Pediatric Neuropsychiatry

A Case-Based Approach

Aaron J. Hauptman
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Dedicated to Bruce Hauptman, MD and Jack Pellock, MD who would have enjoyed a book like this

Editors' Note

Thank you for selecting this book. Our intent is to provide a rich intellectual journey through the complex and fascinating world of pediatric neuropsychiatry. The cases that make up this text were chosen in order to instruct and enliven. The authors themselves grapple with facets of diagnosis, treatment, interpretation, and meaning. As is the case in the field generally, the cases presented here are not always tidy, and the outcomes are not uniformly positive or, in some instances, even determined. Always, the authors engage with the significance of neural correlates for behavior, emotion, cognition, and consciousness. Parts of the discourse may seem novel, and some may feel to be well-trodden terrain. Some may represent diagnostic assessment and treatment decisions that feel comfortable. Others may be cutting-edge or address old topics in new ways; and some address considerations with which readers may not always agree. We welcome that inquiry and are content to prioritize probing questions rather than unblemished answers. Through that process, we consider that true medical knowledge may be advanced. This book has been a wonderful experience to write and to edit; we thank you for joining us.

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Introduction

"Wherever the art of medicine is loved, there is a love of humanity."

-Hippocrates

How many times have we each approached colleagues saying, "I saw a really interesting patient today," or "I have never seen anything quite like this…" This is a standard practice for clinicians, as we all reach out to our professional community for explanation, teaching, guidance or the shared sense of fascination about the experiences of the individuals we treat. As neurologists, psychiatrists, and ultimately, as neuropsychiatrists, we take care of individuals whose complicated conditions challenge us to think deeply about how neuroscience, development, and environment connect the mental and physical functions of the brain. Much of the time, our patients bring unique insights into mind-body connectivity that are on the cutting edge of today's clinical knowledge. As such, evidence or even precedent for management of these illnesses is not common in the medical literature. To work in neuropsychiatry is to live at the deeply fascinating, but often uncomfortable, gray line between the mental and the physical, at the forefront of the exploration of consciousness.

Classically, a case conference has always been the way that physicians do medicine. We see patients with complicated conditions and then discuss clinical experiences at national meetings, local grand rounds, or within our departments with colleagues in order to facilitate our own understanding and that of the community. The insights afforded to clinicians in these settings are valuable; each practitioner can apply a unique perspective to challenging cases, and, in the world of neuropsychiatry, most cases are challenging.

In modern times, the opportunities to meet and discuss cases have been significantly constricted given the increased pressure to see as many patients as possible and "manage" versus to think deeply and carefully about larger neuroscientific theories. Movements to routinize care also work against the field, often streamlining procedures in ways that undercut the exploration that is at the heart of neuropsychiatric medicine. Despite financial pressures in the modern era, most researchers and clinicians acknowledge that the intellectual appeal of a neuropsychiatric mode of thinking has never been greater. The contrast today between the growth of factual knowledge available about the brain and the contraction in allotted time to avail oneself of that knowledge represents a conundrum that is unresolved.

Now, nearly two decades after the end of the "Decade of the Brain" in the 1990s, exploration into brain anatomy and function has soared. We think about networks and coordinated systems not only fixed anatomical brain structures and the roles of individual neurotransmitters. The knowledge of concussions and degenerative conditions has changed how we think about brain injury and cognitive processing. We have an increased understanding of the fragility of brain parenchyma as well as new appreciation for its tremendous capacity for recovery. We have windows into the vast connectivity of the brain with imaging of white matter tracts in diffusion tensor imaging and electrical dipoles as shown by magnetic encephalograms.

Adult neuropsychiatry is now a well-established field with numerous practitioners and reasonable representation in the medical literature. There are increasingly formalized ways to train practitioners for a career in adult neuropsychiatry including residencies, fellowships, national and international conferences, and medical board examinations. While this is a superb development for the field, clinicians who work with children routinely note how the analogous knowledge base and integrated approach in the pediatric world is much less established. Neuroscience education and clinical emphasis on neurologic comorbidities typically are not prominent components in pediatric and child/adolescent psychiatry training programs.

This is an unfortunate development because studying a pediatric population has inherent advantages when it comes to neuropsychiatry. Young brains are designed for growth, recovery, and resilience. Significant vulnerability exists of course, but repair is possible well beyond what may occur later in the life span. In pediatrics, every case of neuropsychiatric illness is contextualized by brain development. Whereas in adult neuropsychiatry, the insult to the brain is framed by mature substrate, in children, not only is function in the moment affected but the ongoing process of development is jarred from its trajectory as well. As such, we can readily gain insights into brain development by monitoring how symptoms change over time and how treatment may influence that change.

Our aim with this text is to highlight the developing brain with a diverse cohort of children and adolescents with neuropsychiatric illnesses. We include some conditions that are common, bread-and-butter child psychiatry and neurological cases, such as ADHD, epilepsy, and Tourette's syndrome. But we have gone out of our way also to include cases that may be a little bit messy and that frame the expected condition in the context of life stress, comorbid developmental disorders, and other neurologic illness. We tried to organize the cases around similar themes but fully recognize that content overlaps between sections. We also intermix cases of conversion disorder, such as psychogenic non-epileptic events, within the sections on the associated conditions. In pediatrics, conversion symptoms may be subtly nested within the context of comorbid neurological disorders and developmentally tinged emotional stressors. As such, we did not want to isolate conversion from related neurologic symptoms even if the etiologies were varied.

Additionally, we want this text to help fill the knowledge gap that currently exists between adult and pediatric neuropsychiatry. We aspire to provide a sense of how to think through aspects of brain dysfunction by means of the oldest tradition in medicine: case-based learning. By highlighting patients' stories, we hope to provide a

broad "case conference" that will generate thought and insight to assist other clinicians facing the daunting and energizing task of deciphering neuropsychiatric illness in children and adolescents. Although the paradigmatic approach utilized in adult neuropsychiatry does not yet have an equivalent in the pediatric realm, there is tremendous interest in its advance, and we hope this type of casebook will contribute toward that goal.

Above all, we want to capture intrigue and express the delight in working as neuropsychiatrists with this age group. Children and adolescents with neuropsychiatric illness are very common yet often struggle in finding professionals adept in diagnosis, treatment, and overall support. We continue to be humbled by this complex field and endeavor to make progress in learning how best to be available for our patients as clinical neuroscientists.

Ultimately, this book is about those patients, telling their stories and, in doing so, teaching us new remarkable insights into brain and behavior relationships. Where possible, our patients and their families have provided personal reflections of their experiences. Their voices, expressing their struggles and successes, are profound reminders of the person-centered nature of this work. We are privileged to have this opportunity and to work alongside our patients in bearing witness into the limitless inner workings of the brain.

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Part I

The Frontal Lobes and Coordination of Movement and Thought

Introduction

The brain is wider than the sky,
For, put them side by side,
The one the other will include,
With ease, and you beside.
Emily Dickinson, 1924

This section focuses on prefrontal cortical (PFC) circuits and their diverse structural and functional connections throughout the brain. Discussion of the frontal lobes, responsible for attention, working memory, executive function, and so much of what defines human emotional and neurocognitive function, quickly gives way to an exploration of subcortical structures such as basal ganglia and limbic regions. The prefrontal cortex doesn't do its work alone, and the section emphasizes the large-scale, circuit-based nature of so many of the functions thought of as "belonging" to the PFC.

These cases focus on frontal-parietal connections in executive function, frontal-striatal-thalamocortical loops in movement, mood and salience detection, and the increasingly appreciated functions of the cerebellum's interaction with other brain regions in cognition and thought processing. Concepts will be introduced crucial to understanding regions of the brain that will come up again and again in subsequent chapters, whether in the discussion of developmental disorders, white-matter connectivity in pediatric multiple sclerosis, the neuropsychiatric aspects of neuroimmunological conditions, epilepsy, or altered mental status.

The first chapter in this section follows three patients with ADHD for decades; their diverse developmental trajectories bring a longitudinal, outcome-driven perspective on a condition often thought of exclusively in its pediatric context. This also provides a broad overview of PFC circuitry and connectivity that scaffolds subsequent discussion of frontal-subcortical and frontal-cerebellar connections. Next is an exploration of traumatic brain injury (TBI) and its potentially devastating effects on mood, personality, and a wide range of emotional and neurocognitive

functions. The chapter also places an emphasis on modes of recovery and approaches for management and shows a pathway toward success in the face of ongoing challenges. A review of tics and Tourette syndrome moves into an exploration of the deeper structures of the telencephalon in the management of a particularly complex case. This entry into frontal-subcortical machinery shifts solidly into a discussion of subcortical structures explored through a case of substance-induced hypoxia in which parkinsonism in an adolescent was confused for a mood disorder. The section then moves on to the cerebellum. This brain area, once viewed as being almost exclusively involved in smoothing of movement, is increasingly seen as playing a significant role in emotional and thought processing and is implicated in a broad range of neurological and psychiatric conditions ranging from autism to schizophrenia to affective disorders. The final case addresses the common question of adolescent concussion with psychiatric sequelae, addressing the overarching concern of long term sequelae following multiple episodes of mild traumatic brain injury.

The Spectrum of Neurobehavioral Outcomes in Attention-Deficit/Hyperactivity Disorder

1

Shereen E. Elmaghrabi and Francisco Xavier Castellanos

Cases

The following cases illustrate three trajectories of individuals who would have been diagnosed with attention-deficit/hyperactivity disorder (ADHD) in childhood, had the contemporary diagnosis existed when they were first evaluated. These cases (with details modified to protect confidentiality) were obtained from a prospective, 33-year longitudinal study conducted by Klein et al. investigating the long-term outcomes of childhood hyperactivity [1]. Probands were predominately middle and lower-middle socioeconomic status males aged 6–12 upon entering the study between 1970 and 1978. They were recruited from a psychiatric research clinic in Queens, NY, to which they had been referred for behavioral issues by their respective schools. Follow-up assessments were conducted at mean participant ages of 18, 25, and 41 years.

Case One: Charlie

Charlie was born full-term at 9 lbs 10 oz. From a young age, he experienced difficulties at school and home. By the second grade, he was in danger of failing several subjects despite receiving individualized instruction. His second grade teacher

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noted he consistently made careless mistakes and was fidgety, easily distracted, and poorly organized. At home, Charlie's parents reported generally good behavior and no significant issues with his three siblings. However, he frequently forgot verbal instructions and lost possessions that he used on a daily basis. Charlie despised homework, and getting him to complete it was a daily struggle. Charlie had several friends at school and particularly enjoyed reading comic books, which his parents reported he was able to do without difficulty. He was diagnosed with hyperkinetic reaction of childhood (as the diagnosis was known in the second edition of the *Diagnostic and Statistical Manual of Mental Disorders*), separation anxiety, and depressive reaction at his childhood research evaluation.

As Charlie grew older, teachers commented less on his inability to sit still, but he continued to struggle academically. He eventually dropped out midway through high school. A few years after, he received his GED and found consistent work in construction. Some of Charlie's difficulties in school stemmed from his use of multiple drugs. He first drank alcohol at age 13 and was drinking heavily by age 19. He began to habitually smoke cigarettes and marijuana at ages 11 and 15, respectively. In his 20s, he received a hydrocodone bitartrate and acetaminophen prescription for an accident at work. Charlie began abusing the drug and developed an opiate dependence that lasted 6 years.

At age 27, Charlie married his girlfriend of 3 years and they had two children. After the birth of his first child, he stopped smoking marijuana. However, his problems with alcohol continued and were a significant cause of marital strife. He entered an intensive addiction treatment program at age 35. Charlie was able to substantially reduce his alcohol intake following the program, but spousal arguments over procrastination and disorganization continued. Despite these traits, Charlie did not meet research criteria for ADHD on blinded assessment at age 39.

Case Two: Frank

Frank was also born full-term at 7 lbs 9 oz. Throughout his development, Frank's parents noticed that he was more active and talkative than his older brother had been. He seemed full of energy, as if driven by a motor, and had a particular fondness for climbing trees. This excessive energy also manifested at school, where Frank was, academically, an average student. He had some difficulty staying in his seat but was otherwise able to perform like his classmates in early elementary grades. As Frank grew older, he became increasingly bored in school. By sixth grade, he was entirely disinterested in schoolwork. His teacher stated he was constantly moving about, refusing to follow directions, and leaving almost all assignments incomplete. His attitude frustrated his teacher and his parents, who were experiencing the same restless and defiant behavior at home. Frank's relationship with his peers mirrored his issues with authority. He constantly disturbed those around him at school, teased them, and lied to them. Frank frequently got into fights in and out of school. Treatment with behavior modification and methylphenidate produced minor improvements.

At age 13, Frank started smoking cigarettes. He had his first sip of alcohol a year later. Between the ages of 15 and 27, in order, Frank experimented with marijuana, cocaine, heroin, and methamphetamine. He also sold drugs intermittently during this time. During his teenage years, Frank engaged in high-risk sexual behaviors. He often had multiple female sexual partners at one time, reporting upward of ten different partners in any 1 month. He joined a gang in his early 20s and was arrested twice, though never incarcerated.

Frank married at age 28. His wife was aware of his many maladaptive behaviors, including constantly losing important objects, interrupting others, and impulsively buying unnecessary, expensive items. She was unaware of his infidelity or regular gambling with members of his gang. Frank had a long history of being fired from jobs for reasons involving stealing, arguing with customers, or making repeated mistakes. At 42 years of age, he met research criteria for combined-type ADHD, as well as antisocial personality disorder and nicotine dependence.

Case Three: John

John was born full-term, weighing 9 lbs 6 oz. By age 5, John seemingly could not sit still. He was constantly moving around and wriggling, whether watching television, playing with toys, or sitting at the dinner table. John was equally restless at school, where he would make noises throughout class or fiddle with objects. Though clearly an intelligent child with above average grades in most subjects (e.g., scoring almost 2 years above grade level in reading in the second grade), John was described as always impatient. He often called out answers, left his seat inappropriately, and compulsively tried to get his teacher's attention. With friends and classmates, he would dominate conversations and interrupt while others were speaking. While doing homework, he could not seem to sit still for more than 15 min. John was diagnosed with hyperkinetic reaction of childhood at his research evaluation and was treated with methylphenidate for several years.

Gradually, John became less restless and better able to focus. He graduated high school and college with honors and attended medical school. Following residency in emergency medicine, John married and had two children. Though his wife and co-workers often described him as talkative and energetic, John was well liked for these traits. At age 41, he no longer met research criteria for ADHD when assessed by a psychologist who was unaware of his previous history.

Discussion

ADHD, one of the most common disorders of childhood, is defined by persistent patterns of inattention and/or hyperactivity in multiple settings. Current estimates suggest around 8% of school-aged children are affected in the United States, with a male to female ratio of 3–4:1 [2, 3]. The specific diagnostic criteria for ADHD and its precursor conditions have been elaborated successively since 1980. The fifth

edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) requires that at least some symptoms (of hyperactivity/impulsivity or inattention) present prior to age 12 and that at least 5 (if above age 16) or 6 symptoms (if below age 17) persist for at least 6 months; interfere with social, academic, or occupational functioning; and occur in more than one setting [4]. DSM-5 differentiates predominantly inattentive, predominantly hyperactive/impulsive, and combined presentations [4]. The presentations tend to vary with age; the predominantly hyperactive/impulsive presentation occurs most frequently in young children and tends to either resolve with maturation or evolve into combined ADHD. The predominantly inattentive presentation is detected more frequently in adolescents and adults, as demands for effective self-management increase.

The cross-situational requirement reflects the assumption that ADHD is a broadly expressed trait. For children, major impairments tend to occur in school, and obtaining information from the child's teacher is an essential component of a comprehensive evaluation. This is typically conducted using one of the myriad behavioral rating scales or checklists that have been developed since the 1960s.

As the core ADHD symptoms of inattention, impulsivity, and hyperactivity frequently result from a multitude of mental and behavioral disorders, the differential diagnosis of this condition is broad. Tic disorders, autism spectrum disorder, seizure disorders, mood disorders, post-traumatic stress disorder, and sleep disorders must all be considered. Oppositional defiant disorder and specific learning disorders are the most common comorbid conditions of ADHD. Conduct disorder frequently complicates the outcome of ADHD and can develop into antisocial personality disorder in adulthood. Frank is representative of the near 20% of children with combined ADHD presentation and comorbid conduct disorder [4]. This group carries a poorer prognosis and an increased risk for neurocognitive impairment [3]. As evidenced in the case of Charlie, anxiety and affective disorders – including depression and bipolar disorder – also frequently coexist in children with ADHD. The presence of comorbidities often influences treatment approaches, namely, the involvement of more specialized care or alternative pharmacological and behavioral therapies.

What was once considered exclusively a disorder of childhood is now recognized as a potentially lifelong condition. Up to 65% of children diagnosed with ADHD continue to manifest impairing symptoms into adulthood [3]. Even among those who do not continue to meet full diagnostic criteria, the social and functional impairments that accompany pervasive ADHD symptomatology are well documented. Klein et al. observed a significant disparity in educational and occupational attainment leading to a relatively worse economic status in those with childhood ADHD, as opposed to prospectively followed comparison subjects [1]. Affected children also had elevated rates of substance use disorders, incarceration, and psychiatric hospitalizations. Remarkably, Caye et al. found similar patterns in a Brazilian birth cohort followed into young adulthood [5]. Higher rates of substance abuse, suicide attempts, criminal behavior, and teenage pregnancies occurred in those diagnosed with ADHD in childhood compared to typically developing peers. Still, many children diagnosed with ADHD do achieve partial or full remission. While John's level of achievement stands as a particularly spectacular outcome, children with ADHD commonly go on to live fairly typical lives as adults. Klein

et al. noted that the occupational and economic disparity evidenced in their study was significant only in relation to non-ADHD peers; the majority of probands were employed (84%) with a median income exceeding the New York State average for Caucasian males in 2007 [1].

Neuroanatomy and Pathophysiology

Genetic Factors

ADHD is a highly heritable (heritability ~76%), polygenic condition [3]. Early molecular genetic studies focused on putative candidate genes, largely based on the hypothesis that abnormalities in dopamine neurotransmission underpin ADHD. Molecular geneticists have abandoned candidate gene approaches due to repeated failure to replicate and the recognition that common genetic factors have small effect sizes, requiring extremely large samples to be detected. Such a large sample, aggregated across many sites, has finally revealed the first genome-wide significant results in ADHD [6]. Although the findings are pending peer review, 12 genome-wide significant single-nucleotide polymorphisms (SNPs) have been identified so far. Each is associated with modest odds ratios (1.077–1.198), supporting the hypothesis that ADHD represents the extreme expression of multiple heritable quantitative traits [6]. This polygenic pattern of common variants conveying modest risks is the rule in complex genetic syndromes, whether schizophrenia or diabetes. The first sets of identified SNPs in ADHD are strongly enriched in conserved regions of the genome, with three of the identified loci containing genes that serve known neurodevelopmental or homeostatic functions – *FOXP2*, *SEMA6D*, and *DUSP6* [6]. Specifically, *FOXP2* encodes a transcription factor necessary for the embryonic development of speech and language regions of the brain and may play a role in pathways influencing later language development. *SEMA6D* is also active during embryogenesis, guiding proper development of neuronal circuitry. *DUSP6* codes for a phosphatase that may be involved in regulating synaptic dopamine levels. Intriguingly, the composite genetic risk factors for ADHD were positively correlated with those of several other health issues, including depression, smoking, obesity, and type 2 diabetes. While these associations still need to be independently confirmed, understanding their biological meaning is likely to become an important priority for the field.

Environmental Factors

Environmental factors, along with gene-environment interplay, are notably implicated in the emergence of ADHD and its trajectory over development. Vulnerability to adverse environmental influences is greatest in prenatal and early developmental periods. Prematurity and low birth weight are associated with ADHD, as are in utero exposure to alcohol, illicit substances, lead, and organophosphates [3]. Severe, early social deprivation is likely causal for an ADHD-like phenotype. Romanian orphans in state institutions who experienced extreme social deprivation during their first

year of life had increased rates of ADHD symptoms, among broader cognitive impairments [3]. As with many psychiatric disorders, poor socioeconomic status and discordant family dynamics are correlated with ADHD.

Neuropsychology of ADHD

ADHD is heterogeneous, and initial attempts to identify a single, core deficit underlying its pathophysiology have been abandoned. Current efforts focus on models of dysfunctional interactions among large-scale brain networks in the genesis of ADHD symptoms. In one such network, fronto-parietal-striatal circuits mediate top-down, cognitive processes essential to the execution of goal-oriented tasks. These processes are jointly referred to as executive function (EF). Impairments in EF – particularly response inhibition, working memory, set-shifting, and interference control – have long been proposed as principal deficits in ADHD. EF impairments are statistically associated with ADHD symptoms, though the relationships are typically modest. For example, Willcutt et al. found fewer than half of children with ADHD exhibited significant impairments on any of 13 tasks testing EF [7]. Increased variability in response times across a wide range of speeded tasks has emerged as one of the strongest and most consistent associations with ADHD [3]. Temporal discounting, the devaluating of delayed rewards, is also consistently greater in individuals with ADHD.

Beyond the heterogeneity documented by Willcutt et al., laboratory measurements of EF often ignore potentially confounding factors ranging from arousal to task familiarity. Currently, most putative EF tasks (e.g., the stop-signal task) invoke processes identified with the dorsolateral prefrontal cortex [8]. These processes are activated in situations with a relative lack of emotional involvement and are known as "cold EF." By contrast, situations with greater emotional salience (e.g., decision-making tasks) are associated with "hot EF," which activates the orbitofrontal and medial prefrontal cortex. While hot EF may be more representative of real-world functioning, its deficits in relation to ADHD have not been examined to the same extent as cold EF impairments. Even so, hot EF deficits have been implicated in the disorder and may constitute an independent route of pathogenesis, along with a distinctive developmental outcome. The two types of EF processes appear to develop at different rates in both typically developing children and children with ADHD, with hot EF maturing later in childhood (>12 years of age) [8].

Neuroimaging of ADHD

Task-Based Functional Imaging

Task-based functional magnetic resonance imaging (fMRI) has been increasingly used in the search for neural correlates of ADHD. Meta-analytic brain imaging methods seek to identify spatial convergence of activation peaks beyond what would be expected by chance. A meta-analysis of pediatric and adult studies, conducted by

Rubia and colleagues (summarized in [9]), found ADHD-related hypoactivation in the right inferior frontal cortex, anterior cingulate cortex, supplementary motor area, and striato-thalamic area during tasks of inhibition [9]. With a focus on attention tasks, ADHD-associated hypoactivation was found in the right dorsolateral prefrontal cortex, parietal regions, thalamus, and posterior basal ganglia.

Meta-analyses can be enhanced by referencing the association between activation in a specific brain region and mental processes across a large number of fMRI studies of healthy subjects, a technique termed functional decoding. Functional decoding may be complemented by meta-analytic connectivity modeling, another data-driven approach that identifies functional coactivation between a specific region of interest and aggregate voxels using cluster analysis. Cortese et al. applied these methods to studies of adults with ADHD and found several regions of relative hypoactivation and no significant areas of hyperactivation [9]. Two hypoactivated regions were located in the putamen, which mirrored findings of a prior meta-analysis of task-based fMRI studies in children. Surprisingly, these basal ganglia regions were related by functional decoding to cognitive aspects of music, including tone discrimination, music comprehension, and music production. The authors speculated that hypoactivation of the aforementioned regions may be related to timing deficits previously identified in ADHD [9]. Cortese et al. also found ADHD-related hypoactivation of the temporal pole, an area linked to language and semantics. As in prior meta-analyses of task-based fMRI studies in children and adults, hypoactivation of the caudate was also identified. This specific caudate region was related to domains of action and execution, the dysfunctions of which are consistent with inhibitory deficits long associated with ADHD. Again in line with prior meta-analyses involving both children and adults, hypoactivation was found within the pars opercularis of the inferior frontal gyrus, a region strongly identified with inhibition.

Resting-State Imaging

Resting-state fMRI has become a mainstream approach to discern correlations in spontaneous brain activity patterns. These spontaneous patterns are defined as functional connectivity and interpreted as "traces" of intrinsic functional circuits. Studies utilizing resting-state fMRI in ADHD have revealed evidence of abnormalities associated with neural networks outside the prefrontal-striatal circuit. The default mode network (DMN), in particular, has emerged as an area of interest across most psychiatric conditions. The DMN refers to widely distributed regions, including the precuneus/posterior cingulate cortex, the medial prefrontal cortex, medial temporal lobe, and the lateral and inferior parietal cortex, that tend to exhibit synchronized spontaneous fluctuations of activity. DMN regions are associated with internally focused cognitions, such as daydreaming, introspection, and assessing others' perspectives [10]. The DMN is suppressed during most external, goal-directed tasks. Failure of such deactivation has been associated with lapses in attention and poorer task performance. During externally oriented tasks, the DMN and task-positive networks, such as the frontoparietal and salience networks, tend to be anticorrelated.

Several studies have found that the strength of these anticorrelations is either reduced or absent in children, adolescents, and adults with ADHD [10]. This neurocognitive model implies that inappropriate activation or impaired suppression of the DMN intrudes upon task-positive network activity, thereby disrupting attention and leading to ADHD symptomatology.

Treatment Strategies

As with many other psychiatric disorders, treatment of ADHD involves both pharmacological and non-pharmacological approaches. Behavioral interventions are an important modality in ADHD management and typically involve training caregivers on how best to use rewards and consequences to support behavioral change. Efficacy of behavioral treatment in ADHD has been established for three particular intervention types: behavioral parent training, behavioral classroom management, and behavioral peer interventions [2].

Stimulants have long prevailed as first-line pharmacological therapy for ADHD. Meta-analyses have demonstrated the robust efficacy of stimulants such as methylphenidate and amphetamine in reducing core ADHD symptoms for both children and adults [3]. The most common adverse effects of stimulant use are loss of appetite, headaches, gastrointestinal discomfort, and sleep disturbance. Despite a theoretical concern that stimulants increase risk of cardiac morbidity and mortality, large-scale studies have found no evidence of an association between stimulant use and sudden cardiac death, acute myocardial infarction, QT interval changes, or stroke [3]. Two selective alpha-2 adrenergic agonists (extended-release guanfacine and extended-release clonidine) have been identified as appropriate adjunctive therapy with stimulant medication [2].

In regard to monotherapy for ADHD, stimulants alone have repeatedly proven superior to behavioral interventions alone. Results from the Multimodal Treatment Study of Children with ADHD, the largest trial of ADHD interventions thus far, did not detect greater short-term benefit from combined therapy compared to pharmacological treatment alone in treating core symptoms of ADHD [3]. Combination therapy outperformed medications alone for improving functional levels and was associated with reduced drug dose requirements. Additionally, parents of subjects undergoing combination therapy reported greater satisfaction with treatment outcomes [2].

Atomoxetine, a selective norepinephrine reuptake inhibitor, is a nonstimulant with demonstrated benefit for ADHD [3]. Though the efficacy of atomoxetine has not been shown to match that of stimulants, it remains a viable option when stimulants are not tolerated or contraindicated, including cases with a history of or high potential for addiction or abuse.

Clinical Pearls: Rating Scales

A variety of rating scales have been developed to aid in the assessment of core ADHD symptoms and behavioral correlates. Commonly used scales for children and adolescents include the Vanderbilt Assessment Scale; the Child Behavior

Checklist; the Swanson, Nolan, and Pelham-IV Questionnaire; the Conners Comprehensive Behavior Rating Scales (Conners CBRS), and the ADHD Rating Scale-IV (ADHD-RS-IV). The Conners CBRS and the ADHD-RS-IV have been validated in preschool-aged children [2].

Most rating scales for ADHD focus on symptom severity. An alternative approach, pioneered by James Swanson in 1999, provides seven options for each probed symptom, from far below to far above average. The resultant Strengths and Weaknesses Assessment of Normal Behavior (SWAN) is increasingly being used in ADHD research studies for its superior psychometric properties. The SWAN is available in the public domain for clinical or research use (http://www.eswan.org/adhd/). Supportive data, rationale, and other rating scales being developed using the same strategy can also be accessed at the Extended Strengths and Weaknesses Assessment of Normal Behavior (E-SWAN) website (http://www.eswan.org/).

Clinical Pearls: ADHD in Adolescence

Although symptomatic remission of ADHD is common, many adolescents and young adults continue to be impaired by their ADHD symptoms. Even when stimulants are acknowledged to be effective, and adverse effects minor and tolerable, maintaining adherence to stimulant treatment through adolescence represents a major challenge to clinicians and parents. We believe this reflects adolescents' appropriately growing insistence on autonomy, along with a developing sense of self. Carrying a psychiatric diagnostic label and being told one must take drugs to function often conveys a sense of being profoundly different, or deficient, at a time when many want to fit in.

In response to this challenge, parents should be alerted at the initiation of stimulant treatment that nearly all children will raise questions about whether medication is still required, typically by age 12–14. If the initial inquiry is ignored or minimized, it may return as an adamant refusal to continue treatment with "toxic and addictive drugs." Such a battle of wills cannot be resolved through parental force – the only recourse is to accept the adolescent's stance for the moment, leaving the door open to future reassessments.

It is preferable to prevent this turn of events by proposing a trial of discontinuation as soon as the adolescent raises the question of whether medications are still needed. Adolescents sometimes open this discussion by reporting that "forgetting a dose" resulted in no perceptible worsening. The question that should then be posed is whether the same conclusion will be reached if medication is discontinued for at least 2 weeks. The adolescent should be instructed that if he or she perceives some subjective worsening (e.g., it becomes more difficult to stay organized), then he or she is authorized to resume the medication without requiring parental or clinician approval. The specifics of when medication is taken and the "envelope" of safe doses are worked out with the clinician *qua* consultant but with the adolescent retaining the decision-making authority regarding whether to take the stimulant or not. Anecdotally, this developmentally informed approach has been effective in the vast majority of cases, and we encourage its rigorous examination in studies of treatment effectiveness.

Lessons Learned About Neuropsychiatry

ADHD is one of the most common neurodevelopmental disorders of childhood. It is a highly heritable, heterogeneous disorder typified by moderate associations with working memory deficits, inhibitory deficits, and increased temporal discounting and stronger associations with intraindividual inconsistency (e.g., increased reaction time variability). However, the challenge remains of how to quantify neuropsychological performance in the lab, in which the testing environment minimizes deficits that often emerge in the classroom or at home.

It is the consensus in the field that multiple developmental pathways can lead to ADHD symptoms. Many of these reflect genetic influences expressed in the interplay with the environment, beginning in utero. Early experience, sleep patterns, caretaker predictability, and the socioeconomic environment all likely influence the course and outcome of ADHD, with outcomes that range from excellent to abysmal. We expect clinical neuroscience approaches to progressively inform our understanding of the neuropsychology and neurobiology of ADHD in the coming decades, accompanied by long-sought improvements in our ability to target treatments and advancements in broad prevention strategies.

