibiotics and potentially corticosteroids for patients with cerebral edema or high levels of bacteria in the CSF (Nejad et al. 2010).

Syphilis is a common infection worldwide, and its infection of the central nervous system, termed neurosyphilis, can occur early or late in the disease and includes syphilitic meningitis and parenchymatous neurosyphilis (tabes dorsalis (also known as demyelination of the dorsal columns of the spinal cord) and general paresis). Neurosyphilis is well-known to mimic many other neuropsychiatric disorders and can present with symptoms of dementia, delirium, psychosis, hallucinations (usually auditory), depression, mania, anxiety, paranoia, delusions (usually persecutory), bizarre or violent behavior, or personality changes. Cognitive changes include poor concentration and memory, executive dysfunction, irritability, and loss of higher cortical functions (Beauchemin and Laforce 2014). Congenital syphilis, acquired in utero or at the time of delivery, is a major cause of stillbirth and newborn mortality. It can result in acute syphilitic meningitis, which presents similarly to bacterial meningitis and which can involve increased intracranial pressure. Congenital syphilis can also result in chronic meningovascular syphilis, which presents with progressive hydrocephalus, neurodevelopmental regression, and seizures. If untreated, neurosyphilis can develop into syphilitic endarteritis, which can lead to cerebral infarction, significant developmental delay, and pituitary involvement (Triemstra et al. 2017).

Viral meningitis rarely involves the brain parenchyma, and when signs of brain dysfunction such as seizures are present, it is usually indicative of encephalitis. Treatment is largely supportive, and while most children make a complete recovery, early life viral meningitis may increase the risk of longer-term cognitive effects and seizure disorders, hydrocephalus, learning disabilities, lower intelligence, and behavior disorders (Norris et al. 1999).

The human immunodeficiency virus (HIV) can impact children and adolescents' neurological, cognitive, and psychiatric functioning in various ways, depending on means and timing of acquisition of the infection, primary CNS effects of the HIV infection, presence of opportunistic infections, and medication side effects (Nejad et al. 2010). HIV infects CNS microglia and macrophages and triggers immune-mediated and inflammatory changes that cause neuronal cell damage and death. In the pediatric population, the late effects of neuronal cell damage result in two types

of HIV encephalopathy: a progressive encephalopathy with acquired microcephaly, loss of previously acquired skills, and corticospinal tract abnormalities and a static encephalopathy with cognitive and motor delays, but without a loss of acquired skills or neurological deficits (Benton 2011). Use of highly active antiretroviral therapy (HAART) has been found to reduce the incidence of progressive encephalopathy (Benton 2011). Cognitive changes in HIV-infected children include deficits in general intellectual functioning, executive functioning, processing speed, working memory, planning/reasoning, attention, visual-spatial ability, and visual memory (Phillips et al. 2016). Compared to non-infected peers, HIV-infected youth evidence higher rates of depression, anxiety, ADHD, behavioral issues, and substance abuse (Benton 2011). Through viral load suppression during infancy or early childhood, combination antiretroviral therapy has resulted in a dramatic decrease in incidence of severe neurocognitive impairment (Crowell et al. 2015).

HIV meningitis presents with fever, headache, acute confusional state, meningeal irritation, and cranial nerve palsies; often occurs at time of seroconversion; and improves with supportive care. CNS opportunistic infections can result in complications of meningitis, encephalitis, and abscesses (Nejad et al. 2010). With progression of HIV to acquired immunodeficiency syndrome (AIDS), children are at risk for progressive multifocal leukoencephalopathy from acquisition or reactivation of the JC polyomavirus. This condition, which is managed with HAART, involves CNS demyelination, which results in hemiparesis, ataxia, and dysarthria (Schwenk et al. 2014).

The autoimmune encephalitides are a new field of active investigation, as these autoimmune disorders often present with neurological and psychiatric manifestations. One of the best studied types is anti-N-methyl-D-aspartate (anti-NMDA) receptor encephalitis, an autoimmune disorder in which antibodies attack the NMDA glutamate receptor and cause a distinct course of illness marked by an initial period of about 1 week with viral illness-like prodrome with lethargy, headache, myalgia, and fever, followed by a 1–3-week period of behavioral changes including delusions, hallucinations, disorganized thoughts and behaviors, anxiety, agitation, paranoia, mood lability and bizarre behaviors, and personality change. Children and adolescents often present with mania-like symptoms, including irritability, behavioral outbursts, sleep dysfunction, hyperactivity, and hypersexuality. Children and adolescents may also experience cognitive changes, including short-term memory deficits, confusion, altered speech (i.e., echolalia, perseveration, mutism), and subsequently neurological involvement with abnormal movements (i.e., orofacial dyskinesias, dystonia, and chorea), autonomic instability, and seizures, which may also occur during earlier stages. This condition, although most commonly affecting young adult women, can affect males and females of all ages ranging from infancy to old age. Diagnosis requires a positive serum or cerebrospinal fluid (CSF) antibody titer, but the diagnosis is often made based on clinical symptoms, abnormal CSF studies (showing pleocytosis or oliogoclonal bands), and EEG (usually abnormal, showing slow, disorganized delta/theta activity, and sometimes seizures). Imaging can be variable and sometimes show mild enhancement. Treatment is becoming increasingly standardized with a focus on immune therapy, including "first-line" treatments of corticosteroids and intravenous immunoglobulin, "second-line" treatments of rituximab and cyclophosphamide, treatment of any underlying

identified tumor, and significant supportive care. During the illness, psychiatric symptoms and agitation are often managed with AEDs, anticholinergics, benzodiazepines, and antipsychotics, including sedating antipsychotics, given that patients appear to be sensitive to dopamine antagonism and at high risk for extrapyramidal symptoms with high-potency antipsychotics (Kayser and Dalmau 2011). Cognitive and psychiatric symptoms are slowest to improve, and current follow-up studies suggest that longer-lasting cognitive deficits in memory and executive dysfunction may occur in almost 90% of patients (Moura et al. 2016).

Conclusion

Children and adolescents with neurological disorders are an especially vulnerable population. For all the conditions described in this chapter, an astute and informed psychiatrist can play essential roles in the healthcare team, during the acute inpatient and outpatient follow-up phases. In either of these contexts, a team-integrated pediatric consultation-liaison psychiatrist can assist with recognizing and diagnosing psychiatric manifestations; managing the emotional and behavioral effects of the illness and its treatment; and managing the long-term cognitive, psychiatric, and behavioral impacts on the developing brain.

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