References

1. Klein RG, Mannuzza S, Olazagasti MA, Roizen E, Hutchison JA, Lashua EC, et al. Clinical and functional outcome of childhood attention-deficit/hyperactivity disorder 33 years later. Arch Gen Psychiatry. 2012;69(12):1295–303. https://doi.org/10.1001/archgenpsychiatry.2012.271.
2. Subcommittee on Attention-Deficit/Hyperactivity Disorder Steering Committee on Quality Improvement Management, Wolraich M, Brown L, Brown RT, DuPaul G, Earls M, et al. ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. Pediatrics. 2011;128(5):1007–22. https://doi.org/10.1542/peds.2011-2654.
3. Thapar A, Cooper M. Attention deficit hyperactivity disorder. Lancet. 2016;387(10024):1240–50. https://doi.org/10.1016/s0140-6736(15)00238-x.
4. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington: American Psychiatric Association; 2013.
5. Caye A, Rocha TB, Anselmi L, Murray J, Menezes AM, Barros FC, et al. Attention-deficit/hyperactivity disorder trajectories from childhood to young adulthood: evidence from a birth cohort supporting a late-onset syndrome. JAMA Psychiatry. 2016;73(7):705–12. https://doi.org/10.1001/jamapsychiatry.2016.0383.
6. Demontis D, Walters RK, Martin J, Mattheisen M, Als TD, Agerbo E, et al. Discovery of the first genome-wide significant risk loci for ADHD. bioRxiv. 2017; https://doi.org/10.1101/145581.
7. Willcutt EG, Doyle AE, Nigg JT, Faraone SV, Pennington BF. Validity of the executive function theory of attention-deficit/hyperactivity disorder: a meta-analytic review. Biol Psychiatry. 2005;57(11):1336–46. https://doi.org/10.1016/j.biopsych.2005.02.006.
8. Skogli EW, Andersen PN, Hovik KT, Oie M. Development of hot and cold executive function in boys and girls with ADHD. J Atten Disord. 2017;21(4):305–15. https://doi.org/10.1177/1087054714524984.
9. Cortese S, Castellanos FX, Eickhoff CR, D'Acunto G, Masi G, Fox PT, et al. Functional decoding and meta-analytic connectivity modeling in adult attention-deficit/hyperactivity disorder. Biol Psychiatry. 2016;80(12):896–904. https://doi.org/10.1016/j.biopsych.2016.06.014.
10. Posner J, Park C, Wang Z. Connecting the dots: a review of resting connectivity MRI studies in attention-deficit/hyperactivity disorder. Neuropsychol Rev. 2014;24(1):3–15. https://doi.org/10.1007/s11065-014-9251-z.

2 Phineas Re-enGage: Long-Term Psychiatric Follow-Up of Pediatric Traumatic Brain Injury

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Author Note

"Phineas Re-enGage" came to the attention of the first author as his first participant in a prospective longitudinal study of children and adolescents aged 6–14 years who were consecutively hospitalized for traumatic brain injury (TBI). We published a study examining the phenomenology of personality change due to traumatic brain injury in 2001 [1]. A detailed case report embedded in that article in which Phineas Re-enGage was referred to as "Subject A10" described his clinical course and multiple problems from his severe TBI at age 14 years until he was aged 22 years [1]. We have continued the prospective study, and the most recent assessment point was the 24-year follow-up. This chapter summarizes the previously published follow-up from age 14 to 22 years and describes Phineas Re-enGage's life course to age 38 years.

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Case

Phineas Re-enGage was aged 14 years when, as an un-helmeted rider, he flew over the handlebars of his bicycle and landed on the dirt road. A Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) for school-aged children interview [2] with parents within 1 week after his injury demonstrated the absence of a preinjury psychiatric disorder. He was considered "well-mannered, well-behaved, and polite." He planned for purchasing desired possessions such as a fishing pole. His academic achievement on preinjury standardized tests was documented to be average. His schoolteacher, who rated his preinjury behavior, endorsed only 2 of more than 150 behavioral symptoms on a standard scale as occurring "often or pretty much" and these were "has a hard time making friends" and "quiet; doesn't talk very much." Preinjury family function was rated by a research family interview soon after the injury, and the family was found to be functioning well [3]. There was no positive family psychiatric history for first-degree relatives [3]. Mother developed an episode of major depression within the first 2 years of follow-up related to the stress of managing Phineas Re-enGage.

Phineas Re-enGage had a lowest post-resuscitation Glasgow Coma Scale (GCS) score of 3, and his duration of impaired consciousness lasted 323 h (over 13 days). Duration of impaired consciousness was defined as the time from injury to reliably following simple commands measured by reaching and sustaining a score of 6 on the motor subscale score on the GCS. Thirteen months after his injury, he was diagnosed with probable complex partial seizure disorder because of several possible staring spells, but the electroencephalogram was not characteristic of epileptiform activity. He did not have seizures thereafter. His research MRI conducted 24 years after injury showed multiple areas of brain injury in the frontal and temporal lobes bilaterally (see Figs. 2.1, 2.2, and 2.3). The radiological report by author, J.H., read as follows: "Ventricles are normal in size and position. Cerebral hemispheres, corpus callosum, deep nuclei, brain stem, and cerebellum are present and normally formed. Myelination and cortical organization are normal. Images show multifocal areas of encephalomalacia in the left frontal lobe, including the gyrus rectus, all orbital gyri, and the pars triangularis and pars opercularis of the inferior frontal gyrus. Injuries to the left temporal lobe include the anterior portions of the superior, middle and inferior gyri, as well as the posterior part of the superior temporal gyrus. Additional injuries are present in the right temporal lobe, including the superior temporal gyrus (anterior and middle parts), middle temporal gyrus (middle and posterior parts), and the middle portion of the inferior temporal gyrus. Susceptibility weighted imaging revealed 2 focal areas of hemosiderin in the middle portion of the right superior frontal gyrus and the posterior aspect of the left putamen."

Volumetric analyses of Phineas Re-enGage's MRI data show significant reduction in the left hemisphere white matter volume (on T1-weighted imaging), accounted for principally within the left frontal lobe. However, FLAIR abnormalities in the left frontal lobe demonstrate white matter "loss" that is even more

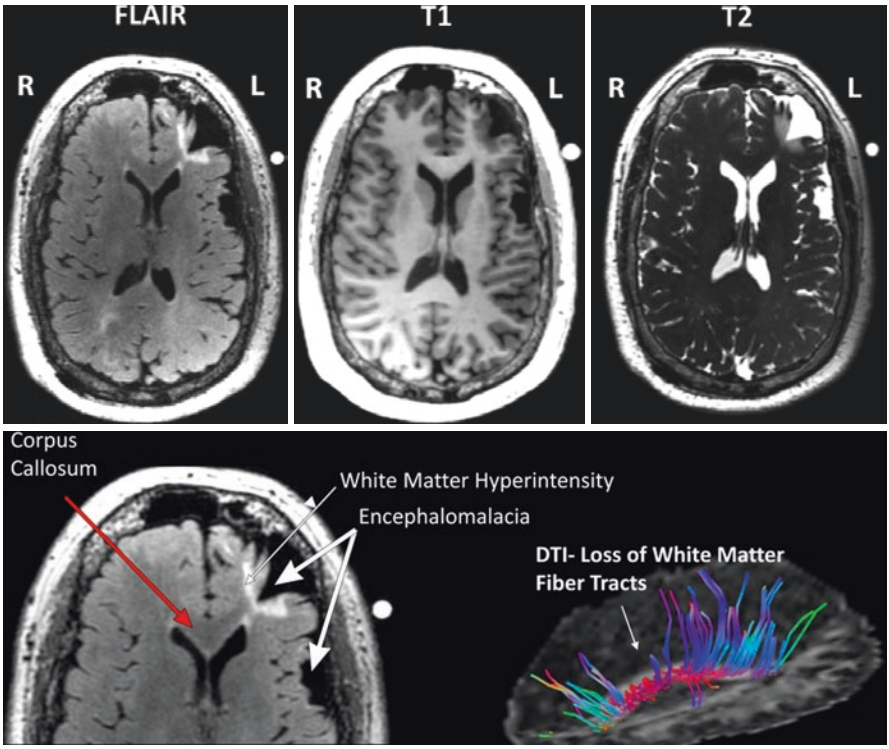

Fig. 2.1 MRI 24 years after original injury. DTI tractography demonstrates a drop-out of fiber tracts across the corpus callosum

extensive than the volume loss visualized on T1-weighted images. Despite the loss of white matter integrity and obvious focal frontal gray matter loss associated with the focal encephalomalacia (both frontal and temporal), at least according to volumetric findings, all subcortical regions are at least within a 95% confidence interval of the region of interest (ROI) mean. This suggests that changes in subcortical gray matter levels are at most modest.

Early Disease Course

Phineas Re-enGage was followed for 2 years as a participant in the prospective study and as a patient for most of the remaining 6 years of follow-up. He had a tumultuous course dominated by affective lability, aggression which ultimately subsided, poor social judgment, and significant executive function difficulties meeting criteria for classic personality change due to TBI (PC) diagnosis. Furthermore, his

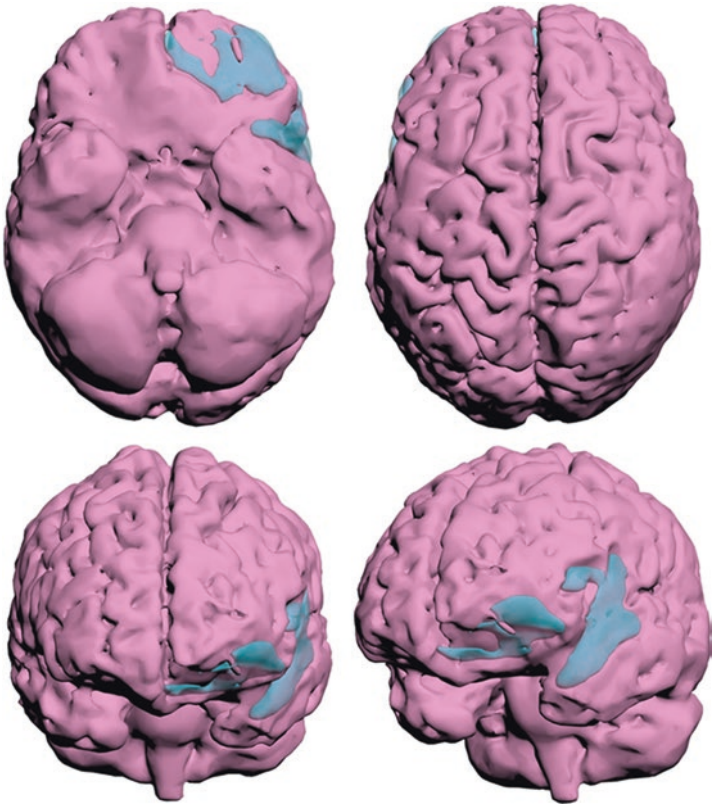

Fig. 2.2 3-D renderings of surface damage. The *blue* depicts focal areas of encephalomalacia in the left frontal and temporal lobe region

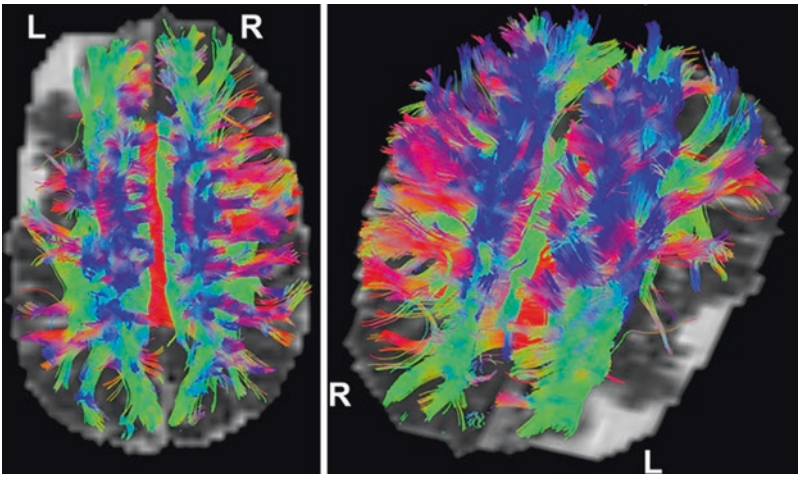

Fig. 2.3 Diffusion tensor imaging at 24-year follow-up. The right hemisphere has abundant warm colored (red-to-orange) tracts with distinctly visualized "generally absent" U-fibers rather than "virtually absent" in the left hemisphere. There is obvious sparsely distributed brain connectivity in the left hemisphere compared to the right

follow-up was filled with multiple episodes of major depression, suicide attempts, episode of mania, episode of hypomania, and development of alcohol abuse with driving under the influence (DUI) and probation. He also developed secondary attention-deficit/hyperactivity disorder (ADHD) between his 3-month and 6-month postinjury evaluation, and the disorder never resolved. At the time of the previous published case report (age 22), he was living at home with his parents. His mother was his legal "representative payee" because of his financial irresponsibility. He volunteered on a farm, taking care of horses and repairing farm structures with his father. He was sad and irritable about his lot in life, which included significant debt from irresponsible purchases and probation from his DUI. He had difficulties with memory, distractibility, and organization. He was more tactful and no longer made inappropriate sexual or personal comments. He talked excessively, although not in a pressured manner. He cared for others and nurtured young nephews and comforted parents if they expressed strong emotions. Details of these travails are documented previously [1].

We now report that Phineas Re-enGage's life, which had been chaotic before he began to abuse alcohol, continued to spiral out of control with continued alcohol abuse until age 25. He worked with a road crew fixing roads. His road crew teammates discovered that he had no sexual experience and arranged for him to be initiated. He was grateful for his social relationships with women initially but found himself in psychosocially complicated and unstable relationships and later resented them for what he interpreted to be manipulative behavior.

Return to Follow-Up

The reengagement of Phineas Re-enGage began after he stopped abusing alcohol at age 25. When he was 27 years old, he met his future wife, a nursing assistant, through online dating. She provided history at his 24-year follow-up as his "significant other" in accordance with the research study design. She described how she had always been obese, and when it came to men, she "would take what" she "could get." In contrast to other men she had encountered, she was struck by his good manners and noted that he was not a "drunkard." Phineas Re-enGage reported that he told her about his head injury on the third date, and that disclosure was when all the women he met would typically disengage. She did not flee, and they moved in together after 3 months; they married when he was 29 years old. They had a 4-year-old child at the time of the evaluation. When topic was raised with Phineas Re-enGage's wife that her husband appeared very fortunate to have found her, she opined that she was the lucky one because not only did she find him but she found a wonderful extended family.

At the 24-year follow-up with Phineas Re-enGage, the following diagnoses were established based on the Neuropsychiatric Rating Schedule (NPRS) [1] and the Mini-International Neuropsychiatric Interview (MINI) [4] administered by the first author: (1) personality change due to TBI, affective instability subtype (excellent control on venlafaxine ER and methylphenidate); (2) major depressive disorder, recurrent, resolved (at least 22 episodes); (3) alcohol use disorder (from age 21 to 25 years); and (4) ADHD, inattentive type (onset at age 14 – postinjury).

The clinical summary based on the 24-year follow-up interview with Phineas Re-enGage and a separate interview with his wife is as follows. Phineas Re-enGage is an apparently good husband and father despite the fact that he receives federal disability payments for not being able to maintain a paying job. He has flexible hours working without pay on a horse farm doing manual labor including feeding horses and bailing depending on circumstances and needs. He has a close and supportive relationship with his parents, particularly his father, who is able to help him return to being calm when he gets distressed. He has monthly stress-induced migraines and takes sumatriptan.

Diagnostic Summation

From a diagnostic point of view, Phineas Re-enGage has personality change due to TBI, affective lability subtype which is exceptionally well controlled as long as he takes his venlafaxine extended release. His symptoms are very severe in terms of irritability and sadness and crying when in the previous 6 months he briefly stopped his medication after failing to refill the prescription in a timely fashion. His wife actually does not see this disorder in him because she has not been around him when he is off his medication, and his overall comportment in recent years has been stable.

However, Phineas Re-enGage and his wife are aware of recurrent episodes of depression, including an episode as recently as 2 months before this assessment. Episodes are typically related to environmental stress, and the latest episode was related to the consequences of his being rear-ended in his vehicle in a non-injury incident. In his lifetime, he reports seven suicide attempts, but he is not currently suicidal and reports euthymia. From age 21 to 25 years, he had significant alcohol use disorder, but he has been in complete remission since then. He has not had any evidence of mania since his previous research assessment which was 2 years after his injury.

He has attention-deficit/hyperactivity disorder, inattentive type which has significantly impacted his ability to maintain a paying job. This is technically considered “secondary ADHD” because its onset was after his injury [5]. He himself sees only four ADHD inattentive symptoms, but his wife and his clinicians see more. This disorder has affected his daily functioning, and the limiting factor in a work situation is that he is unable to process interactions and demands sufficiently. This quickly results in his bosses becoming irate or impatient and his then becoming anxious, overwhelmed, and angry, sometimes leading to an outburst. The barn job minimizes his stress while allowing him to do work that he finds valuable. He has no inordinate difficulties meeting the needs of his 4-year-old daughter with whom he spends a lot of time while his wife works. In fact, he behaves lovingly and is tuned into her needs, e.g., when off medication and crying a lot, he went to significant lengths to shield her from his distress. He also successfully has navigated the spousal relationship, and the couple is open in expressing their satisfaction with each other. His wife is his payee because he can be impulsive with purchases and is rather naïve with salesmen. He reports that stimulant medication such as methylphenidate and mixed amphetamine salts have helped him with his symptoms.

National Institutes of Health (NIH) Toolbox Testing

The results of NIH Toolbox testing completed at the 24-year follow-up assessment reveal overall impaired executive functioning, though the overall Fluid Cognition Composite score on this measure was influenced by significantly impaired performance on the Pattern Comparison Processing Speed Test (a measure of processing speed) and borderline performance for the Dimensional Change Card Sort Test (a measure of cognitive flexibility). List Sorting Working Memory Test (a sequencing task requiring participants to sort and sequence stimuli that are presented visually and auditorily to assess working memory), Picture Sequence Memory Test (a measure of episodic memory that requires the participant to recall sequences of pictured objects and activities in a fixed order over three learning trials), and the Flanker Inhibitory Control and Attention Test (a measure of inhibitory control in the context of selective visual attention) were within the normal range using age-corrected scores. Tasks associated with novelty and processing speed, as are required in the Pattern Comparison Processing Speed Test and the Dimensional Change Card Sort Test, have been previously cited as particularly vulnerable to frontal lesions such as those evident in Phineas Re-enGage (Table 2.1) [6, 7].

Case Reflections

Reengagement

The principal and obvious observation of Phineas Re-enGage is the reversal of his dramatic decline in the quality of his life. His affective instability appears to be a core problem. This problem was only partially mitigated by psychotropic medication in the first 8 years postinjury. His personality change due to TBI diagnosis was the key problem after his injury. His affective lability responded only partially to medication in the first 8 years of his follow-up after severe TBI. The long-term follow-up of nineteenth-century Phineas Gage outlined an inexorable and increasingly dysfunctional almost 12-year life course of a person who was well-adjusted prior to a severe traumatic brain injury [8]. However, there is a suggestion that Phineas Gage may have had spared functional abilities and was able to adapt "moderately well" to

Table 2.1 National Institutes of Health (NIH) toolbox tests version 2.1 at 24-year follow-up

Subtest	Standard score
Pattern Comparison Processing Speed Test	41
List Sorting Working Memory Test	106
Picture Sequence Memory Test	106
Flanker Inhibitory Control and Attention Test	94
Dimensional Change Card Sort Test	63
Fluid Cognition Composite version 1.1	73

Note: Standard scores reflect a mean of 100 and a standard deviation of 15. Therefore, scores under 70 reflect two standard deviations below the mean, indicating impairment. The scores from the first five rows comprise the Toolbox Fluid Cognition Composite

his brain injury [8]. The case of Phineas Re-enGage provides strong evidence that the long-term outcome after frontal and temporal lobe injury is not necessarily disastrous. We have previously documented in prospective studies that 50–60% of children with severe TBI develop a novel psychiatric disorder in the first 2 postinjury years [3]. This means that 40–50% of children with severe TBI have a favorable short-term psychiatric outcome. This case study is extraordinary in several ways including the demonstration of a sustained 13-year reversal of an 11-year catastrophic post-severe TBI socio-emotional course.

Domains of Function and Dysfunction

Phineas Re-enGage continues to suffer from severe consequences of his TBI. He is unable to sustain a paying job because of his executive functioning problems involving planning, organization, processing speed, and cognitive flexibility weaknesses. His executive function deficits have been psychometrically documented (Pattern Comparison Processing Speed Test and Dimensional Change Card Sort Test) and thus, in concert with his underlying proclivity to be affectively labile, result in his becoming overwhelmed, depressed, and suicidal. Yet, Phineas Re-enGage has achieved an unexpectedly good quality of life as a loving husband, father, son, and uncle. It would be difficult to invoke a neural pathway theory that could have predicted these domain-specific functional strengths.

Early potential predictors of these strengths include the fact that even in the midst of his chaotic decline, he maintained the preinjury capacity to care for others, evidenced by his postinjury nurturing of his nephews and ability to recognize and then comfort his parents when they expressed strong emotions. Other research-supported potential predictors include his preinjury function in the average academic range, his favorable preinjury family psychiatric history, and healthy preinjury family function [3]. It was very obvious that Phineas Re-enGage continued to have a supportive family after his injury, which is often associated with more favorable outcome. Postinjury family function is related to preinjury function and new-onset psychiatric disorder and behavioral outcome [9, 10]. His family support is frequently called upon when he becomes overwhelmed. He benefits directly especially by talking with his father and doing some farm maintenance work with his father. Another probable benefit of healthy preinjury family function includes preservation of his previously established good manners and caring attitude to others. His wife specifically noted his good manners, implying that considerateness and being sensitive to the needs and feelings of others made it possible for Phineas Re-enGage to build and consolidate a marriage.

Complementarity of Needs

A review of the science underlying the choice of a mate in a relationship and a marriage is beyond the scope of this chapter [11]. However, complementarity of needs appears to have influenced the formation and strengthening of his relationship with

his wife. In this case, his wife's experiences of abuse from ostensibly able-bodied and functioning men likely compelled her to consider that a man like Phineas Re-enGage was a better life partner despite his vulnerabilities and limitations.

Modern Treatments for Mood Disorders, Affective Instability, and ADHD

Phineas Re-enGage has clearly benefitted from antidepressant and stimulant medication that were not available in the nineteenth century. His serotonin-norepinephrine reuptake inhibitor (SNRI) has stabilized his affective lability enough so that his wife did not even perceive this as a problem. However, even a short period off the medication brought back the full extent of his affective lability in a way that was alarming and illuminating to Phineas Re-enGage. Clinically, his reaction seemed to be a return of underlying symptoms rather than symptoms of withdrawal from the medication. Despite his taking an SNRI, he has had recurrent episodes of major depression in the context of environmental stressors. A related notable observation is that despite the manifestation of a manic and a hypomanic episode in the first 2 years of follow-up, Phineas Re-enGage has not shown evidence of similar episodes in the last 22 years. This does not eliminate the possibility of recurrence, but implies that treatment of depression and affective lability can safely include antidepressant medication.

It is clinically important to diagnose and treat the emergence of post-TBI ADHD. This "secondary ADHD" occurs in 15–20% of cases after severe TBI in children and adolescents [5]. The syndrome appears to have a different neuropsychological profile compared with developmental ADHD in children who have survived a TBI [12]. Secondary ADHD is associated with working memory, attention, and psychomotor deficits compared with developmental ADHD, but not with response inhibition which is considered to be the signature executive function deficit of the latter condition. Although stimulant treatment has not resulted in Phineas Re-enGage being able to maintain paid work, he has benefited in the sense that he is able to accomplish his child care duties and volunteer farm work. Phineas Re-enGage continues to have significant executive function deficits not responsive to stimulant treatment including naiveté, for example, with salesmen and with budgeting. It appears appropriate that his wife functions as his representative payee for this deficit.

Future

Phineas Re-enGage is entering mid-life. His story will continue to unfold, and he will face new challenges and opportunities. It is therefore premature to make conclusions about the likely course of the rest of his life. Nevertheless, this update of his life journey from age 22 to 38 years provides data to clinicians of potentially favorable outcomes after severe TBI in children and adolescents and may influence the quest for effective interventions. This narrative also provides hope for individuals with severe TBI and their family members.

Clinical Pearl

Role of Alcohol Use Disorder

Phineas Re-enGage's postinjury decline preceded his life-threatening use of alcohol. This long-term course shows though that cessation of alcohol use was the pivotal point in his reengagement, not unlike patients who have not had a TBI. The importance of sobriety and treatment for comorbid substance abuse treatment cannot be overstated in patients with TBI.

Lessons Learned About Neuropsychiatry

The pattern of lesions in Phineas Re-enGage is similar to the estimated lesions of Phineas Gage [8]. Both patients had primarily left-sided lesions including the frontal and temporal lobes with associated right-sided damage and extensive white matter network loss. The widespread lesions may be related to the severe psychiatric, behavioral, socio-emotional, and executive function deficits. Phineas Re-enGage had relatively spared subcortical structural integrity, and this suggests that deficits such as he exhibited can occur with damage limited to cortical gray matter and frontal and temporal white matter. It is not clear whether this pattern of relative sparing of subcortical structures may permit the reengagement noted, but the experience of our research participant is noteworthy.

References

1. Max JE, Robertson BA, Lansing AE. The phenomenology of personality change due to traumatic brain injury in children and adolescents. J Neuropsychiatr Clin Neurosci. 2001;13(2):161–70.
2. Orvaschel H, Puig-Antich J, Chambers W, Tabrizi MA, Johnson R. Retrospective assessment of prepubertal major depression with the Kiddie-SADS-e. J Am Acad Child Psychiatry. 1982;21(4):392–7.
3. Max JE, Robin DA, Lindgren SD, et al. Traumatic brain injury in children and adolescents: psychiatric disorders at two years. J Am Acad Child Adolesc Psychiatry. 1997;36(9):1278–85.
4. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998;59(Suppl 20):22–33; quiz 34–57.
5. Max JE, Schachar RJ, Levin HS, et al. Predictors of secondary attention-deficit/hyperactivity disorder in children and adolescents 6 to 24 months after traumatic brain injury. J Am Acad Child Adolesc Psychiatry. 2005;44(10):1041–9.
6. Demakis GJ. Frontal lobe damage and tests of executive processing: a meta-analysis of the category test, stroop test, and trail-making test. J Clin Exp Neuropsychol. 2004;26(3):441–50.
7. Demakis GJ. A meta-analytic review of the sensitivity of the Wisconsin Card Sorting Test to frontal and lateralized frontal brain damage. Neuropsychology. 2003;17(2):255–64.
8. Van Horn JD, Irimia A, Torgerson CM, Chambers MC, Kikinis R, Toga AW. Mapping connectivity damage in the case of Phineas Gage. PLoS One. 2012;7(5):e37454.
9. Max JE, Castillo CS, Robin DA, et al. Predictors of family functioning after traumatic brain injury in children and adolescents. J Am Acad Child Adolesc Psychiatry. 1998;37(1):83–90.

10. Taylor HG, Yeates KO, Wade SL, Drotar D, Stancin T, Burant C. Bidirectional child-family influences on outcomes of traumatic brain injury in children. J Int Neuropsychol Soc JINS. 2001;7(6):755–67.
11. Kavaliers M, Matta R, Choleris E. Mate-choice copying, social information processing, and the roles of oxytocin. Neurosci Biobehav Rev. 2017;72:232–42.
12. Ornstein TJ, Sagar S, Schachar RJ, et al. Neuropsychological performance of youth with secondary attention-deficit/hyperactivity disorder 6- and 12-months after traumatic brain injury. J Int Neuropsychol Soc JINS. 2014;20(10):971–81.

Tricky "Ticcy" Case: Tics/Tourette Syndrome with Co-occurring OCD

3

Erica Greenberg, Angela Essa, and Jeremiah M. Scharf

Case

Jackson is an 11-year-old left-handed boy who presents to the outpatient clinic with what his parents describe as repetitive movements and sounds that occur throughout the day and that he feels he is "unable to control."

His parents report that, a little over a year ago, Jackson developed repeated eye blinking and sniffing, even though he had no history of seasonal allergies. His movements subsequently changed over time, began to involve his arms and trunk, and appeared more complex in nature. While at first Jackson only had simple head and eye movements, he developed shoulder shrugging, abdominal tensing, and an ordered sequence of movements where he would turn his head to the left, pound his

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fist on the table, and grunt. The sniffing continued, but he also developed repetitive throat clearing, a high-pitched squeak, and saying "I see" in a stereotyped manner. When asked to stop, Jackson told his parents that he couldn't. He described an uncomfortable feeling in his body just before he engaged in the movement or sound and that he "felt like he would explode" if he didn't let them out. These movements and sounds seemed to increase when he was either bored, tired, or very excited and to worsen while watching TV and doing homework and when he was worried about an upcoming event. They also improved when he was on the soccer field. His parents have noticed that the movements often occur in "bouts" and worsen whenever someone asks him about them. Jackson initially could hold in, or suppress, the movements/sounds, but over the last few weeks, they have become constant, occurring in school and causing disruption for him and the class. His parents report that they brought Jackson to the pediatrician 6–8 months ago who diagnosed him with "benign tics." She treated him with various alpha-2 agonists, including short- and long-acting clonidine and guanfacine (total daily dose of 0.4–0.6 mg and 4–6 mg, respectively), but these either made him too sleepy or moody and did not reduce his tics.

Jackson lives at home with both parents and an 8-year-old sister. He is in sixth grade at a local middle school. Regarding family history, mom reports that she has obsessive-compulsive disorder, and dad states that he "probably has ADHD." On further inquiry, they report that Jackson was diagnosed with ADHD at age 5, when his Kindergarten teacher and soccer coach both described a pattern of inability to sit still, difficulty paying attention, and increased impulsivity compared to other children his age. He was started on mixed amphetamine salts with improvement both in sustained attention and impulsivity. He remained on stimulants for 3 years, but his parents stopped them at age 8 after he began to fall off the growth curve due to decreased appetite. In retrospect, his parents realized that shortly after starting stimulants, Jackson developed intermittent "sniffles" for about a month, even though he didn't appear to be sick.

Right before fourth grade, Jackson's family moved to another state. He began to have more difficulty separating from his mother, and when school started, he would cry, have tantrums, and would refuse to leave the car upon drop-off. Additionally, he developed a slew of worries, including how he would perform in school despite having good grades and whether something bad might happen to him or his parents. These worries sometimes made it difficult for him to fall asleep at night. He also developed headaches and stomachaches and would leave class to visit the nurse multiple times a day.

Given Jackson's new symptoms of impairing anxiety, his pediatrician diagnosed him with generalized anxiety disorder and recommended that he work with a psychologist to receive cognitive behavioral therapy (CBT). As these symptoms were causing significant impairment and distress in school and at home, she also recommended starting fluoxetine, a selective serotonin reuptake inhibitor (SSRI). Jackson tolerated 10 mg without significant reduction in symptoms or side effects, but upon increasing to 20 mg, he became "activated." His parents describe that he suddenly

developed excessive energy, was more irritable, angry, and rageful, and had difficulty falling asleep. As a result, his parents stopped the fluoxetine, and these symptoms/side effects subsided. They tried another SSRI, but the same activation symptoms returned. Jackson ultimately worked with his therapist for 6 months, which led to an improvement in his generalized anxiety.

Given the frequent co-occurrence of obsessive-compulsive disorder (OCD) in children with tic disorders, Jackson was asked further about various OCD symptoms. He describes a need for "symmetry" (if something touches one side of his body, he has to touch the other side) and a need to engage in repeated actions until he feels "just right." For example, he needs to touch his knees together in sets of threes, which sometimes prevents him from leaving the classroom at the end of class. He will also tap and touch objects. Jackson denies having any worries about contamination or dirt and germs or any need to wash his hands repetitively. He endorses no checking of lights or the TV to make sure they are off, though he does state that he will often check in with his mother to make sure he "didn't do something wrong" or to make sure that he "isn't a bad person." Jackson also states that in school he will sometimes need to reread the text or rewrite his essay if the words aren't aligned correctly. He will also feel uncomfortable when he sees odd numbers. Upon asking Jackson whether he ever gets thoughts, ideas, or images that are unwanted, upsetting, and distressing, he appears embarrassed and sheepishly admits that, for the last few months, he has been having the recurrent image of "stabbing his mother" in his head. He insists he doesn't want to do it and would never hurt anyone, but because he keeps having these intrusive thoughts, he worries that he might actually want to harm his mother. These thoughts cause him a great deal of distress, and therefore he has been avoiding any sharp objects or being in a room alone with his mother for the last 2 weeks.

In a separate meeting with Jackson's parents to gather additional history, they describe that, over the last year or so, Jackson has had episodes at least twice a week where he seems to go from "0 to 100" with rage/anger and that when he is in this state, "it's like he's not there" and "there is no reasoning with him." His parents describe that these episodes typically occur after minimal provocations or triggers, such as not getting what he wants, but also on days when his tics or OCD symptoms are bad or while struggling to finish homework. After these episodes, Jackson is always extremely remorseful and feels guilty about his actions.

As part of his assessment, Jackson and his parents together complete two clinician-administered scales. The first is the Yale Global Tic Severity Scale (YGTSS) – a clinician-administered, semi-structured scale that provides tic severity ratings for motor and phonic (vocal) tics separately and assesses tic number, frequency, intensity, complexity, and degree of interference with actions or speech (rated on a scale of 0–50). There is a separate "impairment" score (also rated 0–50), which is used to characterize effects on self-esteem, social life, family life, and school/job functioning. Jackson scores a 35/50

(moderate severity) on the tic severity component and a 30/50 for impairment, with problems in self-esteem, social acceptance (frequent teasing by peers), and school challenges secondary to tics. They also complete the Child Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) – another semi-structured, clinician-administered scale that rates OCD symptom severity in children and adolescents. Obsessions and compulsions are discussed separately, and questions assess time occupied by interference, distress, and resistance against and degree of control over obsessions and compulsions, each rated 0–4 for a total scale of 0–40. Jackson's primary obsessions include ego-dystonic thoughts about stabbing his mother and worrying that he is a bad person. His primary compulsions include checking/reassurance seeking from his parents, engaging in symmetry/"just right" behaviors, and rereading/rewriting his schoolwork. He scores a 24/40, consistent with "severe" OCD.

Diagnostic Impression

Following the interview and assessment scales, Jackson and his parents are told that he meets criteria for multiple diagnoses, including Tourette syndrome (TS), OCD, ADHD, generalized anxiety disorder, and intermittent explosive disorder (IED). However, the expert neuropsychiatrist emphasizes that while these sound like a lot of separate diagnoses, they are now considered to be different aspects of a common developmental susceptibility of overlapping brain circuits associated with TS, rather than entirely independent disorders [1, 2]. The discussion begins by describing TS and how Jackson fulfills criteria for the disorder by having at least two motor tics and one vocal tic for at least a year (starting before age 18). Furthermore, given that TS, OCD, and ADHD all share certain genetic underpinnings, it is not surprising that his mother has OCD and his father has ADHD. The neuropsychiatrist also notes that Jackson's progression of tic symptoms is well-described, in that tics typically begin between ages 5 and 9, often as simple (one muscle group per tic) motor tics in the head/neck region and, by definition, change in frequency and intensity over time and involve other parts of the body usually in a proximal-to-distal fashion with more coordinated or purposeful appearing tics arising later in a subset of children. His parents are relieved to learn that socially inappropriate utterances such as cursing ("coprolalia") are *not* required for the diagnosis and in fact only occur in ~15% of TS patients. The neuropsychiatrist then discusses that the distinction between TS and a persistent tic disorder with only motor or only vocal tics is completely arbitrary and that all tic disorders likely exist on a continuous developmental spectrum. Lastly, Jackson's parents learn that tics tend to peak at an average age of 10–14 and that most children's tics improve in late adolescence/early adulthood, with ~1/3 experiencing minimal/no tics, ~1/3 with mild tics, and ~1/3 or less with moderate or severe tics as adults.

The neuropsychiatrist then focuses on OCD and notes that OCD affects 30–50% of children and adolescents with TS. Jackson meets criteria for OCD, since his symptoms take up >1 h a day and cause clinically significant distress/impairment. The

clinician next explains that TS and OCD have overlapping genetic susceptibility and that some of Jackson's OCD symptoms can be described as "tic-related OCD" or "Tourettic OCD," which may be genetically more similar to TS than to OCD without tics [3]. Tic-related OCD tends to have an earlier age of onset than the more common late adolescent/young adult onset for typical OCD and is more male-predominant than adult-onset OCD. While patients with TS can have any of the OC symptoms present in patients with OCD without tics, tic-related OCD may be more likely to include aggressive, sexual, and religious obsessions and symmetry, touching, counting, and "just right" compulsions. It can be difficult to discriminate between a compulsive tic and a complex compulsion in tic-related OCD, but one helpful distinction is that compulsions are often performed to relieve thoughts/feelings of anxiety or disgust, while tics are often performed in response to unpleasant internal sensory phenomena ("premonitory urges"). However, these tic/OCD overlap symptoms typically require treatments targeting both tics and OCD to achieve symptom reduction.

Though not a focus at the initial visit, the neuropsychiatrist also discusses that ~85% of those with TS in a clinical setting have at least one co-occurring neuropsychiatric condition, with ~50% having co-occurring ADHD, 30% having non-OCD anxiety disorders, and ~15% to 30% having co-occurring intermittent explosive disorder (characterized by at least two non-premeditated aggressive outbursts weekly, out of proportion to the trigger, and often associated with distress/remorse) [4].

Neuroanatomy and Pathophysiology

Neuroimaging, neurophysiology, and neuropathologic studies in humans, along with experimental data from nonhuman primates, have implicated dysregulated development and/or functioning of orchestrated circuits between the cerebral cortex, basal ganglia, and thalamus, i.e., cortico-striato-thalamo-cortical (CSTC) loops, in TS pathophysiology (Fig. 3.1) [2]. While the basal ganglia have traditionally been viewed as the "habit system" of the brain, playing a role in goal-directed motor planning as well as storing, selecting, and executing overlearned (automatic) motor plans, they are now understood to comprise limbic and associative domains as well, in which emotional, motivational, and cognitive information is processed to influence movement and behavior. These functional domains are thought to map onto parallel sensorimotor, limbic (emotional), and associative (cognitive) CSTC loops. In this context, the frequent co-occurrence of TS, OCD, and ADHD is thought to arise from a shared developmental dysregulation within these parallel CSTC circuits that results in overactive formation of automatic motor plans (tics), repetitive intrusive thoughts that trigger cognitive and motor rituals (obsessions/compulsions), and difficulty prioritizing intended thoughts as well as filtering unwanted thoughts/movements (inattention and hyperactivity/impulsivity).

Within the sensorimotor basal ganglia, like the corresponding areas of sensorimotor cerebral cortex, there is further organization of motor CSTC circuits to reflect a body map, or "homunculus," ascribing certain regions to control motor plans involving the face, arms, and legs, as well as separating simple and complex

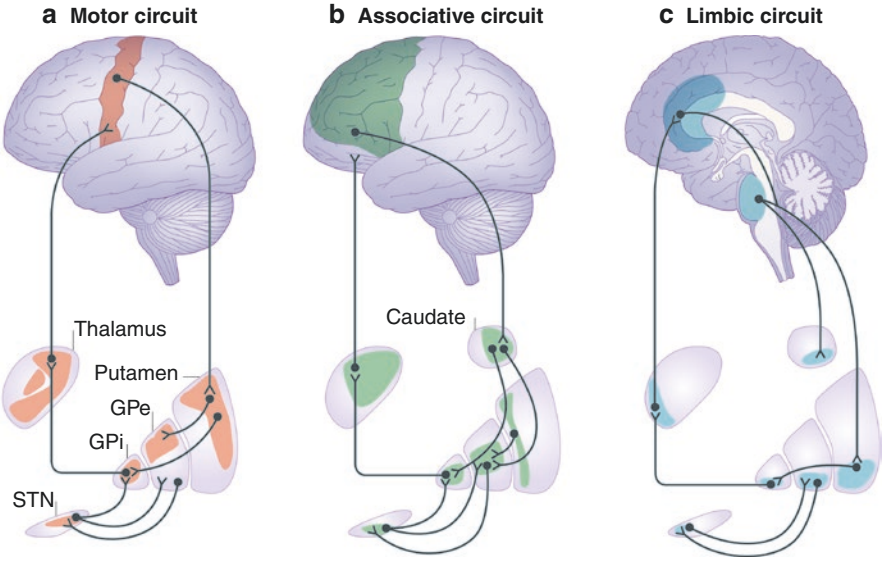

Fig. 3.1 Functional subdivisions of sensorimotor, cognitive/associative, and emotional/limbic cortico-striato-thalamo-cortical (CSTC) circuits. The basal ganglia receive a broad range of descending inputs from across the cerebral cortex (as well as from other subcortical regions) that are processed in parallel, partially overlapping, circuits that project back to the thalamus and subsequently to the frontal cortex. Each of the basal ganglia nuclei – the striatum (caudate, putamen, nucleus accumbens), the globus pallidus externa (GPe) and internal (GPi), and the subthalamic nucleus (STN) – are organized into functionally related subregions that process motor (a, orange), associative/cognitive (b, green), and limbic (c, blue) information that are thought to aid in prioritization, selection, and regulation of movements, thoughts, and emotions. Shared dysregulation in the development and/or maintenance of these parallel CSTC circuits are thought to underlie the frequent co-occurrence of Tourette syndrome, OCD, and ADHD. (Figure reprinted from Jahanshahi et al. [2], and adapted from Rodriguez-Oroz et al. [13], Copyright (2009), with permission from Elsevier)

movements [5]. This somatotopic organization may correspond to clinical observations that tics generally present first in the eyes, head, and neck, with subsequent progression in more severe cases to involve arms and legs, as well as coordinated complex movements.

An additional component of CSTC circuit regulation is the anterior cingulo-insular network (aCIN), also known as the "salience network," which has been identified through functional neuroimaging studies to play a common role in psychiatric illness [6]. The salience network consists of core cortical regions/nodes, including the dorsal anterior cingulate cortex (dACC) and the left and right anterior insula, as well as corresponding non-motor regions of the basal ganglia, ventral tegmental

area (VTA) of the brainstem, and lateral cerebellum (i.e., the structural components of a CSTC circuit). This network is thought to mediate "top-down" processing ("cognitive control") as well as evaluation and prioritization of external and internal sensory and motivational cues, two higher-order processes that are disrupted in most psychiatric disorders. In the case of TS, OCD, and ADHD, the salience network could be conceived as acting (or failing to act) as a brake for lower-order dysregulated CTSC loops and could potentially mediate the frequently observed impairments in impulse control in the most severely affected TS patients.

As noted above, TS, like other neuropsychiatric conditions, is now viewed primarily as a developmental circuit disorder. In this context, neurotransmitter abnormalities in TS likely arise as a secondary result of dysfunctional CTSC circuits. Each of the three major neurotransmitter systems in the basal ganglia – dopaminergic projections from the substantia nigra and VTA to the striatum, excitatory glutamatergic projection neurons from cortex to striatum, as well as inhibitory GABAergic striatal projection neurons and intrinsic striatal interneurons – serves as the basis for the limited number of pharmacological treatments for TS. Typical and atypical neuroleptics acting at postsynaptic striatal projection neurons block the dopamine D2 receptor to slow circuit function; similarly, benzodiazepines act as GABA modulators to boost inhibitory components of CSTC circuits. Recent interest in glutamatergic compounds, such as topiramate for tics as well as memantine, riluzole, and N-acetylcysteine for OCD, have also arisen from observed abnormalities of neurotransmitter function in TS and/or OCD patients. However, the non-specific effects of these medications combined with incomplete knowledge of the primary pathophysiology of the disorder have resulted in high rates of side effects and treatment-refractory cases.

TS and OCD are both highly heritable and have been demonstrated to share a significant portion of genetic risk [1]. Of interest, recent cross-disorder, symptom-driven analyses in TS patients and their relatives suggest that symmetry, ordering/arranging, and counting obsessions/compulsions appear to correlate with aggregated TS genetic (polygenic) risk, while other OCD symptoms correlate best with aggregated OCD polygenic risk [3].

Treatment Strategies

In children and adolescents with TS, it is often the co-occurring conditions (e.g., OCD and ADHD) that cause the most impairment and more frequently require treatment compared to the tics themselves. That said, one often chooses to treat tics when they cause physical pain, social/functional/educational problems, and/or psychological distress. There are no disease-modifying treatments or cures for tics, and so behavioral and pharmacological treatment interventions are aimed at symptom reduction. Given the natural waxing and waning of tic severity and frequency, determining

treatment effectiveness can be challenging. There are only three medications that have US Food and Drug Administration (FDA) labeled indications for tics – haloperidol, pimozide, and aripiprazole. Thus, most pharmacological treatments are off-label [7].

Pharmacological treatment for tics should be conceptualized in three tiers, with each tier corresponding with increased efficacy but also a significant increase in side-effect risk.

Alpha-2 adrenergic receptor agonists (clonidine and guanfacine) represent first-tier treatments and are typically used for mild-to-moderate tics, especially with co-occurring ADHD. Unlike the common off-label use of nightly clonidine for sleep, alpha-2 agonists require at least twice daily dosing (or extended release formulations) to suppress tics. Atypical antipsychotics (specifically those with higher dopamine D2 receptor (D2R) potency such as risperidone, ziprasidone, and aripiprazole) are second-tier agents. The third tier is characterized by the typical antipsychotics with the highest D2R potency, specifically haloperidol, fluphenazine, and pimozide. These medications are typically quite effective, though are often not tolerated due to adverse effects.

Some specialists prefer to use tetrabenazine, a presynaptic vesicular monoamine transporter (VMAT2) inhibitor, as a second-tier alternative to atypical neuroleptics with little/no risk of tardive dyskinesia, though at higher doses this medication can cause significant sedation, weight gain, and parkinsonism and can precipitate depression in ~25% of patients. Other pharmacological agents have been trialed with mixed or limited efficacy including topiramate, benzodiazepines, baclofen, and cannabinoids.

The primary behavioral treatment for tics is Comprehensive Behavioral Intervention for Tics (CBIT) and involves habit reversal therapy (HRT) and function-based interventions, in addition to psychoeducation, parent training, and relaxation training. HRT is designed to help the patient develop an awareness of their tics (identify the premonitory urge) and then engage in a competing response that is incompatible with the tic (e.g. tensing shoulders for a shoulder-shrugging tic). Function-based interventions involve understanding and then modifying the contextual factors that may lead to increased tics. CBIT has been demonstrated in multicenter randomized controlled trials to be effective in both children/adolescents and adults, with a treatment effect comparable to that of atypical antipsychotics [8].

Pediatric OCD can be effectively treated with behavioral and pharmacological treatment interventions as well. The gold-standard behavioral treatment for OCD is a subtype of CBT called exposure and response prevention (ERP). In ERP, the patient is exposed to symptom-specific stimuli to provoke their obsessions and accompanying distress/anxiety and is then prevented from engaging in the associated compulsion/avoidance behavior. Serotonergic agents are currently the most effective pharmacological treatment for OCD, with selective serotonin reuptake inhibitors (SSRIs) being comparably effective and the gold standard first-line treatment. Clomipramine is superior to SSRIs in terms of OCD symptom reduction but has prominent side effects/increased risk of toxicity and thus is not used as first-line treatment. A landmark study (the Pediatric OCD Treatment Study) in 2004 demonstrated that for youth with at least moderate OCD, the combination of medication

(sertraline) and therapy (CBT) was superior to either medication or therapy alone, which were both superior to placebo [9]. Clinicians who specialize in treating OCD and tic-related OCD often find that these patients require doses of SSRIs at the upper end of approved ranges. Interestingly, multiple studies have demonstrated that tic-related OCD tends to be less responsive to SSRIs compared to OCD without tics. Meta-analyses in adults with tic-related OCD demonstrate that augmenting with antipsychotics, specifically risperidone, aripiprazole, and haloperidol, improves treatment response compared to augmenting with placebo. Thus, a similar approach is often used in children/adolescents who haven't responded to a combination of SSRIs and CBT [10].

For ADHD, several studies have now shown that stimulants are safe, well-tolerated, and effective in treating ADHD regardless of whether there is a co-occurring tic disorder. In 2002, the Tourette Syndrome Study Group evaluated the effect of methylphenidate (MPH), clonidine (CLON), clonidine and methylphenidate (COMB), or placebo on ADHD and tic symptoms in youth with ADHD and either TS or chronic tics (CT) [11]. They demonstrated that all three treatment groups were more effective for treating ADHD than placebo (MPH better for inattentive symptoms, CLON better for hyperactive/impulsive symptoms). Somewhat surprisingly, all three treatments *were also more effective in reducing tics* (COMB > CLON > MPH > placebo); transient tic worsening was observed in ~20% of all groups, including placebo. A meta-analysis in 2015 also concluded that stimulants were well-tolerated in youth with TS and that there was no significant association between new onset or worsening of tics and stimulant use [12]. Of note, at least one study has shown that amphetamine-based stimulants may lead to worse tic symptoms.

Case Follow-Up

After the initial meeting, Jackson is referred to a local psychologist who specializes in behavioral therapy for OCD (ERP) and tics (CBIT/HRT). However, given the severity of his symptoms and ongoing distress, his neuropsychiatrist also recommends that he simultaneously restart medication. Jackson's parents were not interested in starting an alpha-2 agonist or SSRI, given these medications' previous lack of response/adverse effects. Therefore, they are informed about the pros/cons and risks/benefits of starting an atypical antipsychotic (especially weight gain and potential metabolic sequelae). He is started on risperidone 0.5 mg first nightly and then twice a day, to target tics. Jackson notices almost immediate improvement in his simple tics and some of his complex tics; however, he continues to suffer from OCD, including his need for symmetry and ongoing "just right" compulsions. Given that SSRI-induced activation symptoms tend to be age-dependent and risperidone has mood-stabilizing qualities that might mitigate an SSRI-induced activation response, his parents agree to a very slow titration of sertraline, and the combination of SSRI, atypical antipsychotic, and behavioral therapy is ultimately very helpful. Two years later, with combined medication and behavioral therapy, Jackson's tics, OCD, and anxiety symptoms are all markedly improved, though he continues to have problems with inattention, distractibility,

and organization, particularly now that he has to change classrooms and keep track of his homework assignments himself in middle school. His neuropsychiatrist refers him for neuropsychological testing, which shows a high average IQ, ADHD combined subtype, and a specific learning disorder (seen in 20–30% of youth with TS). With these results, his parents work with his school to develop an Individualized Education Plan (IEP) to better support Jackson. Additionally, they are reminded that there is no longer a contraindication to using stimulants in those with TS and that he may have a better response to methylphenidate-based stimulants than to the mixed amphetamine salt stimulants he had tried in the past.

Lessons Learned About Neuropsychiatry

1. Tics are not *caused* by anxiety – the phrase "nervous tic" is an erroneous assumption that correlation is the same as causation. Through understanding that tics and OCD arise from abnormal development of parallel CSTC circuits that incorporate both internal mood states and the external environment, the neuropsychiatrist understands the biological basis and causes of tics and OCD, as well as the many triggers that cause symptom exacerbation.
2. While tics may be the reason parents bring children for consultation, co-occurring "hidden" neuropsychiatric disorders often cause greater impairment. In addition, since mood/anxiety symptoms and psychosocial dysfunction can exacerbate tics, treating the whole patient (and family) is often necessary for treatment-refractory TS.

Clinical Pearls

- Thirty to fifty percent of youth with TS have co-occurring OCD. For children and adolescents with tic-related OCD whose OCD symptoms don't respond to SSRI monotherapy, it may be beneficial to augment with antipsychotic treatment.
- "Tourettic" OCD appears to have a distinct phenotypic profile with younger age of OCD symptom onset, aggressive/taboo obsessions, and "just right," symmetry, and counting compulsions. Its genetic architecture appears to be more similar to TS than to OCD without tics.
- Differentiating between complex tics and compulsions in tic-related OCD can be challenging and often represents an overlap of both disorders. In general, compulsions are driven by the need to eradicate or avoid thoughts/feelings of anxiety or disgust, and tics are driven by uncomfortable internal sensory phenomena (premonitory urges).
- Stimulants are no longer absolutely contraindicated for treating youth with TS and co-occurring ADHD (especially methylphenidate-based stimulants). Stimulants are least likely to exacerbate tics when started at subthreshold doses and increased slowly, either alone or combined with alpha-2 agonists.

References

1. Robertson MM, Eapen V, Singer HS, Martino D, Scharf JM, Paschou P, et al. Gilles de la Tourette syndrome. Nat Rev Dis Prim. 2017;3:16097. Epub 2017/02/06. https://doi.org/10.1038/nrdp.2016.97. PubMed PMID: 28150698.
2. Jahanshahi M, Obeso I, Rothwell JC, Obeso JA. A fronto-striato-subthalamic-pallidal network for goal-directed and habitual inhibition. Nat Rev Neurosci. 2015;16(12):719–32. Epub 2015/11/05. https://doi.org/10.1038/nrn4038. PubMed PMID: 26530468.
3. Darrow SM, Hirschtritt ME, Davis LK, Illmann C, Osiecki L, Grados M, et al. Identification of two heritable cross-disorder endophenotypes for Tourette syndrome. Am J Psychiatry. 2017;174(4):387–96. Epub 2016/11/05. https://doi.org/10.1176/appi.ajp.2016.16020240. PubMed PMID: 27809572; PubMed Central PMCID: PMC5378637.
4. Hirschtritt ME, Lee PC, Pauls DL, Dion Y, Grados MA, Illmann C, et al. Lifetime prevalence, age of risk, and genetic relationships of comorbid psychiatric disorders in Tourette syndrome. JAMA Psychiat. 2015;72(4):325–33. Epub 2015/02/12. https://doi.org/10.1001/jamapsychiatry.2014.2650. PubMed PMID: 25671412; PubMed Central PMCID: PMCPMC4446055.
5. Romanelli P, Esposito V, Schaal DW, Heit G. Somatotopy in the basal ganglia: experimental and clinical evidence for segregated sensorimotor channels. Brain Res Brain Res Rev. 2005;48(1):112–28. Epub 2005/02/15. https://doi.org/10.1016/j.brainresrev.2004.09.008. PubMed PMID: 15708631.
6. Downar J, Blumberger DM, Daskalakis ZJ. The neural crossroads of psychiatric illness: an emerging target for brain stimulation. Trends Cogn Sci. 2016;20(2):107–20. Epub 2015/12/15. https://doi.org/10.1016/j.tics.2015.10.007. PubMed PMID: 26655436.
7. Whittington C, Pennant M, Kendall T, Glazebrook C, Trayner P, Groom M, et al. Practitioner review: treatments for Tourette syndrome in children and young people – a systematic review. J Child Psychol Psychiatry. 2016;57(9):988–1004. Epub 2016/05/03. https://doi.org/10.1111/jcpp.12556. PubMed PMID: 27132945.
8. Piacentini J, Woods DW, Scahill L, Wilhelm S, Peterson AL, Chang S, et al. Behavior therapy for children with Tourette disorder: a randomized controlled trial. JAMA. 2010;303(19):1929–37. Epub 2010/05/21. https://doi.org/10.1001/jama.2010.607. PubMed PMID: 20483969; PubMed Central PMCID: PMC2993317.
9. Pediatric OCD Treatment Study (POTS) Team. Cognitive-behavior therapy, sertraline, and their combination for children and adolescents with obsessive-compulsive disorder: the Pediatric OCD Treatment Study (POTS) randomized controlled trial. JAMA. 2004;292(16):1969–76. Epub 2004/10/28. https://doi.org/10.1001/jama.292.16.1969. PubMed PMID: 15507582.
10. Bloch MH, Storch EA. Assessment and management of treatment-refractory obsessive-compulsive disorder in children. J Am Acad Child Adolesc Psychiatry. 2015;54(4):251–62. Epub 2015/03/21. https://doi.org/10.1016/j.jaac.2015.01.011. PubMed PMID: 25791142; PubMed Central PMCID: PMC4460245.
11. Tourette Syndrome Study Group. Treatment of ADHD in children with tics: a randomized controlled trial. Neurology. 2002;58(4):527–36. Epub 2002/02/28 PubMed PMID: 11865128.
12. Cohen SC, Mulqueen JM, Ferracioli-Oda E, Stuckelman ZD, Coughlin CG, Leckman JF, et al. Meta-analysis: risk of tics associated with psychostimulant use in randomized, placebo-controlled trials. J Am Acad Child Adolesc Psychiatry. 2015;54(9):728–36. Epub 2015/08/25. https://doi.org/10.1016/j.jaac.2015.06.011. PubMed PMID: 26299294.
13. Rodriguez-Oroz MC, Jahanshahi M, Krack P, Litvan I, Macias R, Bezard E, Obeso JA. Initial clinical manifestations of Parkinson's disease: features and pathophysiological mechanisms. The Lancet. 2009;8:1128–39.

"Depression" After Hypoxic-Ischemic Injury

4

Tzvi Furer, Aaron J. Hauptman, and Lindsey Gurin

Case

Ronald is a 16-year-old male with a history of Hashimoto's thyroiditis, depression, and opioid substance use disorder as well as a history of marijuana and cocaine use, who presented with a serious drug overdose requiring hospitalization after he was found unresponsive. His pulse was detectable on initial discovery but he was noted to be cyanotic with minimal respirations and respiratory resuscitation was initiated while awaiting emergency services. On arrival, Ronald was given intranasal naloxone 2 mg with subsequent improvement in spontaneous respiration. Ronald had jerking movements concerning for seizures and required multiple doses of diazepam and subsequent intubation with etomidate. On arrival to the emergency department, Ronald had a Glasgow coma score (GCS) of 6 with sluggish but reactive pupils, and he was intubated. Initial labs indicated his serum pH was 7.14 with an elevated partial pressure of carbon dioxide (pCO2) of 74 and serum lactate of 6.2. Serum creatinine was 2.1. Seizure was suspected and he was given a loading dose of fosphenytoin. Epinephrine was initiated for hypotension with systolic blood pressures in the 80s. Urine drug screen was positive for cocaine, benzodiazepines, opioids, and cannabinoids.

Initial computed tomography (CT) scan of the head showed intact differentiation of the gray and white matter without edema or hemorrhage. Magnetic resonance imaging (MRI), shown in Figs. 4.1 and 4.2, revealed numerous foci of acute

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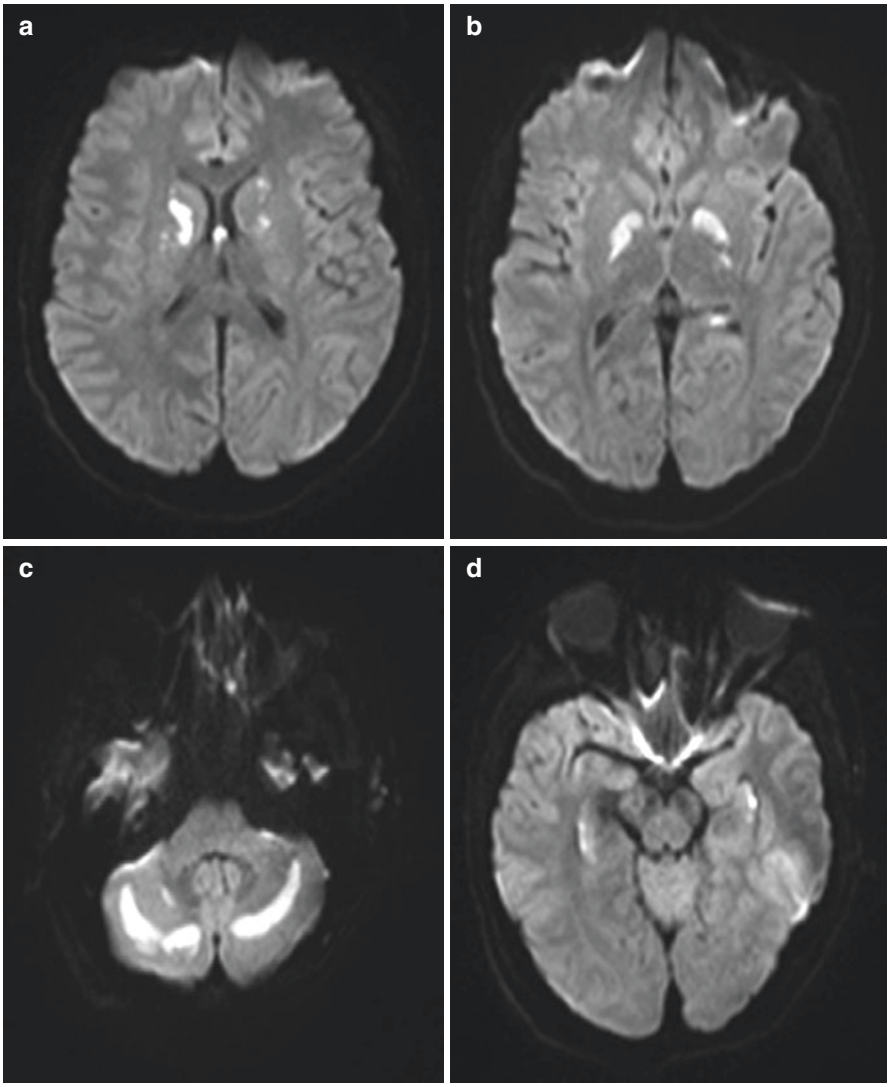

Fig. 4.1 MRI diffusion-weighted imaging (DWI) sequence demonstrates acute infarcts in the basal ganglia (**a**) and specifically in the globus pallidus bilaterally (**b**), as well as in the bilateral cerebellar hemispheres (**c**) and mesial temporal lobes (**d**)

infarction in a symmetric distribution in the bilateral basal ganglia including the caudate and globus pallidus, as well as in the bilateral cerebellar hemispheres, subcortical white matter, corticospinal tracts, and mesial temporal lobes.

Ronald's level of consciousness gradually improved. He was noted by the pediatrics team to be affectively flat and confused. Pediatric psychiatry was consulted to evaluate for possible depression and delirium. History from Ronald's family

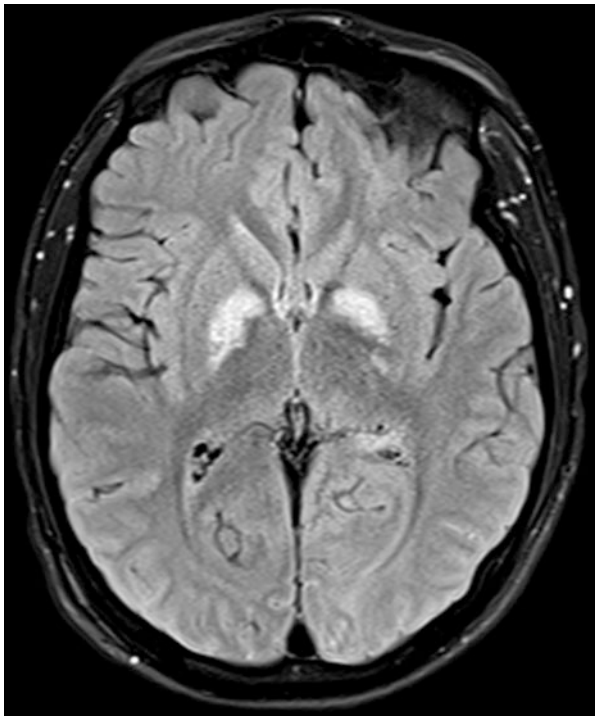

Fig. 4.2 MRI fluid-attenuated inversion recovery (FLAIR) sequence demonstrates hyperintensities in the globus pallidus bilaterally

indicated that he had a similar overdose of multiple substances (likely including cocaine, marijuana, and opioids) about 5 weeks prior to this presentation. At the time of this prior overdose, Ronald had been admitted to the inpatient pediatric psychiatry service for 3 weeks and started on citalopram, a selective serotonin reuptake inhibitor antidepressant. His family reported the medication to have been previously effective for his depression at a dose of 40 mg.

On evaluation by pediatric psychiatry, Ronald was noted to be drowsy, cognitively slowed, and disoriented to time and place. His affect was flat but he denied depressed mood. He struggled to describe or define his subjective emotional states, which was reported by his clinical team as a demonstration of alexithymia. His sleep and appetite were normal. It was recommended that his opioid analgesia be tapered, if possible, due to probable contribution to delirium. Lorazepam, prescribed to prevent benzodiazepine withdrawal, was converted to clonazepam, which was then tapered gradually. Despite persistence in affective flattening as his medical picture improved, Ronald continued to deny depressed mood and he repeatedly denied intentional overdose of substances.

Given his medical stability, he was discharged to acute inpatient rehabilitation, where he continued to improve. Pediatric neurology was consulted for abnormal movements which emerged primarily after completion of his clonazepam taper. These movements were described by the patient's family as intermittent writhing movements of the upper body and one or both arms at various times with occasional abrupt jerking movements. There were also occasional twisting movements of his

legs at night. There were no rhythmic movements that would have suggested seizures. Ronald was not bothered by these movements. His voice was quieter, and he was noted to be speaking less than his reported baseline. When ambulating, he would sometimes fall backwards.

Ronald's neurological exam was notable for flat affect with reduced facial expressivity (hypomimia), slowness of movement (bradykinesia), slowness of thought (bradyphrenia), and reduced vocal volume (hypophonia). No choreoathetotic movements were observed, but physical examination did reveal intermittent brief myoclonic jerks in the hands and arms. He was dysmetric on coordination testing, greater on the left side than on the right. Ronald's gait was noted initially to be significant for shortened steps, an anteriorly flexed posture, and a tendency toward retropulsion, and reduced arm swing bilaterally, though these features improved over his several weeks in inpatient rehabilitation. The clinical impression at that time was of a mixed movement disorder with parkinsonian features and choreoathetoid movements due to bilateral basal ganglia injury as well as a post-hypoxic myoclonus syndrome ("Lance-Adams myoclonus"). It was thought that clonazepam had likely been masking these movements prior to its taper. Neurocognitive and affective features including cognitive slowing (bradyphrenia), flat affect, and decreased spontaneous speech and behavior were also attributed primarily to the basal ganglia injury.

Given his clinical constellation of symptoms, Ronald did not appear to be demonstrating an adjustment disorder with depressed mood or major depressive disorder, but rather was exhibiting sequelae of basal ganglia injury. Dopamine replacement therapy was offered for treatment of parkinsonian cognitive and motor features but Ronald's parents opted against this. Ronald continued to improve clinically, and follow-up MRI at 1 year from the incident showed near complete resolution of the FLAIR hyperintense lesions involving the bilateral basal ganglia and cerebellar hemispheres, with only a small amount of encephalomalacia noted in the bilateral globus pallidus and caudate consistent with ischemic injury. On follow-up with his neurologist, he was noted to have some residual bradykinesia, mild hypophonia, and decreased facial expression, but he no longer had any abnormal involuntary movements.

Neuroanatomy and Pathophysiology

Hypoxic-ischemic brain injury in the setting of circulatory arrest typically produces injury in those brain areas which are most metabolically active or which exist at the border zones of cerebrovascular territories. The CA1 neurons of the hippocampus are highly vulnerable, as are the Purkinje cells of the cerebellum and pyramidal neurons in layers 3, 5, and 6 in the neocortex; the reticular neurons of the thalamus and medium-sized neurons of the striatum can also be affected [1]. While brain injuries due to purely hypoxic events are often grouped with those related to cardiac arrest for ease of discussion, pure hypoxia may induce functional neuronal changes without causing cell death, leading to better recovery potential as compared to

cardiac arrest. Pure hypoxia, which most often occurs in the setting of intoxication or obstructive airway events, tends to affect a younger population with less cerebrovascular disease on average. Perhaps even more importantly, in these cases, because circulation is preserved, nutrients and waste products can still be brought to and from the neurons, helping to maintain a more hospitable local environment than is seen after complete circulatory collapse [1]. In these cases, initial imaging may appear similar to that seen in hypoxic-ischemic injury but tends to evolve and improve over time [2].

Based on all available information, it is likely that Ronald experienced a primarily hypoxic event. The basal ganglia appear to be especially susceptible to prolonged hypoxia, with globus pallidus injury described most frequently in the setting of carbon monoxide poisoning and other substance intoxications. Clinical parkinsonism commonly follows this type of injury, with a classic "akinetic-rigid" motor syndrome described in which patients demonstrate varying degrees of bradykinesia, micrographia, axial rigidity, resting or postural tremor, and postural instability [3]. These findings may improve over time, correlating to improvement seen on neuroimaging.

The basal ganglia are suspected to be involved in regulation of mood as part of its function within the cortical-basal ganglia-thalamo-cortical loop [4]. The globus pallidus is a key part of this circuit, and its injury appears to be one of many possible ways in which depressive symptoms can occur in the context of basal ganglia injury [3]. A classic example of depressive symptomatology seen in basal ganglia injury is described in Parkinson's disease (PD). In PD, depression is suspected to occur, in part, as a result of decreased dopaminergic stimulation of the orbitofrontal prefrontal cortex which interferes with prefrontal serotonergic cortical connections. Depression in PD is associated with poor fronto-executive cognitive function and bradykinesia, bradyphrenia, hypomimia, hypophonia, and tremor. These signs and symptoms are particularly unusual to see in children and adolescents who are not taking neuroleptics. As a result, symptomatic sequelae of basal ganglia injury would likely be lower on the differential diagnosis for clinicians than they might have been in an older individual [5].

Intact anterior cingulate circuitry appears to be necessary for goal-motivated behaviors. Reduced activity in this region can contribute to diminished self-awareness, depression, motor neglect, and akinetic mutism [6]. The globus pallidus forms part of a circuit with the anterior cingulate cortex and appears to be necessary for these functions to remain intact. The neuropsychiatric presentation of bilateral pallidal lesions has been described as "psychic akinesia," marked by prominent apathy and anhedonia with limited initiation of behavior. Injury elsewhere along the circuitry functionally connected to the anterior cingulate circuit results in apathy, lack of motivation, alexithymia, and amotivation [7, 8]. Alexithymia, the inability to access or report subjective emotional experience, may develop because of an interruption in the anterior cingulate cortex, the dorsal pons, cerebellum, and left dorsolateral prefrontal cortex as well as bilateral globus pallidus injury [7, 9–11].

In addition to Ronald's basal ganglia injury, it should be noted that he had bilateral cerebellar ischemia as well. There is evidence that involvement of the cerebellar hemispheres in this case may have also possibly contributed to his affective symptoms. Patients with "cerebellar cognitive affective syndrome (CCAS)" have been described as having personality changes with affective blunting correlating with lesions involving the posterior lobe of the cerebellum and vermis [12].

This case is an excellent demonstration of how disruption in circuitry that includes the globus pallidus elicits symptoms that largely overlap with the appearance of depression but differ due to lack of subjective depressive symptoms, alexithymia, and motoric symptoms of parkinsonism. Ronald's lack of subjective expression of depressed mood, anhedonia, or other subjective symptoms that make up the diagnostic criteria for major depressive disorder provide significant evidence for this.

Treatment Strategies

Depression in the setting of parkinsonian symptoms may need to be treated differently than the other diagnoses on the differential for this patient, namely, an underlying mood disorder, adjustment disorder with depressed mood, and a substance-induced mood disorder. Levodopa and dopamine agonists, the mainstays of idiopathic Parkinson's disease treatment, can be tried for the akinetic-rigid motor syndrome but generally are not helpful [3, 13], consistent with the literature on vascular parkinsonism more generally [14]. While antidepressants continue to be recommended for management of depression in parkinsonism, the prevailing logic at this time is that, since depression is a comorbid syndrome associated with the various motor symptoms, dopamine agonists may be helpful in targeting involved mesocortical and mesolimbic pathways [13].

Specific components of this patient's syndrome may be addressed and treated individually, such as alexithymia, amotivational syndrome, and abulia. Unfortunately, alexithymia is not as easily targeted as the core major depressive symptoms may be [7]. There is no specific recommended treatment for alexithymia; however, some evidence exists for use of antidepressants, with some particular reports of benefit with venlafaxine, a dual serotonin and norepinephrine reuptake inhibitor. There are also reports of benefits from deep brain stimulation [15–17].

Neuropsychiatry Lessons

Overall, the globus pallidus is generally relatively spared in hypoxic-ischemic injury as compared to the caudate and putamen, with bilateral pallidal infarcts most commonly associated with prolonged hypoxia and intoxications such as carbon monoxide poisoning and opioid, MDMA (3,4-methylenedioxymethamphetamine), and cocaine toxicity. In addition to basal ganglia injury, bilateral acute complete

hippocampal ischemia with anterograde amnesia syndrome has also recently been reported in a number of cases of opioid overdose and is not unexpected following hypoxic injury [18].

Ronald demonstrates the classic challenge in pediatric neuropsychiatry of differentiating an underlying psychiatric condition from mood and other sequelae of an acquired brain injury. This patient's complexity and challenging premorbid history further complicated both diagnostic and treatment efforts. His case also exemplifies the extent to which sometimes symptomatic management often must diverge from classic evidence-based treatment due to a lack of data on the management of such patients.

Ronald was initially seen by pediatric psychiatry for assessment of "depression"; however, depression has manifestations that overlap with numerous specific neurological insults. Thus, if symptoms of depression are present in a brain-injured patient, it is important to investigate the location of structural damage associated with the patient's neuropsychiatric presentation in order to differentiate a primary psychiatric illness or reactive adjustment symptoms from a secondary neuropsychiatric syndrome.

Subjective feelings of depression or anhedonia are necessary for a primary psychiatric diagnosis of major depressive disorder [19]. Poststroke depression has been found to correlate with infarctions within specific substrates of the prefrontal-subcortical circuits, such as the caudate and pallidum [20]. Apathy, which can be seen both in depression and prefrontal or subcortical injury, also manifests as an observable behavioral syndrome that results in a noticeable reduction of goal directed or voluntary behaviors [21].

Common between apathy and depression are shared motivational deficits, along with lack of concern and emotional indifference [22]. However, an important distinction between apathy and depression is that those with depression are, in fact, more effortful with their voluntary actions compared to normal subjects [23, 24]. A further complication is that apathy and depression can be comorbid in brain injury due to a disruption in frontal-subcortical circuits.

Regarding Ronald, there was high suspicion for depression based on his history of treated depression and multiple drug overdoses. However, he denied all subjective depressive symptoms and did not demonstrate any typical depressive neurovegetative changes. It was thought most likely that his "depressed" appearance represented apathy and parkinsonism related to basal ganglia injury and that these symptoms would be best targeted through dopaminergic therapies rather than antidepressants. It is evident why depressive symptoms would be of significant concern based on his history, and whether treatment would be recommended, especially based on success of his previous trial of citalopram. However, on detailed examination, despite having a depressed affect and external appearance of depression, he reported no subjective phenomenology consistent with major depressive disorder or other forms of depression.

Ronald, like many individuals with acquired brain injury that impacts frontal and subcortical circuitry, struggled both with behavioral motivation and the ability to describe his emotional states. This absolutely complicates his

diagnosis. A multidisciplinary approach, combining both a detailed neuropsychiatric evaluation and a detailed neurological examination, helped provide key data points which helped better categorize and understand the patient's unusual presentation. Crucially, the one area of his physical and mental examination that showed consistency was that he never described what is classified as classic depression, persistently presenting without any clear suicidality, appetite or sleep changes, excessive guilt, change in interest level, anhedonia, or significantly depressed mood. The energy and psychomotor changes that Ronald did experience, which can be seen in depression, were better attributable to his neurological insult.

The 1-year follow-up MRI demonstrating interval resolution of the majority of the diffusion-restricting lesions lends support to the hypothesis that Ronald experienced a purely hypoxic injury in which there was multifocal transient neuronal dysfunction which ultimately did not evolve to cell death outside of a few small areas of encephalomalacia in the basal ganglia bilaterally. With the help of the patient's supportive family, and extensive participation in physical therapy and rehabilitation, he continues to show much improvement in many areas.

Clinical Pearls

- Bilateral globus pallidus injury is a rare effect of opioid overdose that can mimic signs of depressive syndromes but that lacks subjective depressive phenomenology and also includes symptoms of parkinsonism, apathy, and alexithymia. Bilateral hippocampal lesions from overdose of opioids can also result in an atypical anterograde amnesia syndrome [18].
- Alexithymia and depression differ symptomatically and in treatment effects. While major depression classically improves with psychotherapy and antidepressant intervention, alexithymia characteristically benefits minimally, though it may benefit from SNRI treatment or deep brain stimulation.
- In certain cases, the use of specific dopamine agonists can assist in treating depression with associated parkinsonian symptoms. Still, SSRIs are most effective in treating symptoms of depression.
- Lesions of the medial and posterior cerebellum can present with blunted affect or increased impulsivity, known as "cerebellar cognitive affective syndrome" (CCAS) [12].
- Care must be taken in the diagnosis and treatment of individuals with symptoms of a primary psychiatric illness in the presence of a known or suspected neuroanatomical lesion and must be evaluated thoroughly using a cross-disciplinary approach.

References

1. Busl KM, Greer DM. Hypoxic-ischemic brain injury: pathophysiology, neuropathology, and mechanisms. NeuroRehabilitation. 2010;26:5–13.
2. Vendrame M, Ausim Azizi S. Pyramidal and extrapyramidal dysfunction as a sequela of hypoxic injury: case report. BMC Neurol. 2007;7:18.
3. Lu-Emerson C, Khot S. Neurologic sequelae of hypoxic-ischemic brain injury. NeuroRehabilitation. 2010;26:35–45.
4. Lafer B, Renshaw PF, Sachs GS. Major depression and the basal ganglia. Psychiatr Clin N Am. 1997;20(4):885–96.
5. Ring H, Serra-Mestres J. Neuropsychiatry of the basal ganglia. J Neurol Neurosurg Psychiatry. 2002;72(1):12–21.
6. Devinsky O, Morrell MJ, Vogt BA. Contributions of anterior cingulate cortex to behaviour. Brain. 1995;118(1):279–306.
7. Huang MF, Yeh YC, Tsang HY, Chen CS. Alexithymia associated with bilateral globus pallidus lesions after carbon monoxide poisoning. Kaohsiung J Med Sci. 2010;26(6):333–6.
8. Starkstein SE, Bertheir ML, Leiguarda R. Psychic akinesia following bilateral pallidal lesions. Int J Psychiatry Med. 1989;19(2):155–64.
9. Buchanan DC, Waterhouse GJ, West SC Jr. A proposed neurophysiological basis of alexithymia. Psychother Psychosom. 1980;34:248–55.
10. Moriguchi Y, Decety J, Ohnishi T, Maeda M, Mori T, Nemoto K, Matsuda H, Komaki G. Empathy and judging other’s pain: an fMRI Study of Alexithymia. Cereb Cortex. 2007;17(9):2223–34.
11. Paul LK, Brown WS, Adolphs R, Tyszka JM, Richardsd LJ, Mukherjee P, Sherr EH. Agenesis of the corpus callosum: genetic, developmental and functional aspects of connectivity. Nat Rev Neurosci. 2007;8:287–99.
12. Schmahmann JD, Sherman JC. The cerebellar cognitive affective syndrome. Brain. 1998;121:561–79.
13. Leentjens AF. The role of dopamine agonists in the treatment of depression in patients with Parkinson’s disease: a systematic review. Drugs. 2011;71(3):273–86.
14. Miguel-Puga A, Villafuerte G, Salas-Pacheco J, Arrias-Carrion O. Therapeutic interventions for vascular parkinsonism: a systematic review and meta-analysis. Front Neurol. 2017;8:481.
15. Assogna F, Cravello L, Orfei MD, Cellupica N, Caltagirone C, Spalleta G. Alexithymia in Parkinson’s disease: a systematic review of the literature. Parkinsonism Relat Disord. 2016;16:1–11.
16. Castelli L, Tonello D, Rizzi L, Zibetti M, Lanotte M, Lopiano L. Alexithymia in patients with Parkinson’s disease treated with DBS of the subthalamic nucleus: a case-control study. Front Psychol. 2014;5:1168.
17. Sjoberg RL, Blomstedt P. The psychological neuroscience of depression: implications for understanding effects of deep brain stimulation. Scand J Psychol. 2011;52(5):411–9.
18. Barash JA, Somerville N, Demaria A Jr. Cluster of an unusual amnestic syndrome-Massachusetts 2012–2016. MMWR Morb Mortal Wkly Rep. 2017;66(3):76–9.
19. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington: American Psychiatric Publishing; 2013.
20. Vataja R, Leppavuori A, Pohjasvaara T, Mantyla R, Aronen HJ, Salonen O, Kaste M, Erkinjuntti T. Poststroke depression and lesion location revisited. J Neuropsychiatry Clin Neurosci. 2004;16(2):156–62.

21. Levy R, Dubois B. Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. Cereb Cortex. 2006;16(7):916–28.
22. Andersson S, Krogstad JM, Finset A. Apathy and depressed mood in acquired brain damage: relationship to lesion localization and psychophysiological reactivity. Psychol Med. 1999;29:447–56.
23. Hartlage S, Alloy LB, Vazquez C, Dykman B. Automatic and effortful processing in depression. Psychol Bull. 1993;113(2):247–78.
24. Harvey P-O, Fossati P, Pochon J-B, Levy R, LeBastard G, Lehericy S, Allilaire J-F, Dubois B. Cognitive control and brain resources in major depression: an fMRI study using the *n*-back task. NeuroImage. 2005;25(3):860–9.

The Role of the Posterior Fossa in Pediatric Neuropsychiatry

5

Katherine C. Soe, Cassie D. Karlsson, and David W. Dunn

Case

Johnny is a 15-year-old male with a history of posterior fossa juvenile pilocytic astrocytoma, resected at ages 2 and 9 years old, as well as anxiety, epilepsy, and mild intellectual disability. He presented for inpatient psychiatric admission due to escalating aggression and hallucinations. On arrival, he somersaulted across the floor into the bathroom. He believed he was a superhero and said that he learned his moves from gymnastics or the military, though he had participated in neither activity. He then took off his shirt, saying "I need to take off my shirt...I'm on fire." Parents said this was not their Johnny as they knew him. He was redirectable and replaced his shirt when asked to do so.

He appeared to be responding to internal stimuli, talking to himself at length, frequently looking askance, closing his eyes, and blowing on his hands in various positions. He responded to questions with "we" or "they," saying he heard voices telling him to "push on pressure points" or to hurt others. He claimed to be "from a magic place, The Lockers," and reported living with his parents. Johnny knew he was in the hospital but was not oriented to time. He voiced that he "holds everybody up" and, when asked if he feels safe, stood up and walked away.

Johnny's birth history was unremarkable. His early growth and development were within normal limits with the exception of a delay in walking. He underwent workup for this gross motor delay at 23 months of age, when scans showed a posterior fossa cystic lesion resulting in obstructive hydrocephalus. Neurosurgery placed a ventroperitoneal shunt and performed a subtotal resection of the lesion, ultimately

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found to be a juvenile pilocytic astrocytoma. The shunt was revised 1 year later due to proximal shunt obstruction, after Johnny showed some mutism with paucity of speech and mouth movement. This improved with inpatient speech therapy rehabilitation.

Johnny continued to develop well until 6 years later, at 9 years old, a routine MRI showed large tumor growth, so a second surgery was done which achieved near-total resection. A small tumor burden remained in the upper cerebellar vermis. He underwent 2 years of chemotherapy, which he completed at age 10. He recovered well, and could perform activities of daily living, had clear coherent speech, and loved video games.

About 8 months prior to presentation, teachers noticed Johnny becoming very quiet and seeming more depressed. He started to experience staring spells, drooling, and episodic urinary and bowel incontinence. He had behavioral outbursts in class which was previously unusual for him, as well as worsening memory problems and mild intermittent headaches. He presented to the emergency department (ED) where an X-ray shunt series was unremarkable and brain MRI without contrast showed stable residual tumor in the cerebellar vermis, unchanged from several months prior.

A month later, Johnny's parents noticed marked inattentiveness and distractibility, posturing, tensing and flexing muscles, decreased appetite, difficult-to-understand speech, and disinterest in video games. This gradually worsened over the next 3 months, resulting in four more ED visits for hypertonia and posturing, holding his saliva, behavior outbursts, and confusion. Each time, X-ray shunt series, MRI without contrast, and basic labs were unchanged. Neurological exam suggested voluntary hypertonia, and 24-h video electroencephalography (EEG) showed mild encephalopathy consistent with known postoperative changes but no epileptiform activity. He was diagnosed with psychogenic non-epileptic seizures (PNES), and follow-up was scheduled with outpatient psychiatry. By this point, he was no longer able to function or behave well enough to attend life skills classes in school. Parents called multiple facilities in attempts to obtain therapy for Johnny, but he was denied for unclear reasons, and parents did not believe he could safely participate in group therapy.

Given the severity of his behavioral outbursts, Johnny was given risperidone 0.5 mg. Unfortunately, his parents felt this made his aggression worse, and it was discontinued after 3 days. The constellation of negative symptoms, EEG findings and lack of antipsychotic response raised concern for catatonia, which was treated with lorazepam 2.5 mg daily, with no observable effect. His aggression escalated, such that about 3 weeks prior to our encounter with him, the patient was admitted to a community inpatient psychiatric facility for 3 days. However, he was reportedly not aggressive while there and was discharged on valproic acid 250 mg three times daily.

Clinical Pearl #1: Recognizing the Cerebellar Cognitive Affective Syndrome
Cognitive and emotional disorders may accompany motor impairment in known cerebellar disease or may be the initial presentation of underlying cerebellar dysfunction. Recognizing the clinical presentation of cerebellar cognitive affective syndrome (CCAS), also known as Schmahmann's syndrome, may provide key clues to diagnosis, as well as potential treatment options. The core features of the CCAS include impairments in executive function (planning, verbal fluency, abstract reasoning, working memory), visual-spatial function (organization and memory), and language (agrammatism and aprosodia). It also includes affective disturbances ranging from emotional blunting and depression to disinhibition and psychotic features [1].

After discharge, Johnny's parents felt his aggression improved for a few days but then significantly worsened. His parents started noticing increased anxiety, aggression toward family, anger outbursts, and combative and argumentative behaviors throughout the day. They complained that he was sleeping less with frequent nocturnal awakenings, would talk nonstop as though someone else was there, and would cry or shout spontaneously. He would explain "we are all crying" when parents asked what was wrong. He threatened to kill his family, cursed, and had more frequent urinary and bowel incontinence.

Over the weeks prior to admission, Johnny started hitting, kicking, and biting, which he had never done before, and became resistant to verbal de-escalation. On one occasion, Johnny hit his mother, then grabbed a kitchen knife, and held it toward his body in a gesture of threatening self-harm. Following that incident, evaluation in the ED revealed that his CT head was unchanged, but his valproic acid level was sub-therapeutic, so the dosage was increased to 500 mg twice daily, and quetiapine 50 mg twice daily was added. Johnny was referred for a partial hospitalization program. On intake examination, his behavior suggested florid psychosis, and so he was admitted to the inpatient psychiatry unit for further evaluation.

Hospital and Disease Course

Johnny presented with active psychosis including grandiose delusions, auditory and visual hallucinations, and bizarre and agitated behavior. He also continued to evidence depressed mood, anhedonia, and poor appetite and sleep.

His extensive medical workup was relatively unremarkable and included a complete blood count with mild anemia, but complete metabolic panel, thyroid, urine,

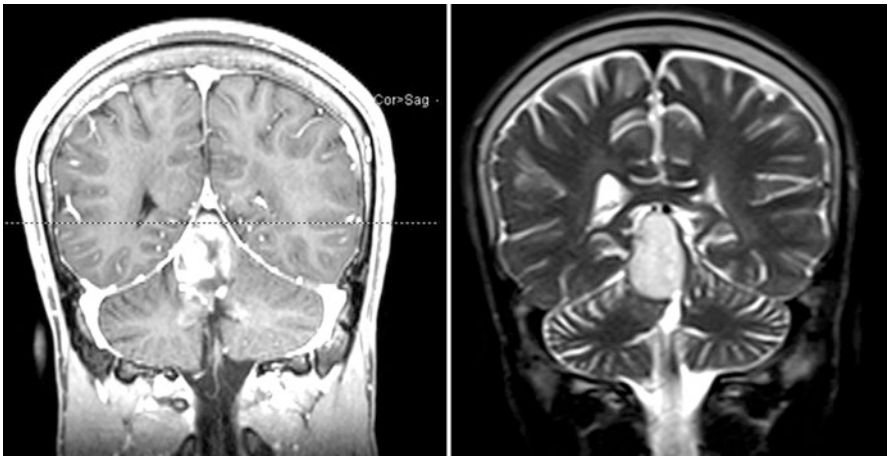

Fig. 5.1 MRI on admission (left) compared to 3 months prior (right) showed postsurgical changes of suboccipital craniectomy with unchanged mass effect on the remaining posterior fossa structures and unchanged lateral, third, and fourth ventricle sizes. Mild interval enlargement of solid enhancing residual/recurrent tumor in the superior vermis, compared to 6 months prior. No new FLAIR signal abnormality. Gliosis from prior treatment is seen

ammonia, copper and ceruloplasmin, serum and cerebral spinal fluid autoimmune markers, viral and meningoencephalitis and paraneoplastic panels, and X-ray shunt series were all normal. A repeat brain MRI with and without contrast showed mildly increased interval residual solid and cystic mass size, unchanged mass effect on the ventricles, and no acute process (Fig. 5.1). Neurosurgery, neurology, and hematology oncology teams also felt the results of the workup could not explain his symptoms.

Quetiapine was discontinued upon admission due to inefficacy. Valproic acid was tapered and discontinued given its lack of benefit despite a therapeutic valproic level of 66 μg/ml. Olanzapine 5 mg was started and titrated to 20 mg daily, with small but short-lived benefit.

In light of his poor response to three different antipsychotics, and persistent symptoms, lithium was initiated. Within 2 days, marked improvements were noted. He slept more regularly, spoke much less to himself, made significantly fewer bizarre gestures, wrote his name correctly, and was oriented to person, place, and time. His eye contact improved, affect was congruent with his stated mood, and he smiled and laughed appropriately, demonstrating a linear and goal-directed thought process. Johnny's delusions improved significantly and he rarely replied with "we" when referring to himself. Given his temporary and partial improvement with olanzapine, but significant, rapid, and consistent improvement with lithium, the patient was diagnosed with bipolar I disorder with acute manic episode with mood-congruent psychotic features.

Clinical Pearl #2: Lithium Use in Children with Neuropsychiatric Disorders
Lithium's efficacy in treating affective symptoms in the setting of both bipolar disorder and depression is well established. Psychiatric symptoms in patients with neurodevelopmental or neuropsychiatric disorders can create diagnostic challenges, as they may not always follow classical descriptions of known disorders. However, it remains important to recognize key affective symptoms which may indicate potential response to specific treatments. For instance, one retrospective chart review showed benefit when lithium was used in the treatment of children with autism spectrum disorders who exhibited two or more mood disorder symptoms, particularly euphoria/elevated mood [2]. Similarly, another case described a 45-year-old male with manic psychosis in the setting of metastatic cerebellar brain tumors, who also responded well to lithium [3]. Lithium's mechanism of action is not well understood, and its role in treating cerebellar affective symptoms is unknown. However, recognizing symptoms of mania in patients with neuropsychiatric disease may lead to consideration of lithium as a treatment of choice, even without classic presentation of bipolar disorder.

Discharge medications included only lithium extended release 450 mg twice daily and olanzapine 20 mg every night. Nearly 1 year after hospital discharge, Johnny remains stable on the same dose of lithium 450 mg twice daily and 20 mg daily of olanzapine, without recurrence of manic symptoms, hallucinations, anxiety, or depression. He reports enjoying school. Parents say he does well in special education classes at school and has no behavior concerns at home or school. He is sleeping well and speaks clearly and logically, though parents have noticed mild short-term memory loss.

Diagnostic Impression

Psychiatric symptoms of mania and psychosis are well documented preceding or co-occurring with new pediatric primary brain tumor diagnoses; however, such acute psychiatric symptoms have rarely arisen several years after resection, in the setting of stable, residual tumors. Posterior fossa tumors, which account for 60% of pediatric brain tumors, are typically surgically resected. Studies of long-term neuropsychiatric sequelae have thus far emphasized the impact of tumor histopathology and type of postoperative therapy on IQ, attention and executive function, and memory in survivors [4, 5]. The few reports of psychosis developing after surgical resection, despite stable lesions on imaging, all occurred in individuals with significant risk factors including family history of mental illness [6, 7].

Johnny's case describes a child with a stable postoperative posterior fossa tumor and negative psychiatric family history, who presented with mania and psychosis responsive to lithium, suggestive of a diagnosis of bipolar I disorder with mood-congruent psychotic features.

This case is distinctive in many aspects:

1. Timing and risk factors: this is a rare and late manifestation of mania with psychosis several years after postoperative surgical resection, despite a stable tumor burden, with no family history of mental illness.
2. Age of onset: such an early initial presentation of mania with psychosis is rare, as the average age of onset is in the third decade of life.
3. Disease progression and treatment: psychosis was preceded by a several-month period of negative symptoms concerning for catatonia, resistant to benzodiazepines. This rapidly progressed to florid psychosis, resistant to multiple antipsychotics, and ultimately proved highly responsive to lithium.

Pediatric Tumors and Psychosis

Overall, posterior fossa tumors are less commonly associated with psychiatric symptoms when compared to temporal and frontal lobe tumors. In one study, few patients with occipital tumors developed significant psychiatric symptoms compared to 35% with frontal and temporal meningiomas [7]. Midbrain lesions have been linked to psychosis in a rare syndrome called peduncular hallucinosis. This has been described in a teenager with a space-occupying midbrain lesion resulting in psychiatric deterioration [6].

A few case reports have described patients with psychosis in the setting of stable brain lesions. Increased pituitary volume has been reported inconsistently in first-episode psychosis in schizophrenia [8]. One study also described a 45-year-old male with persistent metastatic tumors in the right cerebral hemisphere, without any psychiatric risk factors, who presented with psychosis responsive to lithium treatment [3].

Schmahmann [9] described a remarkably similar patient, a young male with delayed psychosis over a decade after cerebellar vermis tumor resection. It is unclear whether this patient had a significant psychiatric family history. This patient noted mood dysregulation at age 17 and presented at age 22. With the combination of selective serotonin reuptake inhibitors (fluoxetine and then citalopram) and olanzapine, he reportedly improved to a functional physical and social level, though was still below baseline emotionally and intellectually [9]. This phenomenon of emotional dysregulation in patients with cerebellar lesions has been observed in both adults and a few pediatric cases, termed cerebellar cognitive affective syndrome (CCAS), and is described further in the next section [1].

Treatment Strategies

The incidence of neuropsychiatric impairments in those with posterior fossa lesions is gaining recognition and offers significant clinical implications. Cases thus far suggest that cognitive behavioral therapy focused on awareness may be beneficial; however, long-term effects are unknown [10].

The role of medications in affective dysregulation in the setting of posterior fossa lesions has not yet been formally studied. The patient with delayed psychosis after cerebellar tumor resection described by Schmahmann exhibited physical and social functional improvement with selective serotonin reuptake inhibitors and an antipsychotic. However, this patient's emotional and cognitive blunting persisted [9].

Johnny's impairments, in comparison, proved resistant to three different antipsychotics as well as valproic acid. Impressively, both his psychosis and affective symptoms nearly fully reversed with a therapeutic dose of lithium over a brief period, in addition to olanzapine. Johnny's parents felt that he was nearly back to baseline at discharge, and he remained stable and returned to school on the same dose of these two medications. Whether or not his symptoms would have resolved with lithium alone is unknown.

These cases suggest a potential role for antipsychotics as part of combination therapy for affective syndromes and psychosis that are coincidental with posterior fossa lesions. Importantly, Johnny's case also emphasizes the importance of considering a diagnosis of bipolar disorder in these patients and using of lithium in such cases of pediatric psychosis.

Lessons in Neuropsychiatry

A link between cognitive and emotional dysregulations with lesions in the vermis and lateral posterior cerebellum has been described as part of CCAS. This is characterized by executive, language, spatial, and affective impairment, with a small number of cases reported in children after resection of cerebellar tumors [1]. The identification of this syndrome provides further evidence of cerebellar involvement in these higher brain functions.

The limbic system, classically associated with emotional regulation, is known to involve circuitry between the amygdala, hippocampus, thalamus, and hypothalamus, as well as important connections with a number of other surrounding brain regions. De Moura et al. [11] recently utilized MRI and machine learning to support the role of the limbic system in first-episode psychosis, demonstrating volumetric change in these patients compared to healthy controls. Prior studies have also implicated limbic white matter pathway injury in cognitive dysfunction associated with multiple sclerosis, with the level of microstructural disruption positively correlated with the extent of cognitive impairment [12].

The cerebellar vermis and fastigial nucleus have been referred to as the "limbic cerebellum" due to their postulated role in CCAS. Case reports of children with CCAS with vermis involvement showed the most pronounced affective symptoms, compared to cases primarily affecting the cerebellar hemispheres which showed mostly cognitive deficits [9]. This is similar to Johnny's case, where his residual tumor burden primarily affected the upper cerebellar vermis. Furthermore, studies have shown that decreased vermis volume has been found in patients diagnosed with schizophrenia, suggesting a potential correlation with the development of psychosis [1]. Johnny's cognitive and psychiatric affective symptoms, including emotional dysregulation, executive impairments, and acute linguistic changes, in the setting of a prior cerebellar lesion, are consistent with CCAS. This supports the concept that the cerebellum and posterior fossa play an important role in limbic circuitry.

Johnny did not experience symptoms of mania and psychosis immediately after the development of his tumor, or even soon after resection. In this case, as in many others, we find ourselves looking for acute brain lesions that could explain such significant mental status changes. In children, we must also consider changes in the context of a developing brain. It is important to recognize that Johnny had a symptomatic cerebellar lesion prior to the age of 2. This means that most of his life, he experienced aberrant development of the cerebellum. Hereditary and developmental disorders which are known to affect the cerebellum, including the spinocerebellar ataxias (SCAs) and Joubert syndrome, may also show symptoms of CCAS in addition to classic motor function impairments [1, 13]. This further supports the notion that developmental forms of CCAS do exist.

Johnny's neuropsychiatric symptoms, in the setting of a stable posterior fossa lesion and negative family psychiatric history, suggest that abnormalities in the posterior fossa in early development, related to residual tumor and postoperative changes, likely conferred an increased risk of mania and psychosis. This is consistent with the growing understanding of the role of cerebellar and brainstem structures in affective disorders and suggests the potential for limbic system disturbance and circuitry interruption in posterior fossa and cerebellar lesions.

There is much to learn about the role of the cerebellum in psychiatric illness, including mania and psychosis, that has been described in this chapter. Further research focusing on inherited cerebellar disorders, as well as continued efforts to identify structural and genetic underpinnings of psychiatric illness, will undoubtedly provide significant advancement in the understanding of this phenomenon.

Observations from Johnny's Family

Johnny's parents had years of experience raising a child who grew up with significant medical issues and developmental delays. His mother kept a watchful eye on him and always made sure he was well supervised. They had been grateful for the fact that he was generally a happy young man who was well-liked by teachers and

peers. He liked to joke around with others and always had a smile on his face. While they had learned to cope with his existing medical issues, this huge change in his personality had been devastating. Never before had he been aggressive or irritable and certainly never threatened to harm himself or others. Johnny loved school, and the fact that his behaviors no longer allowed him to attend class was a huge setback. As Johnny began to improve shortly after starting lithium, his parents told the treatment team, "we've got our Johnny back!", a sentiment they continue to express at his follow-up appointments.

References

1. Schmahmann J. Disorders of the cerebellum: ataxia, dysmetria of thought, and the cerebellar cognitive affective syndrome. Neuropsychol Pract Opin. 2004;16:367–78. https://doi.org/10.1176/jnp.16.3.367.
2. Siegel M, Beresford C, Bunker M, et al. Preliminary investigation of Lithium for mood disorder symptoms in children and adolescents with autism spectrum disorder. J Child Adolesc Psychopharmacol. 2014;24(7):399–402. https://doi.org/10.1089/cap.2014.019.
3. Jamieson R, Wells C. Manic psychosis in a patient with multiple metastatic brain tumors. J Clin Psychiatry. 1979;40(6):280–3.
4. Lassaletta A, Bouffet E, Mabbott D, Kulkarni A. Functional and neuropsychological late outcomes in posterior fossa tumors in children. Childs Nerv Syst. 2015;31(10):1877–90. https://doi.org/10.1007/s00381-015-2829-9.
5. Hanzlik E, Woodrome S, Abdel-Baki M, Geller T, Elbabaa S. A systematic review of neuropsychological outcomes following posterior fossa tumor surgery in children. Childs Nerv Syst. 2015;31(10):1869–75. https://doi.org/10.1007/s00381-015-2867-3.
6. Andrews JP, Taylor J, Saunders D, Qayyum Z. Peduncular psychosis. BMJ Case Rep. 2016; https://doi.org/10.1136/bcr-2016-216165.
7. Bommakanti K, Gaddamanugu P, Alladi S, Alladi S, Purohit A, Chadalawadi S, Mekala S, et al. Pre-operative and post-operative psychiatric manifestations in patients with supratentorial meningiomas. Clin Neurol Neurosurg. 2016;147:24–9. https://doi.org/10.1016/j.clineuro.2016.05.018.
8. Takahashi T, Nakamura K, Nishiyama S, Furuichi A, Ikeda E, Kido M, et al. Increased pituitary volume in subjects at risk for psychosis and patients with first-episode schizophrenia. Psychiatry Clin Neurosci. 2013;67(7):540–8. https://doi.org/10.1111/pcn.12093.
9. Schmahmann J. The neuropsychiatry of the cerebellum – insights from the clinic. Cerebellum. 2007;6:254–67. https://doi.org/10.1080/14734220701490995.
10. Schmahmann J. The role of the cerebellum in cognition and emotion: personal reflections since 1982 on the dysmetria of thought hypothesis, and its historical evolution from theory to therapy. Neuropsychol Rev. 2010;20(3):236–60. https://doi.org/10.1007/s11065-010-9142-x.
11. De Moura A, Pinaya W, Gadelha A, Zugman A, Noto C, Cordeiro Q, et al. Investigating brain structural patterns in first episode psychosis and schizophrenia using MRI and a machine learning approach. Psychiatry Res. 2018; https://doi.org/10.1016/j.pscychresns.2018.03.003.
12. Keser Z, Hasan K, Mwangi B, Gabr R, Steinberg J, Wilken J, et al. Limbic pathway correlates of cognitive impairment in multiple sclerosis. J Neuroimaging. 2017;27(1):37–42. https://doi.org/10.1111/jon.12381.
13. Hickey C, Sherman J, Goldenberg P, et al. Cerebellar cognitive affective syndrome: insights from Joubert syndrome. Cerebellum Ataxias. 2018;5:5. https://doi.org/10.1186/s40673-018-0085-y.

Punch Drunk: Repetitive Concussions in an Adolescent Student-Athlete

6

Shari Thomas and David I. Driver

Case

Cody is a 16-year-old male with no previous psychiatric history who presented 7 months after sustaining a concussion with a loss of consciousness lasting 6 min. On his initial presentation, Cody complained of low mood, initial insomnia, poor appetite, difficulty with concentration, and repetitive ego-dystonic intrusive thoughts of suicide. Cody said he began suffering from some of these symptoms 2 weeks after sustaining his concussion and denied any premorbid psychiatric symptoms.

Cody had no recollection of the injury, but his mother reported he sustained his concussion while playing goalie for his elite level hockey team. She reported that another player struck Cody across the forehead with a hockey stick while skating at full-speed directly toward him. The impact of the blow knocked Cody's protective mask off, and he immediately fell to the ground in a prone position, striking his head a second time.

Upon regaining consciousness, Cody reported numbness and being unable to move the left side of his body. By the time he got back to the locker room, he began regaining feeling and control of the left side of his body. He was cleared by the team trainer and went home with an outpatient neurology evaluation scheduled. That night, he had nausea, and the following day, he woke up with a headache.

By the time Cody was seen the following day, his symptoms had subsided. He was advised to begin physical therapy as he continued to have left-sided weakness. Over the next several weeks, Cody regained his strength but began to suffer from intrusive thoughts about suicide. These thoughts increased in intensity, frequency, and duration and were subsequently accompanied by depressed mood, initial insomnia, and poor appetite. Six months after the initial injury, he experienced command auditory hallucinations to kill himself and asked his parents to schedule an appointment with a psychiatrist.

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Clinical Pearl 1
Athletes are ill-equipped to recognize the sequelae of concussions, and they often have strong incentive to actively ignore these symptoms in order to continue to play. As such, it is unsurprising that Cody did not attribute his mood changes, difficulty with concentration, and sleep disturbance to the head injury. It is incumbent on the clinician to elucidate the mechanism of the injury and the ensuing symptom development in order to accurately arrive at the diagnosis and shape the treatment plan.

Developmental History Cody was the result of a full-term uncomplicated pregnancy. His mother was 31 years old when he was conceived. She received prenatal care and had an unremarkable perinatal course. There were no in utero exposures to alcohol, tobacco, illicit drugs, or medications. Cody was born full-term via normal spontaneous vaginal delivery. His birth weight was 7 lbs 9 oz. He met all of his developmental milestones within expected ranges. His elementary school teachers described him as a friendly child who loved to participate in school. His parents said that he was always a gifted athlete, excelling at various sports, planning to play collegiate hockey ever since his father took him to his first game. Cody's father was also a highly successful athlete, recruited at the college level.

Social History Cody lives with his parents and his younger sister. He earns A's and B's and has a close-knit group of friends. He spends his free time playing sports, hanging out with friends, and playing video games.

Family History of Psychiatric Illness There is no family history of medical or psychiatric illness, including dementia or a primary mood or psychotic disorder.

Disease Course Cody and his family were amenable to the use of medication, but Cody was reluctant to engage in individual therapy. He stated that his schedule didn't allow for him to make a weekly commitment, nor did he have anything that he needed to talk about. Cody started citalopram 10 mg daily which was titrated over 4 weeks to 40 mg daily. His school was contacted to coordinate accommodations that would allow him to engage in psychotherapy.

Over the course of 8 weeks, Cody reported an improvement in his mood symptoms and resolution of the hallucinations. He was sleeping very well and was able to complete his final exams for the school year. Over the summer, Cody remained psychiatrically stable, enjoyed family trips, and also visited college campuses. By winter, he had returned to playing hockey at an elite level and was being actively recruited to play at highly competitive college programs.

Cody remained compliant with his treatment and was stable until late spring. At that time, he reported the return of hearing a voice telling him to kill himself. He described this as intrusive and ego-dystonic. His grades declined, and he reported feeling irritable, aggressive, and depressed. He expressed concern as he also began having headaches, short-term memory loss, and difficulty focusing on the hockey puck. He disclosed that during the last hockey season, he suffered five additional concussions without loss of consciousness. On several of these occasions, he had nausea and vomiting, ear ringing, visual changes, and headaches lasting for several days. Additionally, he had significant amnesia for events on those particular days. He didn't tell anyone about his symptoms because the starting goalie position was highly competitive, and he didn't want to jeopardize his position as a starter. He also did not want to negatively impact his college recruitment process.

A family meeting was held with Cody, and, after obtaining a second opinion from a neurologist at a local academic tertiary care center, Cody made the decision to no longer participate in organized sports.

Diagnostic Impression

Given the seemingly abrupt onset of symptoms, lack of premorbid dysfunction, and lack of family history, it seems likely that the head injury that Cody sustained may have contributed to or even have caused his current symptoms. A recent study by Wallace et al. [1] demonstrates that high school athletes are ill-equipped to recognize the sequelae of concussions; so the fact that Cody did not attribute his mood changes, difficulty with concentration, and sleep difficulties to the head injury is unsurprising. It is incumbent on the clinician to elucidate the mechanism of the injury and the ensuing symptom development in order to accurately arrive at the diagnosis and shape the treatment plan.

Background of Concussion

Dementia pugilistica, also known as punch drunk syndrome, was first described in the 1920s after boxers were observed to have memory lapses, changes in speech, unsteady gait, and tremors. The first article, titled "Punch Drunk" by Dr. Harrison Martland, appeared in JAMA in 1928 [2]. Dr. Martland postulated that symptoms manifested years after repeated brain injuries occurred "…in the deeper portions of the cerebrum." It is now speculated by some that dementia pugilistica is a variant of chronic traumatic encephalopathy (CTE), a recently discovered neuropathological condition seen in individuals with history of repeated head injuries. CTE has gained national attention along with the increasing need to understand the sequelae of concussions experienced by players in the National Football League in the USA [3–5].

Concussion is defined as "any transient neurologic dysfunction resulting from a biomechanical force" [6]. Concussion is distinguished from other forms of

traumatic brain injury (TBI) by the fact that there are no structural injuries to the brain visible on neuroradiological imaging, and symptoms tend to completely resolve over time. However, there is increasing evidence that repeated concussions can cause long-term dysfunction, with children and adolescents being particularly vulnerable.

Between 2001 and 2005, there were over 200,000 emergency room visits for concussions, and over 65% of them were for children between 5 and 18 years old [7]. From 2001 to 2009, the number of TBI-related emergency room visits increased by over 60% [8]. Bakhos et al. [9] showed that approximately 40% of emergency room visits for sports-related concussion are younger children (8–13 years old). Younger children appear more susceptible to the diffuse injury, seen in concussions, which may lead to long-term effects on learning and development. Younger children are also more likely to return to play less than 24 h after sustaining concussion [10]. This same group has increased risk for the catastrophic outcome of second-impact syndrome, herniation of the brainstem from a seemingly minor injury that is sustained after a concussion.

With the emphasis on concussions largely coming from investigations into the biomechanics of football, the incidence and treatment of concussion in girls have received markedly less attention. However, girls are more likely than boys to sustain concussions and typically have more severe symptoms. Girls have more sleep disturbances after one concussion, and sleep disturbance is a harbinger for headaches and mood changes [11]. The need for concussion education and surveillance for young female athletes warrants additional resources as girls have poorer outcomes [12].

Relevant Neuroanatomy and Pathophysiology

Given that the symptoms of concussion typically resolve completely, it is reasonable to assume that symptoms of concussion are caused by neuronal dysfunction and not cell death [6]. The biomechanical force of concussion leads to disruption of the cell membranes which allows for an efflux of potassium and an influx of calcium. The membrane alteration described is evidenced by the increase in choline [13]. In an effort to restore membrane potential, voltage-gated ion channels are activated resulting in an increased need for adenosine triphosphate (ATP). This demand coupled with the disruption in cerebral blood flow leads to glycolysis. With increased glycolysis, more lactic acid is produced. The metabolism of lactate is inhibited by the disruption of oxidative metabolism caused by the sequestration of calcium in the mitochondria. The resulting lactic acidosis causes neuronal dysfunction by altered membrane permeability and cerebral edema.

After the initial transient period of glucose hypermetabolism, hypometabolism can persist for weeks [14]. The neuropsychiatric sequelae seen after concussion may result from the sustained decreased metabolism of glucose in the brain. Further, axonal stretching and the resulting microtubule breakdown may impair axonal transport and cause axotomy.

As indicated above, no consistent structural changes result from a single incidence of concussion. Additionally, a causal relationship has not yet been definitively established; however, the potential for developing CTE in an individual with repetitive head trauma must be considered [15]. Unlike concussion, CTE is associated with the following gross anatomical features including cortical thinning [16], frontal and temporal atrophy [17], smaller hippocampal volumes [18], enlarged ventricles [17], and cavum septum pellucidum (CSP) which may occur. Koerte and colleagues [19] showed that retired American professional football players experiencing psychiatric symptoms had a higher rate of CSP and greater ratio of CSP to septum, which is associated with memory and language deficits. Additionally, the histological lesion that is pathognomonic for CTE is an accumulation of p-tau in cortical sulci in an irregular pattern [20]. The presence of TDP-43-positive inclusions and neurofibrillary tangles is also common in the neuropathology of CTE. Importantly, CTE is a histopathological diagnosis, meaning it can only be diagnosed after viewing a sample of brain tissue under the microscope. As such, it is considered to be a postmortem diagnosis and cannot yet be definitively identified in individuals based on symptoms or biomarkers.

Treatment Strategies

The opportunity to treat anyone who has sustained a concussion rests on that individual's ability and willingness to report his or her symptoms. There is robust evidence that sports-related concussions are underreported [21]. In a study done with high school athletes in Michigan, only 21% reported all of their concussions, and over 55% did not report any concussions [1]. Athletes may think that the injury doesn't warrant medical attention, fear losing playing time, not want to be seen as weak by teammates, or want to avoid disapproval from coaches and trainers [22]. Given the increased risk for children and adolescents to suffer from second-impact syndrome, the implications for an athlete continuing to play after sustaining a concussion are grave.

Though the Centers for Disease Control and Prevention (CDC) recommends all athletes receive concussion education prior to playing any sport, Wallace et al. [1] demonstrated that even high school athletes who receive the CDC "Heads Up" educational documents are unaware of the signs and symptoms of concussion, with many believing that loss of consciousness is a required element of the injury. Further, the type of school environment (i.e., urban vs. suburban, access to athletic trainers, etc.) influences the likelihood that an athlete will report a concussion.

Though there is considerable heterogeneity in pre- and post-concussion assessments, they are often used to elucidate the presence of an injury, its severity, and the need for treatment. These assessments include some or all of the following: clinical evaluation, symptom scales, and computerized neurocognitive testing.

The main treatment for concussion is "brain rest," where the athlete curtails physical and cognitive activities (e.g., no school, no homework, no screens, no

physical activity, no social visits, etc.). Lovell et al. [23] showed that hyperactivation of the brain on fMRI was predictive of longer recovery times. While there are no guidelines on the parameters of brain rest, the resumption of activities depends on the resolution of symptoms [24]. Should any symptoms reemerge, the brain rest protocol should be restarted. Clinicians treating adolescents who have suffered a concussion should consider their readiness to resume driving, as reaction time and concentration are commonly affected [25].

While most symptoms of a concussion resolve over the course of a few days, some patients will experience post-concussion syndrome, also known as persistent concussion symptoms. This occurs anywhere from 6% to 59% of the time and is marked by recurrent headaches, neuropsychiatric changes, and behavioral changes. There is no consensus on the parameters of post-concussion syndrome, such as duration and minimum number of symptoms [26].

All 50 states have Return-to-Play laws that mandate the institution of a protocol for assessment of head injuries and an athlete's ability to resume sports after a concussion. In 2010, the National Collegiate Athletic Association (NCAA) adopted a policy to reduce the incidence of concussions by requiring education, surveillance, and a process for medical clearance. The National Federation of State High School Associations also published educational materials for coaches, trainers, parents, and students. Despite these mandates, compliance remains variable, and enforcement is lacking.

Clinical Pearl 2

In a study of nearly 500 student-athletes, 1/3 reported a previously undiagnosed concussion. Athletes reporting previously undiagnosed concussions had a higher mean Post Concussion Symptoms Scale (PCSS) score and were more likely to have lost consciousness with their current injury than athletes without previously undiagnosed concussions [27].

Lessons Learned About Neuropsychiatry

Until recently, concussions were not regarded as causing significant morbidity and even less so as having the potential for mortality. Cody's experience demonstrates that even one concussion can result in a severe constellation of symptoms. Tragic events have illuminated that repeated concussions have cumulative effects that are destructive. Case reports show that high school athletes can have histopathology consistent with CTE [28, 29].

Because CTE can only be definitely diagnosed postmortem, a valid calculation of incidence and prevalence is challenging. Although traditionally thought of as a diagnosis relevant to middle-age football players, there is limited evidence for its incidence in adolescents and young adults. In a recent study on the postmortem brains of four adolescent athletes, ages 17–18, two of whom committed suicide, changes consistent with a diagnosis of CTE were found [29]. This raises the troubling possibility

that severe neuropathological repercussions of repeated TBI may occur in athletes in adolescence and are not only present later in life. Given that by 10 years of age, 16% of children will have sustained a head injury [26], the inclusion of adolescents in research revolving around repeated head trauma and CTE is warranted.

Educational Tools

1. CDC Heads Up educational materials (https://www.cdc.gov/headsup/youthsports/training/index.html)
2. CDC Heads Up Concussion and Helmet Safety App
3. Consensus Statement on Concussion in Sport – the 5th International Conference on Concussion in Sport held in Berlin, October 2016
4. NCAA Sport Science Institute concussion educational resources (http://www.ncaa.org/sport-science-institute/concussion-educational-resources)
5. National Federation of State High Schools concussion course (https://nfhslearn.com/courses/61129/concussion-in-sports)
6. National Operating Committee on Standards for Athletic Equipment (NOCSAE) (http://nocsae.org/)

References

1. Wallace J, Covassin T, Nogle S, et al. Concussion knowledge and reporting behavior differences between high school athletes at urban and suburban high schools. J Sch Health. 2017;87:665–74.
2. Martland HS. Punch drunk. J Am Med Assoc. 1928;91:1103–7.
3. Stern RA, Riley DO, Daneshvar DH, et al. Long term consequences of repetitive brain trauma: chronic traumatic encephalopathy. PMR. 2011;3(10 Suppl 2):S460–7.
4. Stern RA, Daneshvar DH, Baugh CM, et al. Clinical presentation of chronic traumatic encephalopathy. Neurology. 2013;81(13):1122–9.
5. Mez J, Daneshvar DH, Kieman PT, et al. Clinicopathological evaluation of chronic traumatic encephalopathy in players of American football. JAMA. 2017;218(4):360–70.
6. Giza CC, Hovda DA. The neurometabolic cascade of concussion. J Athl Train. 2001;36(3):228–35.
7. CDC. Nonfatal traumatic brain injuries from sports and recreation activities – United States, 2001–2005. MMWR Morb Mortal Wkly Rep. 2007;56:733–7.
8. CDC. Nonfatal traumatic brain injuries related to sports and recreation activities among persons aged ≤19 years – United States, 2001–2009. MMWR Morb Mortal Wkly Rep. 2011;60(39):1337–42.
9. Bakhos LL, Lockhart G, Myers R, Linakis J. Emergency department visits for concussion in young child athletes. Pediatrics. 2010;126:e550–6.
10. Kerr Z, Zuckerman S, Wasserman E, et al. Concussion symptoms and return to play time in youth, high school, and college American football athletes. JAMA Pediatr. 2016;170(7):647–53.
11. Oyegbile TO, Delasobera BE, Zecavati N. Gender differences in sleep symptoms after repeat concussions. Sleep Med. 2017;40:110–5.
12. Farace E, Alves W. Do women fare worse? A meta-analysis of gender differences in traumatic brain injury outcomes. J Neurosurg. 2000;93:539–45.

13. Koerte IK, Lin AP, Muehlmann M, et al. Altered neurochemistry in former professional soccer players without history of concussion. J Neurotrauma. 2015;32:1287–93.
14. Bergsneider M, Hovda DA, Lee SM, et al. Dissociation of cerebral glucose metabolism and level of consciousness during the period of metabolic depression following traumatic brain injury. J Neurotrauma. 2000;17:389–401.
15. McCrory P, Meeuwisse W, Dvorak J, et al. Consensus statement on concussion in sport–the 5th international conference on concussion in sport held in Berlin, October 2016. Br J Sports Med. 2017;51:838–47.
16. Koerte IK, Mayinger M, Muehlmann M, et al. Cortical thinning in former professional soccer players. Brain Imaging Behav. 2016a;10:792–8.
17. Baugh CM, Stamm JM, Riley DO, et al. Chronic traumatic encephalopathy: neurodegeneration following repetitive concussive and subconcussive brain trauma. Brain Imaging Behav. 2012;6:244–54.
18. Strain JF, Womack KB, Didehbani N, et al. Imaging correlates of memory and concussion history in retired National Football League Athletes. JAMA Neurol. 2015;72:773–80.
19. Koerte IK, Hufschmidt J, Muehlmann M, et al. Cavum Septi Pellucidi in retired American profootball players. J Neurotrauma. 2016;33:346–53.
20. McKee A, Cairns N, Dickson, D, et al. The First NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy. Acta Neuropathologica. 2016;131:75–86.
21. Rowhani-Rabar A, Chrisman SPD, Drescher S, et al. Agreement between high school athletes and their parents on reporting athletic events. J Neurotrauma. 2016;33:784–91.
22. McCrea M, Hammeke T, Olsen G, et al. Unreported concussion in high school football players: implications for prevention. Clin J Sport Med. 2004;14(1):13–7.
23. Lovell MR, Pardini JE, Welling J. Functional brain abnormalities are related to clinical recovery and time to return-to-play in athletes. Neurosurgery. 2007;61:352–60.
24. Moser RS, Schatz PA. Case for mental and physical rest in youth sports concussion: it's never too late. Front Neurol. 2012;3:1–7.
25. MacDonald, J., Patel, N., Young, J. Returning adolescents to driving after sports-related concussions: what influences physician decision making. J Pediatr. 2017; pii: S0022-3476(17)31381-1. https://doi.org/10.1016/j.jpeds.2017.10.032.
26. Zemek R, Farion K, Sampson M, et al. Prognosticators of persistent symptoms following pediatric concussion. JAMA Pediatr. 2013;167(3):259–65.
27. Meehan WP, Mannix RC, O'Brien MJ, et al. The prevalence of undiagnosed concussions in athletes. Clin J Sport Med. 2013;23(5):339–42.
28. McKee AC, Cantu RC, Nowinski CJ, et al. Chronic traumatic encephalopathy in athletes: progressive tauopathy after repetitive head injury. J Neuropathol Exp Neurol. 2009;68:709–35.
29. Tagge CA, Fisher AM, Minaeva OV, et al. Concussion, microvascular injury, and early tauopathy in young athletes after impact head injury and an impact concussion mouse model. Brain. 2018;141(2):422–58.

Part II

Autism and Neurodevelopmental Syndromes

1.1 Introduction

Different...Not less.
Temple Grandin, PhD

Moving on from relatively identifiable disruptions in specific brain regions and circuits, the focus of this section is on a number of important neurodevelopmental syndromes which may be superimposed upon less well-understood brain networks and connections. The presentation and management of neurodevelopmental conditions such as autism spectrum disorder are subjects covered in extraordinary depth in the psychiatric, neurological, and developmental pediatric literature. Thus, this section, instead, explores aspects of a few neurodevelopmental conditions that give particular lessons about brain structure and functioning. Complex aspects of multimodal management, such as treating psychosis in the context of complex neurodevelopmental syndromes or challenging behavioral manifestations, are highlighted here.

One important skill for a pediatric neuropsychiatrist is to be able to differentiate typical from atypical presentations of psychiatric disorders in children with developmental disabilities. For example, while idiopathic autism spectrum disorder is considerably more common than that resulting from any single etiology, when ASD occurs in the setting of another developmental syndrome, many aspects of diagnosis and management change.

With this in mind, the section begins with a discussion of the most common, known, single-gene cause of autism spectrum disorder, fragile X syndrome. Aspects of evaluation in the setting of atypical autism presentations are explored as well as genetic, structural, and functional neuroanatomic details that frame the subsequent discussion of neurodevelopment. From here, the complicated subject of psychosis in children is broached, first with a case of 22qDS syndrome, also called velocardiofacial syndrome, which is the most common neurodevelopmental disorder associated with schizophrenia. The subject of psychosis is further explored in the next chapter, where the processes of determining whether atypical thought processes or

odd experiences in the child are psychosis or aspects of normal development, trauma, or other factors are highlighted. This case is a reminder that psychosis certainly can occur in children and require special considerations in terms of diagnosis and management. From here, the focus moves to the common challenge of managing aggression and self-injury sometimes seen in neurodevelopmental disorders. Although the specific neurobehavioral pathways and networks may be less understood, syndromic and otherwise categorized developmental disabilities are common conditions under the purview of the pediatric neuropsychiatrist.

Fragile X: Autism in the Setting of a Known Genetic Syndrome

7

Jessica Simberlund and Jeremy Veenstra-VanderWeele

Case

AJ is a 15-year-old male with a history of autism spectrum disorder (ASD) who was referred by his pediatrician for a psychiatric evaluation due to irritable mood and an increase in compulsive behaviors. On initial evaluation, AJ's mother reported a 5-month history of AJ being easily frustrated, especially during the transition period from home to school. She explained that AJ would yell and bang his fists on his legs prior to the scheduled arrival of the school bus, which he refused to enter. As a younger child, AJ often had outbursts during transition periods; however, for the past 5 years at his new school, this behavioral dysregulation had subsided. AJ's mother also described that he was consistently biting his lips and would take his eyeglasses on and off throughout the day to the point that they would break due to his manipulation. AJ's mother attributes this change in behavior to an incident on the school bus when the driver reportedly screamed and called AJ derogatory names. A peer's father had told AJ's mother about the encounter, as AJ never spoke of the event.

AJ was born full term without any complications and no reported prenatal exposure to medications or substances. As an infant, AJ made minimal eye contact, and as he grew older, he would not point to objects or demonstrate interest in joint play with peers and family members. AJ enjoyed playing alone and would easily get

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angry when he was prompted to transition to a different task. AJ's speech did not progress beyond one to two words after 24 months, prompting evaluation by a developmental pediatrician who diagnosed AJ with ASD. AJ received services to target his language delay and support for academic difficulties in elementary school. Testing demonstrated that AJ had a full-scale intelligence quotient (FSIQ) of 48.

AJ's mother denied that AJ had any significant medical history; he was not taking any medications and had no allergies. AJ did not have a family history of psychiatric or developmental disorders (including ASD); however, his mother reported that she had learning difficulties during childhood.

On initial mental status exam, AJ was a tall, thin male who appeared his chronologic age, with prominent ears and scant facial hair. He was wearing eyeglasses and was casually dressed in blue jeans and an oversized plaid shirt. He did not maintain eye contact and often diverted his gaze to objects on the desk or to the floor. AJ was observed to frequently remove his eyeglasses, adjust the frame, and place the glasses back on his face. AJ remained silent for the first portion of the interview and eventually answered close-ended questions with yes or no responses. His speech was not spontaneous; it was laconic, soft, and monotone. His mood was reported as fine; his affect was constricted and bashful. His thought process was concrete. There was no evidence of delusions or perceptual disturbances. He denied suicidal ideation and homicidal ideation.

It was determined that AJ had not undergone genetic testing when he was initially diagnosed with ASD. A fragile X DNA test was sent and was significant for a diagnosis of fragile X syndrome (FXS). AJ and his family were then referred for genetic counseling.

After the initial evaluation, given the history obtained and AJ's clinical presentation, it was apparent that AJ had symptoms consistent with anxiety, and he was initiated on the selective serotonin reuptake inhibitor (SSRI), sertraline. AJ was also referred for weekly cognitive behavioral therapy (CBT); however AJ proved difficult to engage, and this treatment modality was terminated after five sessions. AJ seemed to benefit from sertraline as his compulsive behaviors and irritability improved at a dose of 150 milligrams (mg) daily. There was an attempt to titrate sertraline to a total daily dose of 200 mg, to target residual symptoms of anxiety, such as lip biting. However, on this increased dose, AJ demonstrated signs of activation, including sleep difficulties, which resolved when sertraline was tapered to 150 mg daily. AJ's mother was able to advocate on AJ's behalf, and a new bus driver was placed on AJ's route, which helped with AJ's transition back to school. As treatment progressed, AJ became more comfortable in the presence of the psychiatrist and would discuss topics that he found interesting. Throughout treatment, AJ never acknowledged the incident on the school bus.

Discussion

Diagnostic Impression

ASD is a neurodevelopmental disorder with onset in early childhood, characterized by (1) persistent deficits in social communication and social interaction across multiple contexts and (2) restricted, repetitive patterns of behavior, interests, or

activities [1]. The development of these patients can vary significantly, and it is important for the clinician to understand the individual's developmental history, highlighting language development (often delayed) and communication patterns [1]. Symptoms must be evaluated relative to developmental level, taking language ability into account.

The prevalence of ASD across the United States and non-US countries is about 1%, and it is diagnosed four times more often in males than in females [1]. ASD is considered to be a multifactorial disorder, risk of which can be elevated by various hereditary causes ranging from copy number variants to monogenic disorders [2]. The correlation between genetic factors and ASD is considered significant, with a heritability estimate of 70–90% [3]. It is approximated that 10% of ASD cases are the result of a known genetic syndrome, including FXS, tuberous sclerosis, neurofibromatosis, chromosome 16p11.2 deletion or duplication, and maternal chromosome 15q11–q13 duplication [3].

Clinical Pearl #1

When patients present with deficits in specified ASD symptom domains, the American Academy of Child and Adolescent Psychiatry (AACAP) practice parameter recommends a medical assessment including physical examination, hearing screen, and genetic testing [4]. Recommended genetic testing includes a chromosomal microarray and fragile X gene testing. Furthermore, dysmorphic features in the child should prompt additional genetic evaluation, usually requiring referral to a clinical geneticist [4]. For clinicians, it is important to identify genetic syndromes, as these diagnoses will help guide appropriate care, which can include behavioral, academic, and medical interventions [3].

Additionally, it is valuable for parents to understand genetic risk for future pregnancies, as well as understand the medical cause of their child's developmental disorder.

In AJ's case, his FXS diagnosis remained unknown until his teenage years when he underwent genetic testing. His family reported a sense of relief in knowing that there was an underlying genetic etiology and that their parenting was not to blame for AJ's behaviors. AJ was an only child; however, his mother noted that the FXS diagnosis would have been important information for her to understand if she considered having more children.

FXS is a neurogenetic syndrome that is thought to be the most common inherited cause of intellectual disability and the most common monogenic risk factor for ASD [5]. Worldwide, FXS occurs in approximately 1 in 4000 males and 1 in 4000–6000 females [5]. FXS is the result of disruption of *FMR1* gene expression due to expansion of a cytosine-guanine-guanine (CGG) trinucleotide repeat in the proximal untranslated region of the gene [6]. Unaffected individuals typically have fewer than 45 CGG repeats, while those with a full mutation have over 200 [5]. FXS is an X-linked disorder that impacts all affected males and has variable penetrance in females as a result of random inactivation patterns on the X chromosome [5].

FXS physical abnormalities are typical and include a long face with prominent ears, arched palate, hyperextensible joints, pectus excavatum, mitral valve prolapse, strabismus, and macroorchidism (present only in postpubertal patients) [3, 7]. Individuals with FXS display deficits in cognition, language, and social and behavioral development [2]. Intellectual disability is characteristic of males who have a full mutation, with an average IQ of 40 [3]. It is common for these individuals to demonstrate gaze avoidance, sensory hypersensitivity, stereotypic movements, and delayed speech development [7]. Hyperactivity is very common and tends to be observed in children more so than adults. Many of the symptoms observed in individuals with FXS overlap with the ASD phenotype.

Individuals with FXS often present to clinicians as a result of developmental delay and features of ASD [3]. The estimated prevalence of ASD in FXS is 25–52%, and of those individuals who do not meet the diagnostic criteria for ASD, over 90% demonstrate one or more ASD symptoms [2, 3].

Many studies have attempted to characterize similarities and differences in idiopathic ASD and ASD in FXS, as well as the broader FXS population. One consistent area of overlap in idiopathic ASD and ASD in FXS is deficits in social interactions [2]. With regard to repetitive behaviors, individuals with FXS were observed to have lower rates of higher-order repetitive behaviors but similar rates of lower level motoric repetitive behaviors [2]. Individuals with FXS tend to have less impaired reciprocal social interaction and communication skills and maintain emotion sensitivity, compared to idiopathic ASD [3]. Importantly, without the genetic diagnosis, most individuals with ASD in FXS would blend into the general ASD population, as occurred with AJ. Interpersonally, AJ often appeared bashful and would shift his gaze during a conversation. He had expressive and receptive language impairment and engaged minimally in an interview outside of a rote greeting, followed by a few phrases related to his favorite topic, major league baseball. AJ did not demonstrate significant hyperactivity, though he did have stereotypies ranging from vertical eye movements to hand flapping. Physically, AJ did not have prominent physical signs of FXS.

Development plays a role in ASD symptom manifestation in individuals with FXS. This hypothesis prompted Lee and colleagues to perform a longitudinal study to characterize ASD phenotypes in boys and girls with FXS, in comparison to boys with idiopathic ASD [2]. They found that as individuals with FXS aged, they demonstrated an increase in ASD symptoms in addition to heightened social language impairment [2]. Males with idiopathic ASD were found to have significantly greater restricted interests at the later time point [2].

Clinical Pearl #2

Clinicians should assess symptoms across multiple time points and incorporate a developmental perspective when evaluating children with complex neurodevelopmental disorders.

Relevant Neuroanatomy and Pathophysiology

FXS demonstrates significant symptom overlap with ASD, even when ASD is not present, prompting investigations to understand the interplay between genes, brain, and behavior [2]. Disruption of *FMR1* leads to reduction of fragile X mental retardation protein (FMRP), which is involved in brain development and regulation of dendritic translation [2, 6]. Human brains have widespread FMRP expression, as this protein can be found in mature astrocytes and neurons, and disruption is thought to have an impact on the macroscopic, microscopic, and molecular level [5]. FMRP has multiple functions in the neuron including regulation of mRNA translation and mRNA transport to synapses for protein synthesis [6]. FMRP suppression seems to impact synaptic plasticity, with subsequent effects on learning and memory due to malfunction of various signaling cascades, resulting in failure to establish mature synaptic connections [2, 5]. Synaptic disruption is implicated in the pathophysiology of ASD, more broadly, including changes in dendritic spine density that may parallel FXS [8].

FMRP also regulates genes that have been associated with ASD. Substantial data indicate excessive signaling downstream of group 1 metabotropic glutamate receptors (mGluRs) in FXS, with rescue by mGluR5 inhibitors in mouse models [5]. Impaired inhibition has been found in the hippocampus, striatum, amygdala, and cortex in mouse models of FXS [8]. Neurotransmitter signaling cascade disruption (e.g., dopaminergic, GABA, serotonergic) is thought to be involved in idiopathic ASD but with less specific findings [2].

In terms of brain development, the global brain volume of FXS individuals is larger compared to typical controls but not significantly different compared to individuals with idiopathic autism [9]. Individuals with FXS show specific enlargement in temporal lobe white matter, cerebellar gray matter, and caudate nucleus, with significantly smaller amygdalas [5, 9]. Studies suggest that both ASD and FXS may involve abnormalities of the caudate nucleus and posterior cerebellar vermis [7].

Treatment Strategies

At this time, there is no medical "cure" or specific treatment for ASD with or without FXS. Consequently, treatment strategies tend to focus on symptom management. Although research groups have identified potential drugs that effectively impact neuroanatomical, electrophysiological, and behavioral characteristics of FXS in animal models, when these compounds are applied to humans, at least adult humans, efficacy results have not reached significance. Lack of targeted treatments may in part be due to the challenge of translational research for neurodevelopmental disorders, including uncertainty around clinical trial designs and outcome measures [5].

Numerous studies have focused on metabotropic glutamate receptors (specifically mGluR5) and GABA receptors in FXS [5]. It has been proposed that blocking mGluR5 may dampen the response of excess protein synthesis and altered synaptic

plasticity, resulting in a rescue of abnormal signaling and subsequent improvements in behavior [6]. In adults and adolescents, no differences were observed in an mGluR5-negative allosteric modulator compared to placebo [5]. Berry-Kravis and colleagues studied the effect of the GABA-B agonist, arbaclofen, in a fixed dose trial with FXS subjects ages 5–11 and two phase III placebo-controlled trials for FXS subjects ages 12–50 [10]. Arbaclofen did not lead to statistically significant improvement in social avoidance in adolescent and adult FXS subjects. However, secondary measures in the child study suggest that this patient population may derive benefit, as they demonstrated improvement in measures of irritability and parenting stress [10].

An important limitation in the studies of mGluR5 antagonists and GABA-B agonists has been participant populations of the large-scale clinical trials, which typically include adolescents and adults. FXS is a neurodevelopmental disorder, and treatments may be more effective in younger children, though the ability to study this age range is restricted by regulations requiring initial studies to be conducted in older ages. The success of FXS targeted treatment may additionally be impacted by lack of validated outcome measures for FXS [11]. Measures used for individuals with idiopathic ASD have been adopted; however these metrics may not be the most sensitive or specific when evaluating treatment efficacy in individuals with FXS [5, 11]. For example, the Aberrant Behavior Checklist-Community (ABC-C) is commonly applied as a primary outcome measure in FXS studies, with a focus on behavioral irritability [5, 11]. Irritability, however, seems to be a less prominent symptom in FXS, compared to that of idiopathic ASD [5]. Instead, Erickson and colleagues emphasize cognition and communication as core deficits in FXS that may serve as more reliable outcome measurements [5].

Despite these challenges, research continues to concentrate on FXS treatment strategies. For example, studies are underway using acamprosate, a compound that is thought to affect glutamate, GABA, and NMDA receptors, to reduce neuronal hyperexcitability [8]. Acamprosate is approved by the FDA for maintenance treatment of alcohol dependence in adults, and its impact on these excitability/inhibitory pathways is postulated to be helpful in the treatment of FXS. Schaefer et al. completed a study with *FMR1* knockout mice and found that acamprosate reduced anxiety-like behavior and hyperactivity and attenuates certain electrophysiological dysregulation that may play a role in FXS [8].

Lessons Learned About Neuropsychiatry

AJ's case highlights the importance of considering a genetic etiology when treating an individual with a developmental disorder. Recommended testing in ASD includes a chromosomal microarray, which can identify copy number variants, and fragile X gene testing in all boys and in girls with intellectual disability (ID) or a family history of ID. After a thorough physical examination, additional tests to consider include phosphatase and tensin homolog gene testing for a head circumference more than 2.5 standard deviations above the mean for age and methyl CpG binding

protein 2 gene testing in girls with severe ID to identify Rett syndrome, and if a chromosomal syndrome is suspected, a karyotype analysis can be ordered.

AJ's presentation demonstrates that a developmental disorder does not protect from other common psychiatric problems during childhood or adolescence. ASD, FXS, and intellectual disabilities may increase vulnerability to mental illness, though it is often unrecognized. Clinicians should screen and monitor for psychiatric comorbidities including attention deficit hyperactivity disorder (ADHD), anxiety and mood disorders, and trauma- and stressor-related disorders. In AJ's case, he demonstrated symptoms of anxiety and irritability that may have been related to the incident on the school bus. Traumatic experiences to someone with a developmental disorder may not match the general population, as in this case example. The communication, language, and intellectual deficits associated with ASD and FXS can make it difficult for these individuals to express their reactions to a traumatic experience. Studies demonstrate that children with ASD can show symptoms of anxiety, regression in adaptive behavior, increased behavior problems, and suicidal ideation in response to a traumatic event [12]. Clinicians should be mindful of abrupt changes in symptom presentation in this patient population and consider trauma in the differential diagnosis. It remains unclear if children with ASD suffer the symptoms that characterize post-traumatic stress disorder (PTSD) including reexperiencing the event, negative alterations in cognition and mood, avoidant behaviors, and hyperarousal [12].

In FXS, in the absence of specific evidence, clinicians should attempt to diagnose and treat co-occurring disorders. For example, if a patient with FXS fits criteria for a diagnosis of ADHD, it is reasonable to adopt treatment strategies from the general ADHD literature or from populations with ASD and ADHD, although there is only limited data for the use of stimulants specifically in FXS [13, 14]. Similarly, atypical antipsychotic medications could reasonably be administered for aggression in this patient population, based upon their efficacy in idiopathic ASD. It is also important to consider the utility of behavioral therapy and parent training strategies. In the case of AJ, he demonstrated symptoms of anxiety that significantly improved with administration of an SSRI. Due to his cognitive and social limitations, he was not able to tolerate psychotherapy.

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM 5. 5th ed. Arlington: American Psychiatric Association; 2013.
2. Lee M, Martin GE, Berry-Kravis E, Losh M. A developmental, longitudinal investigation of autism phenotypic profiles in fragile X syndrome. J Neurodev Disord. 2016; https://doi.org/10.1186/s11689-016-9179-0.
3. Zafeiriou DI, Ververi A, Dafoulis V, Kalyva E, Vargiami E. Autism spectrum disorders: the quest for genetic syndromes. Am J Med Genet B Neuropsychiatr Genet. 2013;162B(4):327–66.
4. American Academy of Child and Adolescent Psychiatry. Practice parameters for the assessment and treatment of children and adolescents with autism spectrum disorder. J Am Acad Child Adolesc Psychiatry. 2014;53(2):237–57.

5. Erickson CA, Davenport MH, Schaefer TL, Wink LK, Pedapati EV, Sweeney JA, et al. Fragile X targeted pharmacotherapy: lessons learned and future directions. J Neurodev Disord. 2017; https://doi.org/10.1186/s11689-017-9186-9.
6. Bagni C, Oostra BA. Fragile X syndrome: from protein function to therapy. Am J Med Genet. 2013;161A(11):2809–21.
7. Belmonte MK, Bourgeron T. Fragile X syndrome and autism at the intersection of genetic and neural networks. Nat Neurosci. 2006;9(10):1221–5.
8. Schaefer TL, Davenport MH, Grainger LM, Robinson CK, Earnheart AT, Stegman MS, et al. Acamprosate in a mouse model of fragile X syndrome: modulation of spontaneous cortical activity, ERK1/2 activation, locomotor activity and anxiety. J Neurodev Disord. 2017; https://doi.org/10.1186/s11689-017-9184-y.
9. Hazlett HC, Poe MD, Lightbody AA, Styner M, MacFall JR, Reiss AL, et al. Trajectories of early brain volume development in fragile X syndrome and autism. J Am Acad Child Adolesc Psychiatry. 2012;51(9):921–33.
10. Berry-Kravis E, Hagerman R, Visootsak J, Budimirovic D, Kaufman WE, Cherubini M, et al. Arbaclofen in fragile X syndrome: results of phase 3 trials. J Neurodev Disord. 2017; https://doi.org/10.1186/s11689-016-9181-6.
11. Budimirovic DB, Berry-Kravis E, Erickson CA, Hall SS, Hessl D, Reiss AL, et al. Updated report on tools to measure outcomes of clinical trials in fragile X syndrome. J Neurodev Disord. 2017; https://doi.org/10.1186/s11689-017-9193-x.
12. Hoover DW. The effects of psychological trauma on children with autism spectrum disorders: a research review. Rev J Autism Dev Disord. 2015;2:287–99.
13. Roberts JE, Miranda M, Boccia M, Janes H, Tonnsen BL, Hatton DD. Treatment effects of stimulant medication in young boys with fragile X syndrome. J Neurodev Disord. 2011;3(3):175–84.
14. Rueda JR, Ballesteros J, Tejada MI. Systematic review of pharmacological treatments in fragile X syndrome. BMC Neurol. 2009;9:53.

Does a Diagnosis of Velocardiofacial Syndrome Mean Schizophrenia?

8

Jonathan Picker

Case

Tee is a 16-year-old, 11th grade teenage girl who has an individualized education plan due to learning disabilities and who attends a modified special educational program. Tee carries a diagnosis of the genetic syndrome 22q11 deletion syndrome [22q11DS] also called velocardiofacial syndrome [VCFS] or DiGeorge syndrome, due to a microdeletion in chromosome 22 at the location q11.2. In addition to new-onset visual phenomena, she describes an ongoing desire to cut herself in the setting of a history of superficial self-laceration in the past. She reports that life has been particularly stressful recently. She has been unhappy with school, work, and, more recently, her boyfriend. At school she feels overwhelmed. She says she only has one longstanding friend, though she recently has begun to express some uncertainty about him. She describes her classmates and peers as "backstabbers" and notes chronic problems in particular with one girl in her class who bullies Tee and has a history of self-injury by means of self-laceration. In general, Tee has tended to worry about school, her ability to work, and her difficulties socializing. She also started to work in a local supermarket as a cashier 3 months earlier and "hates it." She feels the people at work are against her and talk about her. She also notes that her boyfriend who works there says to her that "You have no friends; they all hate you."

In relation to these many stressors, she notes worsening thoughts of suicide and a desire to cut herself. It should be noted that Tee's mother reports that she tends to copy the behaviors of her peers and the incident of her prior self-injury occurred in conjunction with the cutting episodes of her peer whom Tee mentioned had bullied her. Tee has thoughts of suicide but stated that she has not considered any specific

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method by which she would kill herself and has never made a prior attempt. Her mother, however, reports that Tee has previously indicated to her that she felt like running in front of a car when she was upset in the setting of being overwhelmed and distressed with her previous boyfriend.

Tee now reports having seen dead people "in the flesh, as real as those of us who are in the clinic room" though she also notes that she knew that "they were not real people." They do not talk to her and generally are described as being fairly inert, though, during one recent episode in her mother's car she notes the person did sit up and lay down in the back seat of the car. These episodes had gone on for a number of months though there had been none in the last few weeks. She does not describe or appear to have any neurocognitive decline suggestive of "negative psychotic symptoms" or classic prodromal schizophrenia. She also does not report ideas of reference or delusional thoughts, although some degree of paranoia regarding her peer group was notable in her description of recent stressors. Her mother reports that Tee had once previously complained of seeing a coyote in the closet when she was in fourth grade during a transitional period with high expressed anxiety. Otherwise, Tee and her mother report no other history of hallucinations or other unusual experiences.

Her mother describes Tee as generally having good self-esteem and that she usually stands up for herself but mother feels that, recently, she has been moodier and angrier than is characteristic of her personality. Tee describes herself as a shy person though she enjoys dancing and gymnastics and feels that she is skilled at these endeavors. Her ability in these pastimes led to her being able to participate in large prestigious parade the previous year. She reports that her ambition is to work in a beauty salon.

Past Psychiatric/Developmental History

There has been no history of psychiatric medications or psychiatric hospitalizations. She has been undergoing psychotherapy since turning 10 years old for anxiety, mood lability, and difficulties coping. She has a history of having problems going to school, especially in fourth and then again at sixth grade, both transition periods in her district. She had required home tutoring during those periods. She has been on an IEP since beginning school for 22q11.2 deletion-related learning issues but does not carry a diagnosis of intellectual disability.

Social/Family History

Eight people currently live in the house including Tee's biological parents, her older biological siblings, and two younger adopted girls including a 6-year-old girl with ADHD. In addition, her mother reports that Tee's father has very significant ADHD but remains untreated due to previous stimulant side effects. Though he is able to work, Tee's mother feels that her father is not very functional. He concurs with this assessment. Both Tee and her father report being disturbed by the fairly high amount of noise and activity in the house, whereas her mother feels comfortable and pleased with the "very lively" environment.

In the extended family, the history includes two uncles with a history of alcoholism, substance abuse, and depression, one of whom committed suicide, and a cousin with a history of auditory and visual hallucinations but no formal diagnosis of schizophrenia.

Pertinent Medical History

In infancy, Tee had hypocalcemia-induced neonatal seizures. She has a history of polycystic kidney disease and had one kidney removed at 2 months of age. She has a mild septal defect and sees a cardiologist every 2 years. All of these complications were related to the underlying 22q11DS. She is followed for migraines as well as some staring and shaking episodes that are not epileptic in origin. She also has a mild hearing deficiency, as well as mild scoliosis and lordosis. Tee takes acetaminophen as needed for migraines.

On examination, Tee was well groomed and dressed. Her presentation demonstrated a fashionable bent that was not overtly atypical. Healed scars from the previous cutting were visible, but there were no signs of recent self-injury. Tee had the external physical characteristics consistent with 22q11DS, specifically short stature (third percentile for height), narrow palpebrae, columnar nose, and mildly dysplastic upper ear helices. Much of the time, she looked to her mother to provide answers; however, with improved rapport, over time, Tee's eye contact improved. She was also able to smile and laugh appropriately with jokes. Her answers were expressive and appropriate with normal prosody and good tone in her voice. Her speech had the hypernasal quality characteristic of velocardiofacial syndrome. Tee's diagnoses at the time were consistent with adjustment disorder with mixed anxiety and labile mood, velocardiofacial syndrome, migraines, hearing and speech impediment, scoliosis and lordosis, and heart murmur.

Case Reflections

Tee is a 16-year-old girl with a history of 22q11DS and multiple related medical complications and a family history of depression, substance abuse, ADHD, psychosis, and suicide, with a history of anxiety, who presents with new-onset perceptual disturbances of seeing things but no auditory hallucinations or neurocognitive decline. This new symptom occurred in the context of multiple stressors including school and a troubled relationship with her boyfriend. She denies depressive symptoms and does not demonstrate signs of major depression. There is also a history of self-injurious behavior such as superficially cutting her wrists three times in the past, but no current self-injurious behavior or suicidal plan or activities. She experiences ongoing passive suicidal thoughts that are somewhat exacerbated in the context of recent stressors but are not dramatically worse than during previous episodes of stress. She continues follow-up regularly with her long-term individual therapist.

This teenage girl presents with acute psychiatric symptoms in the setting of a genetic disorder, environmental stressors, and a significant family history. While there is an additive and possibly synergistic consequence to these factors, the interrelationship of each is unclear. Unfortunately, an absence of extended family genetic testing leaves a question mark over whether the 22q11.2 microdeletion could be affecting others in the family. This is important as there is a family history of possible psychosis; thus, the absence of the 22q11.2 microdeletion would speak to other genetic factors possibly playing a greater role of the family's issues and potentially of added significance for Tee. The potential role of these factors must therefore be assigned as uncertain and attention focused on those patho-etiological factors that are amenable to interrogation, namely, the 22q11.2 microdeletion itself and her recent psychosocial stressors.

22q11.2 microdeletion is likely highly relevant in this case and bears further consideration. 22q11DS is a multisystem disorder that is highly variable in expression though often with a core phenotype of physical features [1]. These include the DiGeorge sequence of third and fourth branchial arch defects resulting in variable cleft palate/velopharyngeal insufficiency (VPI), dysplasia of parathyroid and thymic development, conotruncal congenital heart defects, renal dysplasia, and characteristic physical features including narrow palpebrae, columnar nose, mildly dysplastic ear helices, and long tapering fingers. There is often vascular tortuosity. Less frequent anomalies affect most systems in the body.

The majority of individuals have learning deficits that may cross into intellectual disability. Visuospatial skills are often especially compromised. While verbal IQ is a relative strength, deficits in serial memory, social cognition coupled with hearing deficits, and VPI mean that speech is often delayed. Speech is often of quiet, nasal quality that can be difficult to understand. As a result, these children are often introverted and tend to watch and listen.

From a behavioral perspective, these children are at high risk for psychopathology that may be compounded by the physical and developmental issues. Specific psychopathological concerns will evolve over time for the individual. The behavioral aspects of the disorder were first described in 1985 [2] in children who often had blunted affect, monotonous voice, disinhibited or shy behavior, and poor social interactions. In school-age children, up to 60% suffer from a range of problems that typically start with anxieties and phobias as well as ADHD. Oppositional defiant disorder and obsessive compulsive issues can become more apparent over time. Depression and psychosis may occur in young children but typically occur in teens. Adults have a 25–30% risk of schizophrenia and 5% risk of bipolar disease or other psychosis NOS. Depression and OCD are common [3].

The question of why schizophrenia has a 30-fold greater incidence of 22q11DS than the general population points to the significance of the genetic region involved in the genesis of this disorder and is relevant to considering the proband's presentation, prognosis, and management. The common three million base pair deletion that incorporates the DiGeorge critical region includes 30 genes, 9 of which are expressed in the brain (*COMT*, *PRODH*, *GNB2*, *PIK4CA*, *ZDHHC8*, *DGCR8*, *Ufd11*, *CDCrel1*, and *BCR*). Much of the research to date has focused on COMT and

PRODH as discussed below, but they are not the only genes to be implicated in studies of schizophrenia. *GNB2* appears to be involved in neuronal connectivity; *ZDHHC8* is involved in neuronal signaling, and *DGCR8* alters prefrontal and hippocampal transcript activity and appears to impact spatial memory and sensorimotor gating.

At this point, the two primary-risk candidates are *COMT* and *PRODH*, both of which, in common with the other genes in the locus, are haplo-insufficient. Deficiency of *COMT*, responsible for the metabolism of dopamine, results in an excess of dopamine, particularly in the frontal lobes, whereas PRODH is central to the pathway that metabolizes proline to L-glutamine, deficiency of which directly impacts the amount the glutamine available to the NMDAR. Thus, critical upstream components that play to both the dopamine and glutamine hypotheses of schizophrenia would appear to heighten risk from the two primary candidate pathways hypothesized in the genesis of schizophrenia [4].

Assuming the veracity of these hypotheses, it might then be wondered why more individuals with 22q11DS are not affected. Looking at the profile of individuals with 22q11DS, the evidence suggests that mean ages of onset for both clinical risk and threshold psychotic disorders are similar between 22q11DS and the general population. Among 22q11DS without positive psychosis-spectrum symptoms who were followed prospectively, 39% experience emergent symptoms after 4 years follow-up. Furthermore, psychosis-spectrum outcomes in 22q11DS are similar between the 22q11DS and idiopathic clinical risk populations; they primarily include lower baseline functioning, higher baseline symptoms—especially negative symptoms—and greater impairment in cognition. Dysphoric mood and anxiety are additionally predictive of psychosis in 22q11DS. It should be noted, however, that presence of autistic spectrum disorder does not predict psychosis risk [5].

Neuropsychiatry Lessons

While there is no consistent evidence that neuroanatomical trajectory in 22q11DS differs from that of unaffected relatives, there is evidence for decline in prefrontal cortical gray matter volume preceding psychosis in 22q11DS. Furthermore, there appear to be structural cortical differences in patients defined to be at ultrahigh risk for psychosis, based on the presence of attenuated psychotic symptoms, a brief psychotic episode, or other clinical deteriorations. In these individuals, there was a positive association between surface area and the rate of change of global functioning, in addition to accelerated cortical thinning during adolescence. The results appear to suggest that alterations in cortical volume and surface area and development of cortical thickness may be associated with a greater probability for developing psychosis in 22q11DS [6]. At this time however, brain imaging is not recommended as a prognostic factor.

Onset of psychotic disorders can occur over a wide range of ages, peaking in late adolescence. Threshold psychotic disorders are generally preceded by subthreshold positive symptoms and negative symptoms, which may appear earlier in adolescence

and be gradually progressive or episodic in nature. The peak incidence for negative symptoms appears to be in early adolescence, whereas positive subthreshold symptoms appear most commonly during middle adolescence. Threshold psychotic disorders often begin in late adolescence. This pattern allows targeting of therapies both to reduce symptoms and attempt to prevent development and progression of the disorder. Thus, those aimed at alleviating negative symptoms and supporting social and occupational functioning can play an important role and may start early [5].

From a treatment perspective, this timeline is important as the biochemical disruption may be more amenable to therapy than the more common, but likely more polygenetically driven, cases of schizophrenia. Anecdotally it has been suggested that the 22q11DS individuals are indeed more responsive to medication that targets these pathways than the general schizophrenic population. However, data does not clearly support this, though the number of individuals who constitute study participants remains relatively low [7]. What does seem clear, however, is that there are opportunities to prospectively intervene in an attempt to ameliorate the disease process to bring the individual below symptomatic threshold for schizophrenia or other psychotic illnesses.

Evidence suggests that these individuals may be responsive to psychotherapy. Data across five of preliminary studies notes improvements across several domains of neuropsychological functioning, including working memory, attention, and social cognition both immediately after intervention and at 12 weeks post-intervention. Of note, these studies included relatively small sample and other confounding factors [8].

From the pharmacotherapeutic perspective, at this time most groups recommend standard pharmacotherapy as used in the general schizophrenic population with mindfulness of the systemic physical issues that may predicate choice of drug, such as risk of endocrine dysfunction.

The evidence from systematic review indicate that there is insufficient data available to warrant adjustments to current clinical guidelines for 22q11DS therapies [7, 8]. Current guidelines indicate that a proactive approach to reducing the stressors, biochemically or behaviorally, is warranted. These approaches, in addition to the reducing biochemical drivers, include cognitive and educational support and address any medical issues that impact systemic health or increase anxiety and medicalization of the individual.

Case Follow-Up

Returning to the patient with this information in mind, it was recommended to continue to monitor her mood as well as perceptual disturbances and further gather information in regard to her anxiety and use that information to determine the best medication and psychotherapeutic interventions. Her medical status was reviewed, but no changes were deemed necessary from a physical perspective. Given the risks of neuroleptics and known medical complexities associated with 22q11DS, avoidance of this medication category, unless symptoms were thought to truly constitute emerging schizophrenia or life-impacting psychotic symptoms, was stressed.

Over the next few months, no further visual or other hallucinatory experiences or other prepsychotic/psychotic symptoms/signs were reported. Tee was placed on fluoxetine which appeared to help her anxiety. Her mood stabilized and was helped by ceasing the relationship with her boyfriend and stopping the job.

Tee was lost to follow-up for a number of years but returned to attention 10 years later at the age of 26. At this this time, she continued to have a complex medical life even more strongly impacted by her anxiety which evolved to include agoraphobia. Her inability to leave the house for appointments led to frequently missed medical follow-up. There was no recurrence or development of further symptoms or signs concerning for psychosis. Her new psychiatrist transitioned her from fluoxetine to sertraline, which helped alleviate some of her symptoms but also appeared to be associated with significant jaw pain which radiated down the left arm. As a result, Tee's sertraline was stopped, and she has avoided psychotropic medication since. From a general medical perspective, current issues requiring ongoing management include autoimmune hypothyroidism, mild aortic root dilation, and mitral valve prolapse with mild regurgitation with general review of her past systemic issues that have not caused additional problems. Tee went on to attend a community college where she received an Associate's Degree. She currently works part time at medical care facility and lives at home with her parents.

Clinical Pearl

Awareness of the role of genetic syndromes in psychopathology allows potential insights that may directly impact treatment. In this case, 22q11DS not only has a known high risk for schizophrenia, but there is some understanding of the biology that directly underlies this risk as well as understanding of the greater management of other features of this disorder that may exacerbate the psychopathology. Taking the time to consider if a patient has a genetic disorder and what that disorder is and then incorporating that information into the treatment plan can significantly improve neuropsychiatric management and outcomes.

References

1. McDonald-McGinn DM, Emanuel BS, Zackai EH. 22q11.2 deletion syndrome. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, editors. GeneReviews® [Internet]. Seattle: University of Washington, Seattle; 1993–2018. 1999 Sep 23 [updated 2013 Feb 28].
2. Golding-Kushner KJ, Weller G, Shprintzen RJ. Velo-cardio-facial syndrome: language and psychological profiles. J Craniofac Genet Dev Biol. 1985;5:259–66.
3. Squarcione C, et al. 22q11 deletion syndrome: a review of the neuropsychiatric features and their neurobiological basis. Neuropsychiatr Dis Treat. 2013;9:1873–84.
4. Zarchi O, et al. Schizophrenia-like neurophysiological abnormalities in 22q11.2 deletion syndrome and their association to COMT and PRODH genotypes. J Psychiatr Res. 2013;47(11):1623–9. https://doi.org/10.1016/j.jpsychires.2013.07.004. Epub 2013 Aug 1.

5. Tang SX, Gur RE. Longitudinal perspectives on the psychosis spectrum in 22q11.2 deletion syndrome. Am J Med Genet Part A. 2017;1–11.
6. Padula MC, et al. Cortical morphology development in patients with 22q11.2 deletion syndrome at ultra-high risk of psychosis. Psychol Med. 2018;17:1–9.
7. Boot E, et al. Pharmacological treatment of 22q11.2 deletion syndrome-related psychoses. Pharmacopsychiatry. 2015;48(6):219–20.
8. Buijs PCM, Bassett AS, Boot E. Non-pharmacological treatment of psychiatric disorders in individuals with 22q11.2 deletion syndrome; a systematic review. Am J Med Genet Part A. 2018;1–6.

The Interface Between Rare Genetic Variation, Psychosis, and Trauma

9

Alcy Torres, Catherine Brownstein, Anthony Deo, and Joseph Gonzalez-Heydrich

Case

Susan is a 13-year-old female who was brought to the emergency department (ED) by her adoptive parents because she was reporting that her invisible friends were telling her to hurt her family and she was scared that she would not be able to resist these commands. Her parents reported that Susan has "two genetic disorders," a presumed history of alcohol exposure in utero and a history of abuse and neglect prior to coming to live with them at age 5 months. Susan was taking lisdexamfetamine 50 mg each morning for treatment of attention deficit hyperactivity disorder

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(ADHD) and risperidone 0.25 mg in the evenings for treatment of mood dysregulation. She was in regular psychotherapy for attachment-related challenges thought to be secondary to trauma and neglect in the months of life before she came to live with her adoptive parents.

Susan's parents were told that Susan's biological mother had grown up in foster care herself and had several children prior to Susan, all of whom had been removed from her care. Her biological mother was reported to have cognitive impairment but not to have used substances. Her prenatal history was not known to her adoptive parents. Nothing is known about Susan's biological father's psychiatric or developmental status; however, he was said to be physically and emotionally abusive. Susan and her mother took refuge from him in a shelter temporarily until Susan was removed from her biological mother's care. Susan then went into another foster home for a few months before returning at the age of 5 months to the home of her soon-to-be adoptive parents. Neither Susan nor her adoptive parents have had subsequent contact with Susan's biological parents.

Susan's parents report that as an infant she had marked intolerance to being touched or held and was sensitive to loud sounds. She was behaviorally volatile and would bite herself or others when angry. She was delayed in walking and received occupational therapy. All other milestones were reached on time. She was indiscriminate in her social interactions, for example, hugging strangers on the street and had trouble interpreting social cues. She was hyperactive and impulsive and by age 6 years received a diagnosis of ADHD. Treatment with stimulant medications was helpful, but her temper continued to be quite dysregulated, and she was given the additional diagnosis of disruptive mood dysregulation disorder and treated with risperidone 0.25 mg per day. She had a pattern of stealing possessions from her classmates starting at age 8 and was frequently untruthful. She was thought to suffer from the effects of in utero alcohol exposure though she did not clearly have characteristic facial dysmorphology. She had ongoing difficulties with eating and gaining weight and was diagnosed with gastroesophageal reflux.

Since Susan was 6 years old, she was observed to play extensively with multiple imaginary friends, but only at home. This was thought to be a coping strategy as she has difficulty making and keeping friends. The interaction with the imaginary friends was always happy and was thus not a concern. Susan was treated long term with trauma-based psychotherapy and was making behavioral gains until about 13.5 years of age, about the same time as menarche. At that point, her parents noted that she was spending more time interacting with imaginary friends and had started calling them invisible friends. On the school bus, she had been exposed to a computer game loosely based on a series of horror films, and her invisible friends took on the names of characters in the computer game. Her temper became more explosive to the point that her long- term nanny quit and the entire household was on edge. She started accusing her brothers of stealing her things and of "looking at her funny."

Susan told her psychiatrist at the time that her invisible friends were hiding and stealing her possessions. On one occasion, Susan appeared dissociated and told her parents that one of her brothers had to die. She wrote a note about a classmate needing

to die. Susan was observed to dancing around chanting, "Kill, Kill, Kill," repeatedly. When asked about this, she said she was playing a game with her invisible friends. She also stated that her invisible friends were real. Her parents then brought her to the emergency room. She told the social worker that several of her invisible friends had "turned bad," that she could "feel them on her skin," and that they were telling her to hurt her family. Susan was frightened that they would force her to do harm to her family. The social worker made a provisional diagnosis of psychosis and recommended inpatient psychiatric hospitalization; however, the managed care plan disagreed with the recommendation, and Susan was discharged home. The reason appeared to be that the history of an alcohol-related neurodevelopmental disorder indicated that Susan's statements should be interpreted like those of a much younger child and hence were developmentally appropriate and not a sign of psychosis.

As soon as she arrived home, Susan's behavior worsened, and she continued interacting with her invisible friends and insisting that they were real. Her parents brought her to another crisis team evaluation. This time history of early neglect was reinterpreted, and the symptoms were considered to be better explained by dissociation or psychosis, and hospitalization was recommended.

In the hospital, Susan's lisdexamfetamine was stopped and her risperidone was increased. The invisible friends went away. As Susan's ADHD symptoms worsened off the lisdexamfetamine, atomoxetine was given, but the invisible friends returned, and it was stopped. Risperidone was increased further. Susan reported that the invisible friends had gone except for one female friend that was nice. This invisible friend had become fainter, Susan reported. Susan was observed to continue to interact with this invisible friend.

Diagnostic Dilemma

The inpatient team continued to debate to whether Susan's symptoms where dissociative versus psychotic. After discharge from the inpatient unit, a new child psychiatrist reevaluated the characteristics of "the two genetic disorders" and noted that Susan had a duplication of a region of the 16th chromosome, the 16p13.11 region, and CGG repeats within the Fragile X gene (47) that was just shy of the lower limit of CGG repeats that would clearly be considered a Fragile X premutation (generally 55–100 CGG repeats).

Since the hospitalization Susan reported more trouble focusing, "zoning out" during the day, and losing things, which she blamed partly on her invisible friends taking them. Her parents described times when Susan would stare blankly, and several verbal prompts would be necessary to get her to come out of this state. On mental status examination, Susan said that the invisible friends were still present though much fainter. She said that she could still see and hear them and sometimes feel them. She denied symptoms of paranoia. The rudimentary cognitive exam did not detect problems with concentration or immediate or more distant recall. Susan retained some insight stating that her invisible friends were coming from her imagination but that she had lost control of them.

The working diagnosis at this point was very early onset schizophrenia spectrum illness (very early onset being defined as before age 13 years). It was noted that the 16p13.11 duplication increases the risk for schizophrenia and that Susan's early trauma and neglect may have added to this risk and led to the psychosis presenting so early [1]. The Fragile X premutation may have added to the risks from the 16p13.11 duplication, though usually this premutation does not cause severe symptoms in female carriers.

Neuropsychological Profile and Neurological Examination

At age 14 years, Susan underwent repeat neuropsychological evaluation and review of past testing results in part due to the continued question of whether Susan's symptoms were dissociative or psychotic. Comparing WISC-IV test results obtained at age 8, 11, and 14 years of age revealed a startling pattern of marked decreases especially in verbal comprehension and working memory with significant, albeit less drastic, decreases in processing speed. She showed an unusual pattern of increased perceptual reasoning scores from age 8 to 11 years (then attributed to the special education supports Susan had been given especially with motor output) with a subsequent drop in that score by age 14 years. More specifically her WISC-IV Verbal Comprehension Index (VCI) fell from 125 (in the superior range) at age 8 to 101 at age 11 then to 82 (at the border of the intellectual disability range). Her Working Memory Index (WMI) was 105 at age 8, 103 at age 11 (both average), and 80 (at the border of the intellectual disability range) at age 14. Processing Speed Index (PSI) was 98 at age 8, remained approximately steady at 105 at age 11, and dropped to 87 at age 14. Perceptual Reasoning index (PRI) was 97 at age 8, had improved to 117 at age 11, and then dropped from that high point to 107 at age 14.

Subtest scores also dropped. For example, on the verbal comprehension subtest, Susan dropped from a high score of 16 at age 8 to an average score of 9 at age 11 years to a very low score of 3 at age 14 years. Similar patterns were seen for her Vocabulary, Block Design, Letter-Number Sequencing, and Symbol Search subtests. An exception to this was an opposite pattern on the Matrix Reasoning subtest, going from 8 to 11 to 13 across the testing at 8, 11, and 14 years of age, respectively. It should be noted at the first available WISC-IV testing, Susan showed a significantly better VCI than PRI. The subsequent pattern of cognitive decline, including a 43-point (nearly three standard deviations) drop in VCI, steadily accruing over the two testing episodes 3 years apart is statistically and clinically very significant. It has relatively spared her perceptual reasoning (PRI) and some higher-order reasoning skills (as implied by her improved Matrix Reasoning subtest) leaving perceptual reasoning which was a relative weakness at age 8, now a relative strength, while her language-based abilities have dropped from the superior range to the border of the range expected in patients with intellectual disability.

Susan was referred to a child neurologist to evaluate for any known and especially treatable cause for her cognitive decline and also for evaluation of her staring

spells. Physical and neurological examination was unremarkable; however, it was noted that an old EEG report showed the following: intermittent sharply contoured slowing over the left posterior regions and rare spikes over the left temporal occipital region. To evaluate whether ongoing seizure activity might be contributing to the cognitive regression and staring spells, a 24 h EEG was obtained which was normal. Susan had some staring spells noted during the EEG, but there was no electrographic correlate, meaning it is very unlikely that these staring episodes were related to seizures. A brain MRI was normal, and laboratory studies for metabolic and inflammatory disorders leading to psychosis and/or cognitive decline were done, and all returned normal.

Normal Fantasy Versus Dissociation Versus Psychosis

Concluding that Susan had a psychotic illness requires some understanding about perceptual disturbances, including hallucinations, and how they present in healthy children, those with psychotic illnesses, and those with dissociative disorders.

In psychotic spectrum disorders, one model states that in early stages, increasing deficits in communication between the frontal cortex and thalamus lead to excessive associative striatal activity such that internally generated phenomenon is perceived as coming from the outside world [2]. Early in this process, the confusion involves simple percepts that the patient can dismiss as not real but later extends to more formed ideas and perceptions, and the patient starts to lose the ability to distinguish what is real. At more advanced stages, these perceptual disturbances are frequently accompanied by loose associations, tangentiality, or incoherence of thoughts. Together these perceptual disturbances, the resulting delusional ideas, and disorganized thoughts are the "positive symptoms" of psychosis.

Psychosis can occur as part of an affective disorder such as major depression or bipolar I disorder or in the context of schizophrenia or schizoaffective disorder. The majority of patients with the "non-affective psychoses" and a minority of patients with affective psychosis have a significant neurocognitive decline or fail to make expected developmental gains in verbal memory, attention, and processing speed. Additionally patients with non-affective psychoses develop avolition and diminished expressiveness that present as what are termed "negative symptoms" characterized by decreased emotional responsiveness, motivation, socialization, speech, and movement. While the positive symptoms usually improve with antipsychotic medication, cognitive and negative symptoms generally do not and are associated with greater long-term functional impairments in patients.

The positive symptoms of hallucination and delusions are often central in making a diagnosis of a psychotic illness, and so their identification, epidemiology, and differentiation from developmentally normal fantasy in childhood are important. When children are in an imaginative state of play, they control the fantasy and do not have the perceptual experience of seeing and hearing the object of their

imagination. When children are hallucinating, they do not control the hallucination. Non-hallucinatory, imaginary friends are vivid fantasies associated with better neurocognitive functioning and are not a cause for concern. Almost two-thirds of the children will endorse at least one psychotic-like experience such as hallucination; when not persistent or accompanied by distress, these are not usually a cause for concern.

The largest population-based study to date evaluating psychotic symptoms and neurocognition in youth (8–21 years old) found that those who endorsed more psychotic-like experiences than is typical for their age on average have neurocognitive delays of 6–18 months, and the degree of the delay is proportional to the severity of the psychotic-like experience. Children with more psychotic-like experiences than typical for age also have increased odds of depression, anxiety, behavioral disorders, substance use, and suicidal ideation [3]. Thus hallucinations that are frequent and distressing and cause impairment signal a need for further evaluation and monitoring.

Pathological hallucinations can occur in dissociative disorders etiologically linked to trauma as well as in psychotic disorders, and the characteristics of the hallucinations can overlap considerably in both groups. Additionally trauma is a risk factor for psychotic disorders as well as dissociative disorders. Thus, characteristics of the hallucinations and the history of trauma are less helpful in deciding whether Susan's hallucinations were due to trauma and dissociation versus psychosis and in deciding how to focus her treatment [4]. The accompanying symptoms of cognitive decline and the decrease in hallucinations in response to stopping stimulant treatment and in response to antipsychotic treatment argue that Susan is suffering from a primary psychotic illness.

Clinical Pearl #1
Hallucinations that are frequent and distressing and cause impairment signal a need for further evaluation and monitoring at any age, including childhood. The characteristics of the hallucinations will be of less value in distinguishing between the different psychotic illnesses and hallucinations due to trauma than accompanying cognitive changes and treatment responses.

Staring Spells

Staring spells are a common referral to pediatric neurology for an evaluation of seizures. The differential diagnosis includes focal (onset) impaired awareness seizures (previously known as complex partial seizures), absence seizures (a type of generalized onset seizures previously known as petit mal), and daydreaming or other non-epileptic phenomena. Focal (onset) impaired awareness seizures typically last 1–2 min and start on one side of the brain after which they spread to involve brain areas that are required for alertness and awareness [5]. Absence-type generalized onset seizures begin in both sides of the brain at the

same time. They begin and end abruptly, lasting only a few seconds. These brief seizures can be difficult to distinguish from daydreaming. If time allows some maneuvers like a gentle touch of the face to see if one can get a response can show if the patient is aware of the stimulus making the diagnosis of seizures less likely. Comorbid conditions such as autism spectrum disorder, ADHD, behavioral problems, or psychiatric conditions like catatonia can make correct diagnosis more difficult [6–8]. Routine interictal EEG may not pick up the signs that would lead identification of the staring spells as seizures. If sufficiently frequent then a prolonged EEG coupled with video can determine if episodes are associated with epileptiform activity [9].

Clinical Pearl #2
A normal EEG does not rule out a seizure disorder just as an abnormal one does not mean that the patient has epilepsy; clinical correlation is essential.

Genetic Mutations and Their Significance

Copy number variants (CNVs) are chromosomal rearrangements involving large segments of DNA, ranging from 1000 to several million base pairs in length. CNVs are results of deletions or duplications and are potentially accompanied by inversion or translocation events. CNVs have been identified as a major source of human genetic variation. While many CNVs are believed to be benign polymorphisms, others are associated with highly variable and pleiotropic phenotypes that often include both neurodevelopmental and somatic disruptions. Information about individual CNVs is accumulating though for the majority the information available is still incomplete. Importantly, breakpoints on the chromosome for CNVs that are called by the same name often vary, and thus what genes are deleted or duplicated also will vary.

The 16p13.11 duplication has been implicated in childhood as well as adolescent and adult-onset schizophrenia [10]. In the large schizophrenia case control studies, the 16p13.11 duplication was associated with twofold increased risk of schizophrenia as well as intellectual disability, autism, seizure disorders, dysmorphic features, and congenital anomalies [11]. It is important to note, however, that it has also been found in individuals with no psychiatric or neurodevelopmental disorder [12]. Due to study selection biases, increase in the risk for psychotic illness from this CNV may be underestimated.

Borderline Fragile X Premutation

Nearly all cases of Fragile X syndrome are caused by a mutation in the FMR1 gene. The *FMR1* gene provides instructions for making a protein called FMRP. This protein is present in many tissues, including the brain, testes, and ovaries. In the brain,

FMRP helps regulate synaptic plasticity, which is important for learning and memory. One region of the *FMR1* gene contains a particular DNA segment known as a CGG trinucleotide repeat, so called because this segment of three DNA building blocks (nucleotides) is repeated multiple times within the gene. In most people, the number of CGG repeats ranges from fewer than 10 to about 40. As the number of CGG repeated increases beyond around 55, there is tendency for the number of repeats to increase with subsequent generations. When more than 200 CGG repeats are present, the affected FMR1 allele gets methylated, and there is reduction of FMRP production. This is particularly devastating in boys as they do not have another FRM1 allele. Thus patients having 55–200 CGG repeats in the FMR1 gene are said to be premutation carriers.

It has been shown that boys with a premutation in the *FMR1* gene and girls with the premutation and X inactivation greater than 50% favoring X chromosome that carries the premutated FMR1 have increased psychological symptoms, predominantly obsessive-compulsive symptoms and psychoticism [13]. How Susan's borderline Fragile X premutation of about 47 repeats might interact with the risks conferred by her 16p13.11 duplication is unknown.

Cognitive Decline

The etiology of Susan's cognitive decline during the years that her psychosis became more pronounced remains unexplained. A thorough evaluation for known causes of cognitive decline was unrevealing. Cognitive decline especially in verbal areas is a frequent accompaniment to non-affective psychoses such as schizophrenia, though a drop of 43 points is larger than what would typically be expected. Her 16p13.11 duplication may make her more vulnerable to a larger cognitive decline as it contains genes that have known associations with pathways disrupted in neurodegenerative disorders and genes that have also been linked to dysregulated neurogenesis [14, 15].

Clinical Pearl #3
Knowledge of copy number variants and other rare mutations and their interactions with genetic "second hits," as well as environmental risk such as early neglect or trauma, is still in its infancy. However, it is important to note when a patient carries potentially pathogenic mutations and carefully consider whether neurodevelopmental disorders with which it is associated are present.

Case Reflections

Appropriate treatment of Susan's psychosis was delayed because of confusion about whether her psychotic statements were due to developmental immaturity, the effects of trauma as an infant, or both, rather than heralding worsening psychosis.

After contributing genetic factors were appropriately identified, her psychosis responded well when stimulants were stopped and improved further on antipsychotic medication. Extensive evaluation has not revealed a known etiology for her cognitive regression; thus it seems to be related to her emerging psychosis, even though the steepness of the drop especially in verbal comprehension and related domains is surprising for idiopathic psychosis. Her genetic mutations may well be interacting with each other and with her prior trauma to cause this early psychotic and cognitive regression. Appropriate treatment of her psychosis was delayed by what appears to be reductionistic thinking that Susan's developmental immaturities or her past trauma fully explained her symptoms.

Lessons Learned About Neuropsychiatry

This is a unique moment in human history. Not that long ago, the first human genome was sequenced at a cost of about a billion dollars. Now a patient's entire genome can be sequenced for 1000–2000 dollars, and the cost is dropping rapidly. Variability is introduced into DNA sequences in a significant proportion of meiotic and mitotic events leading to more genetic variability than previously recognized. Practicing neuropsychiatry now is like practicing general medicine when the first microscopes became available. It will take lots of work and careful observation to make all this new data maximally useful. Already it is apparent that the distinct psychiatric categories of the DSM do not map onto distinct genetic causes. Instead, the genetic mutations are proving pleiotropic and the psychiatric categories heterogeneous with borders that are blurring. With the rapid advance of genetic testing, entirely new disease entities will be uncovered, and many will cross the prior borders of psychiatry and neurology. This is a very exciting but also sobering conceptual shift. As a result of these many changes, patients will benefit from better diagnostics, genetic counseling, and new translational therapies based on the mechanism stemming from newly discovered pathogenic mutations.

Clinical Pearl #4
In the evaluation of a child with psychiatric and neurological symptoms, regression, even in the absence of genetic features, it is important to consider the potential contribution from one or more genetic abnormalities.

References

1. Ingason A, Rujescu D, Cichon S, Sigurdsson E, Sigmundsson T, Pietiläinen OP, Buizer-Voskamp JE, Strengman E, Francks C, Muglia P, Gylfason A, Gustafsson O, Olason PI, Steinberg S, Hansen T, Jakobsen KD, Rasmussen HB, Giegling I, Möller HJ, Hartmann A, Crombie C, Fraser G, Walker N, Lonnqvist J, Suvisaari J, Tuulio-Henriksson A, Bramon E, Kiemeney LA, Franke B, Murray R, Vassos E, Toulopoulou T, Mühleisen TW, Tosato S, Ruggeri M, Djurovic S, Andreassen OA, Zhang Z, Werge T, Ophoff RA, GROUP investigators, Rietschel M, Nöthen MM, Petursson H, Stefansson H, Peltonen L, Collier D, Stefansson

K, St Clair DM. Copy number variations of chromosome 16p13.1 region associated with schizophrenia. Mol Psychiatry. 2011;16(1):17–25. https://doi.org/10.1038/mp.2009.101. Epub 2009 Sep 29.
2. Kesby JP, Eyles DW, McGrath JJ, Scott JG. Dopamine, psychosis and schizophrenia: the widening gap between basic and clinical neuroscience. Transl Psychiatry. 2018;8:30. https://doi.org/10.1038/s41398-017-0071-9.
3. Gur R, Calkins M, Satterthwaite T, Ruparel K, Bilker W, Moore T, Savitt A, Hakonarson H, Gur R. Neurocognitive growth charting in psychosis spectrum youths. JAMA Psychiat. 2014;71(4):366–74. https://doi.org/10.1001/jamapsychiatry.2013.4190.
4. Waters F, Fernyhough C. Hallucinations: a systematic review of points of similarity and difference across diagnostic classes. Schizophr Bull. 2017;43(1):32–43. https://doi.org/10.1093/schbul/sbw132.
5. Kiriakopoulos E, Shafer OP. Focal onset impaired awareness seizures (complex partial seizures). 2017. https://www.epilepsy.com/learn/types-seizures/focal-onset-impaired-awareness-seizures-aka-complex-partial-seizure.
6. Syeda A, Karim MR. The mean age of petit mal epilepsy. J Pediatr Neurosci. 2016;11(2):112–4. https://doi.org/10.4103/1817-1745.187627.
7. Dawoud S, Ingram JB. Top 10 facts you should know about absence epilepsy. J Miss State Med Assoc. 2016;57(7):210.
8. Qiu W, Yu C, Gao Y, Miao A, Tang L, Huang S, Jiang W, Sun J, Xiang J, Wang X. Disrupted topological organization of structural brain networks in childhood absence epilepsy. Sci Rep. 2017;7(1):11973. https://doi.org/10.1038/s41598-017-10778-0.
9. Lee HJ, Kim EH, Yum MS, Ko TS, Kim HW. Attention profiles in childhood absence epilepsy compared with attention-deficit/hyperactivity disorder. Brain Dev. pii: S0387-7604(17)30260-7. 2017; https://doi.org/10.1016/j.braindev.2017.09.006.
10. Brownstein CA, Kleiman RJ, Engle EC, Towne MC, D'Angelo EJ, Yu TW, Beggs AH, Picker J, Fogler JM, Carroll D, Schmitt RC, Wolff RR, Shen Y, Lip V, Bilguvar K, Kim A, Tembulkar S, O'Donnell K, Gonzalez-Heydrich J. Overlapping 16p13.11 deletion and gain of copies variations associated with childhood onset psychosis include genes with mechanistic implications for autism associated pathways: two case reports. Am J Med Genet A. 2016;170A(5):1165–73. https://doi.org/10.1002/ajmg.a.37595. Epub 2016 Feb 16.
11. Marshall C, Howrigan D, Schizophrenia Working Groups of the Psychiatric Genomics Consortium. Contribution of copy number variants to schizophrenia from a genome-wide study of 41,321 subjects. Nat Genet. 2017;49:27–35. https://doi.org/10.1038/ng.3725.
12. Ramalingam A, Zhou XG, Fiedler SD, Brawner SJ, Joyce JM, Liu HY, Yu S. 16p13.11 duplication is a risk factor for a wide spectrum of neuropsychiatric disorders. J Hum Genet. 2011;56(7):541–4.
13. Hessl D, Tassone F, Loesch DZ, Berry-Kravis E, Leehey MA, Gane LW, Barbato I, Rice C, Gould E, Hall DA, Grigsby J, Wegelin JA, Harris S, Lewin F, Weinberg D, Hagerman PJ, Hagerman RJ. Abnormal elevation of FMR1 mRNA is associated with psychological symptoms in individuals with the fragile X premutation. Am J Med Genet. 2005;139B:115–21. https://doi.org/10.1002/ajmg.b.30241.
14. Brower SC, Piatkov IK, Varshavsky A. Neurodegeneration-associated protein fragments as short- lived substrates of the N-end rule pathway. Mol Cell. 2013;50(2):161–71. https://doi.org/10.1016/j.molcel.2013.02.009.
15. Fujitani M, Zhang S, Fujiki R, Fujihara Y, Yamashita TA. Chromosome 16p13.11 microduplication causes hyperactivity through dysregulation of miR-484/protocadherin-19 signaling. Mol Psychiatry. 2017;22:364–74.

Growing Up with Autism: Incorporating Behavioral Management and Medication to Manage Self-Injurious Behavior

10

Ahmad M. Almai and Aaron J. Hauptman

Case

Khaled is a ninteteen-year-old young man with autism spectrum disorder who first presented for evaluation and psychiatric management at age twelve. His history of ASD is complicated by multi-domain developmental delays, ADHD, epilepsy, aggression, and self-injurious behavior. His treatment had included many medication trials that were minimally efficacious. At the time of presentation, Khaled was attending a full-time, specialized school for autistic children where he received a variety of services including speech therapy, occupational therapy, and behavioral therapy as well as developmentally appropriate academic services and art classes. He was being treated with escitalopram 15 mg daily, naltrexone 25 mg twice a day and olanzapine 5 mg daily. However, he continued to experience symptom breakthrough that put his and others' safety at risk.

Khaled was born at 28 weeks gestation by uncomplicated spontaneous vaginal delivery without prenatal trauma or exposures. His birth weight was 1.5 kg, and he was hospitalized for 27 days due to initial breathing and feeding difficulties. His early development was within normal limits, and his parents described him as playful, smiling, and very socially responsive. He started to walk and speak in single words at about thirteen months.

When Khaled was eighteen months old, however, his parents observed behaviors that concerned them. In particular, they remark that he had stopped responding when called by name and had become less responsive during play. His parents and primary care physician suspected a hearing problem due to decreased

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responsiveness, but an audiology evaluation showed results within normal limits. He was evaluated at 26 months by a speech pathologist who concurred that there were significant language delays. Speech and language therapy was initiated.

A full psychological evaluation, including formal autism assessment and Vineland adaptive skills scale, was done which indicated autism spectrum disorder. The psychologist also noted the presence of hyperactivity, which met the criteria for comorbid attention-deficit/hyperactivity disorder, combined type. His neurological evaluation was grossly normal at that time, and all ancillary tests, including brain MRI, EEG, urine amino acids, and chromosomal analysis, were normal. Additional tests at age four including karyotype, fragile X testing, and infectious, metabolic, and autoimmune panels all were normal as was a repeat brain MRI.

When Khaled was 4, his parents noted that he had shown some developmental progress: He was using single words to express his needs, such as "water" when he wanted a drink. He would use idiosyncratic words to represent specific terms, such as "dodo" for sleep, "naughty" when he was upset with his sister, or "wawa" when he was about to hit himself. Additionally, he was developing socially and behaviorally; the family commented that he was more responsive to play, would cuddle, and frequently sought his mother's affection and expressed affection for her. These gestures would include hugging and placing his head over her shoulder. He enjoyed going out with the family to the shopping mall. He also started routinely visiting a nearby public park every evening. Despite these improvements, Khaled continued to demonstrate dysregulated and hyperactive symptoms that were treated initially with methylphenidate 10 mg to allow him to attend to his speech and behavioral therapy sessions. His neurologist also treated him with haloperidol 1 mg daily, which was later increased to 3 mg. His therapist observed that he was better engaged, more responsive, and making stronger gains in learning activities. Methylphenidate was increased over time to 10 mg twice daily to address worsening behavioral and attentional problems.

When Khaled was 4.5, his parents had become concerned that his medication might be negatively affecting his behavior and eventually worked with his neurologist to discontinue them gradually. Irritability and hyperactivity subsequently increased. IVIG infusion treatment was done over the course of a 3-day hospitalization without apparent benefit. A course of risperidone 0.5 mg daily was started to address worsening behavioral difficulties. Trials of clonidine 37.5 μg were added, and fluoxetine was started and soon titrated up to 7 mg per day. Brief improvement was noted. However, fluoxetine was soon discontinued due to apparent inefficacy.

At age five, Khaled started to exhibit new behaviors. He would become angry when his demands were not met and would become dysregulated when told "no." He would throw temper tantrums with episodes of screaming and throwing himself on the floor. He began to become uncharacteristically oppositional and stubborn. Despite this, he did show improvements in hyperactivity and was able to sit alone at a table and attend to the task of completing a jigsaw puzzle for over 45 min with little adult involvement. He loved to sit alone and play with toys. These periods of calm, on the other hand, were punctuated by episodes of self-stimulating behaviors including spinning around and repeatedly clenching his fist.

Khaled's self-injurious behavior began at age ten. These include punching himself in the head and face repeatedly and banging his head against the wall to the point of causing severe contusions. These self-injurious episodes would occur

several times throughout the day and would be preceded by arm flapping and verbal and physical agitation which would gradually escalate into more violent self-directed aggression. At first, these behaviors were mild and were presented only during periods of transition or interruption of rituals or schedules. They occurred before meals, shower time, or before his daily walks with the family to the nearby mall or public park. They would especially occur if there was any delay by his family members, his nanny, or behavioral therapist in starting the activity on time. He also would engage in self-injurious behavior in response to feeling cold, yet he refused at times to wear warm clothes.

With time, episodes of self-injury evolved to take place when family members or caregivers would refuse to give in to his demands such as leaving the house for a walk at unscheduled times. There was a degree of situational selectivity to the behavior at times. For instance, he would be observed to be punching himself harder and more repeatedly if his mother was watching. The behaviors would abate when his demands were met.

Initially, the self-injurious behavior could be managed through minor behavioral intervention; however, over time, they became worse and uncontrollable to the point where he would have to wear a helmet and gloves to prevent serious injury. A sponge ball was also used at times to distract him from those behaviors and could sometimes occupy him for short periods. By this time, he would no longer respond to verbal prompts or redirection. Several dietary interventions were attempted by his family including introducing casein-free and gluten-free diets which were discontinued due to a lack of efficacy.

Over time, the behaviors became more frequent and difficult to control and, as Khaled grew in age and size, he became physically harder to manage. Family members and caregivers frequently gave in to his demands to prevent him from hurting himself. Additionally, at age 12, Khaled was admitted to the hospital emergency room after having an unprovoked generalized tonic-clonic seizure with loss of consciousness and loss of bladder and bowel control. He had an extensive workup in the emergency room including non-contrast head CT, chest X-ray, EKG, CBC, electrolyte panel, liver functions, CRP, PT/INR, and random serum glucose. All results were within normal limits apart from slightly low serum sodium, chloride, and phosphorus that were resolved with repletion. He was diagnosed with a seizure disorder and was discharged with a referral to pediatric neurology. The neurologist who saw him for outpatient follow-up started topiramate which was gradually increased to 50 mg twice a day. Over the course of the following three months, he had two other episodes of generalized tonic-clonic seizures. Behavioral dysregulation was noted to markedly worsen around the times of his seizures.

Neuropsychiatric Reevaluation

Khaled and his family presented for reevaluation and further pharmacotherapeutic management at a point of crisis at age twelve. His medication at that time included escitalopram 15 mg daily, naltrexone 25 mg twice a day, topiramate 50 mg BID, and olanzapine 5 mg daily. His parents reported that they had continued the

current medication regimen because they feared that his behavior would regress even further.

In the context of his intake evaluation, the role of behavioral reinforcement as an escalating factor worsening Khaled's behaviors became particularly salient. Focusing on behavioral intervention was determined to be a priority at this stage in addition to the medication regimen, which had previously been the focus of treatment. The behavioral goals were to decrease self-injurious behaviors while minimizing necessity for restraint and protective gear while simultaneously increasing positive behaviors and tolerance of schedule changes and transitions. Effective use of verbal prompts and directions was emphasized. Full Applied Behavioral analysis (ABA) services were not initiated, but a system was put into place that utilized behavioral principles. For instance, both antecedent and extinction-based strategies were put into place at home and at school.

As part of a careful behavioral plan, Khaled's caregivers were directed to keep themselves from rushing into physically stopping him from hurting himself and to utilize judicious "active ignoring." With time and careful behavioral technique instruction with his caregivers, Khaled was able to tolerate a relative decrease in restraint and an increase in verbal redirection. Soft hand restraints were applied for short periods during repeated and prolonged episodes of self-injurious behavior.

Multiple medication trials were utilized concurrently, including risperidone, which was ineffective. Clonidine was titrated to 75 μg three times a day, and naltrexone was increased to 75 mg daily. Khaled's parents soon stopped clonidine due to excessive sedation. Chlorpromazine was added up to 50 mg twice a day when necessary for periods of more severe increased agitation. With behavioral interventions, administration of chlorpromazine could be reduced from daily to almost once a month. Khaled would still experience periods of increased agitation primarily because of summer vacation and a change in his daily routine. During these periods he would have increased occurrences of wetting himself at night with interrupted sleep. Additional behavioral interventions were successfully introduced at these times to address any novel behavioral issues.

The next few years were better but still included periods of marked behavioral fluctuations. Lorazepam 1 mg twice a day was introduced as needed in addition to other behavioral interventions including soft hand restraint. Chlorpromazine was gradually also titrated to 500 mg at nighttime but was changed to quetiapine XR due to inefficacy, and naltrexone was increased to 50 mg twice a day to target self-injury. Memantine 10 mg daily was introduced to target some of the core symptoms of autism, but was discontinued a month later because of escalating behavioral problems. Interrupted sleep was addressed over time as necessary with lorazepam but could eventually be discontinued. Ultimately, he stabilized on the following regimen: quetiapine XR 200 mg in the morning and 400 mg at night, naltrexone 50 mg twice a day, topiramate 50 mg twice a day, omega-3, and multivitamins.

Now nineteen years old, Khaled's receptive language has improved, and he is able to follow verbal commands. He continues to receive substantial ongoing therapeutic services. He has limited level of expressive language, and his parents estimated that, currently, he is consistently able to use about 30 words. When calm, he is able to utilize

three-word sentences but has limited verbal communication during periods of regression. He has acquired basic reading and writing skills including the ability to tell time on a clock, read the day and date on a calendar, and write using single letters and filling in the blanks. He is mostly independent with regard to self-care with some occasional help for activities such as showering. His schedule continues to be rigid. He generally goes to sleep at 9 pm and is able to sleep uninterrupted through the night without interruption.

He is calm and frequently participates in group activities at school, although he often chooses to sit or play alone outside the classroom. He continues to be bothered by loud noises made by others, even though he enjoys listening to music and dancing. He struggles with seasonal temperature changes and is bothered by heat in the summer time, preferring to stay indoors. He wears a baseball cap nearly all the time and becomes irritated when unable to do so. He goes out of the house for walks or to the mall at specific times in the day when the weather is not hot.

Khaled's self-injurious behavior has essentially subsided permitting medications to be weaned as tolerated. At his most recent visit, in addition to ongoing discussion of academic and educational optimization, independence in self-care, and some instrumental activities of daily living, the focus has shifted toward helping Khaled transition to adulthood which includes increased independence and development of vocational skills. His parents are working toward placement in a long-term adult residential program specializing in treatment and rehabilitation of adults with autism in another country where such resources are more readily available.

Case Reflections

Khaled's case reflects early signs of developmental disability and the evolution of symptoms to include dangerous self-injury. As is often the case in treating individuals with neurodevelopmental disabilities with behavioral challenges, many treatments were attempted, often out of a sense of desperation, with varying degrees of evidence base and efficacy. Self-injury, and tolerance of therapeutic interventions, gradually and painstakingly improved with close monitoring and the combination of behavioral psychotherapeutic techniques and pharmacotherapy. Understandably, Khaled's family and caregivers felt overwhelmed with Khaled's behaviors and, at times, unknowingly reinforced those behaviors. Many alternative therapies were tried with little report of success from the family.

Khaled's seizure disorder, with his first generalized tonic-clonic seizure at age twelve, further complicated his management. Notably, his history included a strong correlation between seizure episodes and behavioral escalation which improved once seizures were adequately controlled. However, these episodes, often resulted in prolonged behavioral setbacks that required additional behavioral and psychotropic medication modification. It is important to consider the impact of uncontrolled seizures on neurocognitive development as well as the impact of antiepileptic medication on cognition. Self-injurious behaviors in individuals with limited communication and intellectual disability can often occur in the setting of medical illness, such as untreated pain, constipation, and dental or periodontal disease. This is particularly

the case when there are changes in baseline behaviors, such as new-onset or increased frequency or intensity of self-injury.

Khaled was started on psychotropic medications at a very young age to control hyperactivity behavioral dysregulation. His treatments, as they occurred outside of the United States, did not necessarily follow quite the same pattern of prescribing (e.g., initial neuroleptic trial with haloperidol, early use of chlorpromazine), though it was generally focused on the same categories of pharmacotherapeutic treatment as are often trialed in the United States. The choice of pharmacotherapy was also heavily impacted by medication availability and cost. His medication regimen evolved over time, striking eventual success with a combination of neuroleptic management, naltrexone, antiepileptic medication, and strong behavioral management protocols.

Neuroanatomy

Neuroanatomy studies suggest that individuals with autism and self-injurious behavior (SIB) may have somatosensory cortex and thalamus abnormalities along with structural and functional alterations in related white matter pathways [1]. Abnormalities in the cortico-striato-thalamo-cortical loops appear to be involved as well, with particular implication of altered striatal morphology in SIB in both idiopathic autism spectrum disorder (ASD) and fragile X [2]. Functional neurosurgical interventions have targeted this loop, specifically at the the globus pallidus internus, in Lesch-Nyhan syndrome, a developmental disorder with very high rates of SIB and intellectual disability (ID) [3, 4]. One study utilizing functional neurosurgery in ASD for intractable SIB targeted the basolateral nucleus of the amygdaloid complex. Authors argue that this was successful due to its inhibitory GABA-ergic connections to a broad range of brain regions [5].

Most major neurotransmitter systems have been implicated in SIB in ASD and ID. Alterations in serotonin and dopamine have been implicated in studies in both ASD and other neurodevelopmental conditions associated with SIB, particularly Lesch-Nyhan syndrome (dopamine), cri du chat syndrome (dopamine), Prader-Willi syndrome (serotonin), and Cornelia de Lange syndrome (serotonin). GABA and glutamate, inhibitory and excitatory neurotransmitters respectively, have also been implicated [6].

Importantly, alterations in the endogenous opioid system have been suspected in SIB in ASD and other developmental conditions. There are two primary models. In the "endorphin model," pain stimulates endogenous opioid release resulting in postsynaptic downregulation of receptors which results in a sort of "addiction" to self-injurious behaviors [6–8]. An alternative model theorizes that individuals with SIB have increased levels of endogenous opioids which result in subsequent pain insensitivity, possibly mediated by stress or anxiety. It appears that there are alterations in the opioid pathway, including proopiomelanocortin, which shows abnormal regulation in 30–70% of individuals with SIB, and downstream beta-endorphin and adrenocorticotropic hormone, all of which are involved in the hypothalamic-pituitary-adrenal axis and stress response [6, 9].

Lessons Learned About Neuropsychiatry

The data available on self-injury in ASD is limited; studies in SIB and ASD are often limited by study design, sample size, and methodology. Self-injurious behavior (SIB) and aggression are two serious concerns in autism that result in care-level escalation and hospitalization. Estimated rates of SIB in ASD range from 15% to 50% with one report as high as 74% in a cohort of hospitalized individuals [10, 11]. Aggression can be seen in as many as two-thirds of individuals with ASD and is reported as a primary reason for medical and pediatric behavioral service referrals [12, 13]. These are phenomenologically different than in self-injurious or aggressive behaviors in typically developing individuals. For the most part, self-injury occurs on a continuum of repetitive or self-stimulatory behaviors, and aggression tends to be reactive and occurs in a setting of overwhelming sensory experience and emotional dysregulation.

Behavioral management for SIB in intellectually disabled individuals with ASD can take several forms. Commonly, behavioral management techniques follow Skinner's operant conditioning model, where behavior constitutes the physical behavior itself, the environmental events preceding it, and the subsequent outcomes [14]. The aim of treatment is to utilize the theory of operant conditioning, wherein the immediate consequences around a behavior will strengthen or weaken that behavior over time [15]. According to this, SIB, regardless of its precise neurochemical mechanism, can be thought of as a learned behavior that can be reinforced or extinguished based on environmental reinforcement [6].

Several steps involved in the process of behavioral management are outside of the scope of this chapter. However, a few points are necessary to mention, namely, use of intervention strategies targeting antecedents, reinforcements, and extinction. Preemptive management of antecedent factors can involve environmental enrichment, provision of alternative sensory experiences that are less dangerous or inappropriate, use of visual schedules and other techniques to facilitate ease of transitions, and careful management of demands to minimize the escape-avoidance function of SIB. Much can be said about reinforcing behaviors; however, in the case of Khaled, the reinforcing role of parental attention as well as the way SIB provided a form of control over his environment and possible escape from unwanted activities are of particular importance. Noncontingent reinforcement, such as parental attention given frequently and not in response to SIB, can decrease the need to engage in SIB. Expressions of distress, such as verbalizing frustration, can help substitute the dangerous behavior for one that is safer. This can be coupled with the use of extinction, where "planned" or "active" ignoring is done in the face of the unwanted behavior so as to decrease the social reward that may be associated with that behavior [6].

In many circumstances, behavioral management is sufficient; however, at times, particularly with more dangerous and dysregulated behaviors, medication may be necessary as well. No medication is specifically approved for treatment of self-injurious behavior in autism, and there are no treatments for the diagnostic core symptoms of autism. At present, only two psychotropic medications have regulatory indications for the treatment of irritability associated with ASD, risperidone

and aripiprazole. Significant efficacy and overall tolerability have been demonstrated after the administration of risperidone and aripiprazole for serious behavioral problems in ASD [16–19]. Risk of tardive dyskinesia, as well as metabolic, hormonal, cardiovascular and other side effects and risks, must be taken into consideration with this class of medication. First-generation antipsychotics have a long history in the treatment of hospitalized individuals with ASD or ID and SIB [20]. A small number of trials exist that show equivocal and inconsistent findings with haloperidol, chlorpromazine, and thioridazine [6]. They continue to often be used, though generally less frequently due to the burden of extrapyramidal and tardive dyskinesia risks [21]. Better benefit has been reported in second-generation neuroleptics including small trials of clozapine and olanzapine [22–25]. One of two studies on risperidone showed separation from placebo for SIB in ASD [26, 27]. Aripiprazole has been explored for agitation and a range of behavioral disturbances in autism, but not SIB specifically [6]. Ziprasidone has also been explored with some benefit in a few, small trials for severe disruptive behavior in ASD [28].

Alpha-2 agonists have shown some efficacy in irritability, attentional symptoms, sleep, impulsivity, hyperactivity, and overall severity of symptomatology in ASD [29]. Beta blockers, such as propranolol, have also been explored for treating disruptive behaviors including hypersexuality, self-injury, and aggression. While the results may appear promising, data is limited [30].

Selective serotonin reuptake inhibitors (SSRIs) are often used in the setting of self-injury and underlying psychiatric conditions, though data in children with ASD are mixed [6]. SSRIs are often used to treat comorbid symptoms that can cluster with autism such as anxiety, depression, obsessive-compulsive disorder, and other conditions. They have also been explored for the treatment of repetitive behaviors, which can sometimes overlap with compulsions, stereotypy, and self-injury in autism. Where trials in adults with autism are generally positive, pediatric trials are somewhat less consistent, and there have been negative results in two large placebo-controlled trials [31]. Antidepressant medications broadly seem to have marginal effects on irritability in children and adolescents with ASD. The data available for the is limited, but a small number of case studies in ID, a double-blind, controlled trial in compulsive skin picking, and a trial in self-injury in Prader-Willi syndrome all showed benefits [6, 32–35]. Paroxetine and fluvoxamine have also showed benefit in small trials [36, 37]. One open trial and one small double-blinded placebo-controlled trial with clomipramine, a tricyclic antidepressant, demonstrated benefit for SIB, but the latter was limited by a significant side effect burden [38, 39].

Buspirone has been explored to a much smaller degree. A single, small, open-label trial found benefit for anxiety and irritability in ASD, and a small placebo-controlled trial showed benefit for restrictive and repetitive behaviors as an adjunctive therapy [40, 41]. Uncontrolled studies and individual case reports have suggested some benefit in SIB in ASD, and buspirone tends to be relatively well-tolerated [6].

Mood stabilizers and antiepileptic agents have demonstrated variable results in aggression, irritability, and self-injury in ASD. Valproate shows mixed results in the management of these symptoms, particularly in children [31, 42]. In a single small

randomized, controlled study with lamotrigine for individuals with ASD and severe behavioral disruption, the treatment group did not separate from placebo in any measures [43]. Studies on oxcarbazepine, carbamazepine, gabapentin, and topiramate in these populations have limited data, though positive case series and reports are present in the literature [31]. There is limited literature on the use of lithium, but benefits have been reported in symptoms associated with Phelan-McDermid disorder as well as in a thirty-person retrospective review of youth with ASD and comorbid manic-like symptoms [44, 45]. Small studies in the 1970s exploring lithium for SIB in ID found efficacy in the setting, However, they were methodologically limited [6].

There is intriguing, but limited, data on a number of medications that interact with other neurotransmitter systems. Naltrexone is increasingly being tried in individuals with self-injurious behaviors in the setting of autism and other neurodevelopmental disabilities, possibly due to its impact on the endogenous opioid system. However, studies show mixed efficacy [46, 47]. Similarly, there is small-cohort, limited research into memantine, an anti-glutamatergic NMDA receptor antagonist, to treat various symptoms associated with autism which demonstrates some possible potential benefit [48]. N-acetylcysteine (NAC), a glutamatergic modulator, has been explored for the treatment of irritability and other symptoms associated with autism and has shown some benefit in a small, randomized, placebo-controlled trial, though other studies show equivocal effects [49–51].The baclofen enantiomer, R-baclofen, a selective GABA-B agonist, has been evaluated in a small, open-label study [52]. Electroconvulsive therapy has been successfully used for individuals with severe, treatment-refractory SIB in ASD and other developmental conditions, particularly if there are overlapping catatonic features [53–55].

Clinical Pearls

1. Psychotherapeutic behavioral management is a crucial component in treating self-injurious behavior and aggression in autism spectrum disorder and intellectual disability.
2. No psychotropic medications are formally approved for treating the core symptoms of ASD; however, aripiprazole and risperidone carry indications for associated agitation and dysregulation. Many other medications are considered for off-label use when behaviors are dangerous or severe. However, such medication must be used judiciously in light of limited data and side effect profiles in individuals with ASD.
3. Behavioral challenges in ASD and ID can wax and wane based on medical events, life circumstances, or causal triggers that may not be externally obvious. Close attention and hand-in-hand collaboration between family members, other caregivers, teachers, and the treatment team, as well as the patients themselves, are crucial to providing ongoing and carefully tailored management of symptoms.

References

1. Duerden EG, et al. Self-injurious behaviours are associated with alterations in the somatosensory system in children with autism spectrum disorder. Brain Struct Funct. 2014;219(4):1251–61. ISSN 1863-2661. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/23644587 >.
2. Wolff JJ, et al. Repetitive and self-injurious behaviors: associations with caudate volume in autism and fragile X syndrome. J Neurodev Disord. 2013;5(1):12. ISSN 1866-1947. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/23639144 >.
3. Deon LL, et al. Pallidal deep-brain stimulation associated with complete remission of self-injurious behaviors in a patient with Lesch-Nyhan syndrome: a case report. J Child Neurol. 2012;27(1):117–20. ISSN 1708-8283. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/21940691 >.
4. Taira T, Kobayashi T, Hori T. Disappearance of self-mutilating behavior in a patient with lesch-nyhan syndrome after bilateral chronic stimulation of the globus pallidus internus. Case report. J Neurosurg. 2003;98(2):414–6. ISSN 0022-3085. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/12593632 >.
5. Sturm V, et al. DBS in the basolateral amygdala improves symptoms of autism and related self-injurious behavior: a case report and hypothesis on the pathogenesis of the disorder. Front Hum Neurosci. 2012;6:341. ISSN 1662-5161. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/23346052 >.
6. Minshawi NF, et al. Multidisciplinary assessment and treatment of self-injurious behavior in autism spectrum disorder and intellectual disability: integration of psychological and biological theory and approach. J Autism Dev Disord. 2015;5(6):1541–68. ISSN 1573-3432. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/25395094 >.
7. Richardson C. Self-harm: understanding the causes and treatment options. Nurs Times. 2004;100(15):24–5. ISSN 0954-7762. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/15119257 >.
8. Richardson JS, Zaleski WA. Endogenous opiates and self-mutilation. Am J Psychiatry. 1986;143(7):938–9. ISSN 0002-953X. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/3717448 >.
9. Sandman CA, et al. The role of proopiomelanocortin (POMC) in sequentially dependent self-injurious behavior. Dev Psychobiol. 2008;50(7):680–9. ISSN 1098-2302. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/18688808 >.
10. Baghdadli A, et al. Risk factors for self-injurious behaviours among 222 young children with autistic disorders. J Intellect Disabil Res. 2003;47(Pt 8):622–7. ISSN 0964-2633. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/14641810 >.
11. Handen BL, et al. Risk factors for self-injurious behavior in an inpatient psychiatric sample of children with autism spectrum disorder: a naturalistic observation study. J Autism Dev Disord. 2018. ISSN 1573-3432. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/29368233 >.
12. Arnold LE, et al. Parent-defined target symptoms respond to risperidone in RUPP autism study: customer approach to clinical trials. J Am Acad Child Adolesc Psychiatry. 2003;42(12):1443–50. ISSN 0890-8567. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/14627879 >.
13. Davis NO, Carter AS. Parenting stress in mothers and fathers of toddlers with autism spectrum disorders: associations with child characteristics. J Autism Dev Disord. 2008;38(7):1278–91. ISSN 0162-3257. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/18240012 >.
14. Skinner BF. The behavior of organisms; an experimental analysis. New York/London: D. Appleton-Century Company; 1938. p. ix. 457 p.
15. Cooper JO, Heron TE, Heward WL. Applied behavior analysis. 2nd ed. Upper Saddle River: Pearson/Merrill-Prentice Hall; 2007. xxvii, 770 p. ISBN 0131421131978013142134.
16. McCracken JT, et al. Risperidone in children with autism and serious behavioral problems. N Engl J Med. 2002;347(5):314–21. ISSN 1533-4406. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/12151468 >.
17. McDougle CJ, et al. A double-blind, placebo-controlled study of risperidone in adults with autistic disorder and other pervasive developmental disorders. Arch Gen Psychiatry. 1998;55(7):633–41. ISSN 0003-990X. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/9672054 >.

18. Owen R, et al. Aripiprazole in the treatment of irritability in children and adolescents with autistic disorder. Pediatrics. 2009;124(6):1533–40. ISSN 1098-4275. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/19948625 >.
19. Shea S, et al. Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders. Pediatrics. 2004;114(5):e634–41. ISSN 1098-4275. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/15492353 >.
20. Parikh MS, Kolevzon A, Hollander E. Psychopharmacology of aggression in children and adolescents with autism: a critical review of efficacy and tolerability. J Child Adolesc Psychopharmacol. 2008;18(2):157–78. ISSN 1044-5463. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/18439113 >.
21. Patel NC, et al. Trends in the use of typical and atypical antipsychotics in children and adolescents. J Am Acad Child Adolesc Psychiatry. 2005;44(6):548–56. ISSN 0890-8567. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/15908837 >.
22. Cohen D, et al. Absence of cognitive impairment at long-term follow-up in adolescents treated with ECT for severe mood disorder. Am J Psychiatry. 2000;157(3):460–2. ISSN 0002-953X. Disponível em: < http://www.ncbi.nlm.nih.gov/pubmed/10698827 >.
23. Hammock R, Levine WR, Schroeder SR. Brief report: effects of clozapine on self-injurious behavior of two risperidone nonresponders with mental retardation. J Autism Dev Disord. 2001;31(1):109–13. ISSN 0162-3257. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/11439749 >.
24. Janowsky DS, Barnhill LJ, Davis JM. Olanzapine for self-injurious, aggressive, and disruptive behaviors in intellectually disabled adults: a retrospective, open-label, naturalistic trial. J Clin Psychiatry. 2003;64(10):1258–65. ISSN 0160-6689. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/14658977 >.
25. McDougle CJ, Kem DL, Posey DJ. Case series: use of ziprasidone for maladaptive symptoms in youths with autism. J Am Acad Child Adolesc Psychiatry. 2002;41(8):921–7. ISSN 0890-8567. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/12164181 >.
26. Aman MG, et al. Double-blind, placebo-controlled study of risperidone for the treatment of disruptive behaviors in children with subaverage intelligence. Am J Psychiatry. 2002;159(8):1337–46. ISSN 0002-953X. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/12153826 >.
27. Snyder R, et al. Effects of risperidone on conduct and disruptive behavior disorders in children with subaverage IQs. J Am Acad Child Adolesc Psychiatry. 2002;41(9):1026–36. ISSN 0890-8567. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/12218423 >.
28. Malone RP, et al. Olanzapine versus haloperidol in children with autistic disorder: an open pilot study. J Am Acad Child Adolesc Psychiatry. 2001;40(8):887–94. ISSN 0890-8567. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/11501687 >.
29. Jaselskis CA, et al. Clonidine treatment of hyperactive and impulsive children with autistic disorder. J Clin Psychopharmacol. 1992;12(5):322–7. ISSN 0271-0749. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/1479049 >.
30. Sagar-Ouriaghli I, Lievesley K, Santosh PJ. Propranolol for treating emotional, behavioural, autonomic dysregulation in children and adolescents with autism spectrum disorders. J Psychopharmacol. 2018;269881118756245. ISSN 1461–7285. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/29484909 >.
31. Accordino RE, et al. Psychopharmacological interventions in autism spectrum disorder. Expert Opin Pharmacother. 2016;17(7):937–52. ISSN 1744-7666. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/26891879 >.
32. Bloch MR, et al. Fluoxetine in pathologic skin-picking: open-label and double-blind results. Psychosomatics. 2001;42(4):314–9. ISSN 0033–3182. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/11496020 >.
33. Hellings JA, Warnock JK. Self-injurious behavior and serotonin in Prader-Willi syndrome. Psychopharmacol Bull. 1994;30(2):245–50. ISSN 0048-5764. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/7831463 >.
34. Sovner R, et al. Fluoxetine treatment of depression and associated self-injury in two adults with mental retardation. J Intellect Disabil Res. 1993;37(Pt 3):301–11. ISSN 0964-2633. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/8334322 >.

35. Stout RJ. Fluoxetine for the treatment of compulsive facial picking. Am J Psychiatry. 1990;147(3):370. ISSN 0002-953X. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/2309961 >.
36. Davanzo PA, et al. Paroxetine treatment of aggression and self-injury in persons with mental retardation. Am J Ment Retard. 1998;102(5):427–37. ISSN 0895-8017. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/9544340 >.
37. McDougle CJ, et al. A double-blind, placebo-controlled study of fluvoxamine in adults with autistic disorder. Arch Gen Psychiatry. 1996;53(11):1001–8. ISSN 0003-990X. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/8911223 >.
38. Garber HJ, et al. Clomipramine treatment of stereotypic behaviors and self-injury in patients with developmental disabilities. J Am Acad Child Adolesc Psychiatry. 1992;31(6):1157–60. ISSN 0890-8567. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/1429420 >.
39. Lewis MH, et al. Clomipramine treatment for self-injurious behavior of individuals with mental retardation: a double-blind comparison with placebo. Am J Ment Retard. 1996;100(6):654–65. ISSN 0895-8017. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/8735578 >.
40. Buitelaar JK, Van Der Gaag RJ, Van Der Hoeven J. Buspirone in the management of anxiety and irritability in children with pervasive developmental disorders: results of an open-label study. J Clin Psychiatry. 1998;59(2):56–9. ISSN 0160-6689. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/9501886 >.
41. Chugani DC, et al. Efficacy of low-dose buspirone for restricted and repetitive behavior in young children with autism spectrum disorder: a randomized trial. J Pediatr. 2016;170:45–53. e1-4. ISSN 1097-6833. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/26746121 >.
42. Hellings JA, et al. A double-blind, placebo-controlled study of valproate for aggression in youth with pervasive developmental disorders. J Child Adolesc Psychopharmacol. 2005;15(4):682–92. ISSN 1044-5463. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/16190799 >.
43. Belsito KM, et al. Lamotrigine therapy for autistic disorder: a randomized, double-blind, placebo-controlled trial. J Autism Dev Disord. 2001;31(2):175–81. ISSN 0162-3257. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/11450816 >.
44. Serret S, et al. Lithium as a rescue therapy for regression and catatonia features in two SHANK3 patients with autism spectrum disorder: case reports. BMC Psychiatry. 2015;15:107. ISSN 1471-244X. Disponível em: < http://www.ncbi.nlm.nih.gov/pubmed/25947967 >.
45. Siegel M, et al. Preliminary investigation of lithium for mood disorder symptoms in children and adolescents with autism spectrum disorder. J Child Adolesc Psychopharmacol. 2014;24(7):399–402. ISSN 1557-8992. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/25093602 >.
46. Roy A, et al. Are opioid antagonists effective in attenuating the core symptoms of autism spectrum conditions in children: a systematic review. J Intellect Disabil Res. 2015;59(4):293–306. ISSN 1365-2788. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/24589346 >.
47. Symons FJ, Thompson A, Rodriguez MC. Self-injurious behavior and the efficacy of naltrexone treatment: a quantitative synthesis. Ment Retard Dev Disabil Res Rev. 2004;10(3):193–200. ISSN 1080-4013. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/15611982 >.
48. Ghaleiha A, et al. Memantine as adjunctive treatment to risperidone in children with autistic disorder: a randomized, double-blind, placebo-controlled trial. Int J Neuropsychopharmacol. 2013;16(4):783–9. ISSN 1469-5111. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/22999292 >.
49. Dean OM, Gray KM, Villagonzalo KA, et al. A randomised, double blind, placebo-controlled trial of a fixed dose of N-acetyl cysteine in children with autistic disorder. Aust N Z J Psychiatry. 2017;51(3):241–9.
50. Hardan AY, et al. A randomized controlled pilot trial of oral N-acetylcysteine in children with autism. Biol Psychiatry. 2012;71(11):956–61. ISSN 1873-2402. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/22342106 >.
51. Wink LK, Adams R, Wang Z, et al. A randomized placebo-controlled pilot study of N-acetylcysteine in youth with autism spectrum disorder. Mol Autism. 2016;7:26.

52. Erickson CA, et al. STX209 (arbaclofen) for autism spectrum disorders: an 8-week open-label study. J Autism Dev Disord. 2014;44(4):958–64. ISSN 1573-3432. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/24272415 >.
53. Consoli A, et al. Medical and developmental risk factors of catatonia in children and adolescents: a prospective case-control study. Schizophr Res. 2012;37(1–3):151–8. ISSN 1573-2509. Disponível em: < http://www.ncbi.nlm.nih.gov/pubmed/22401837 >.
54. Dhossche DM, Wachtel LE. Catatonia is hidden in plain sight among different pediatric disorders: a review article. Pediatr Neurol. 2010;43(5):307–15. ISSN 1873-5150. Disponível em: < http://www.ncbi.nlm.nih.gov/pubmed/20933172 >.
55. Wachtel LE, et al. ECT for self-injury in an autistic boy. Eur Child Adolesc Psychiatry. 2009;18(7):458–63. ISSN 1435-165X. Disponível em: < http://www.ncbi.nlm.nih.gov/pubmed/19198918 >.

Part III

Developmental Networks

Introduction

Emotions are enmeshed in the neural networks of reason.
Antonio Damasio, MD, PhD

Networks may be the key to how the brain can be understood. What makes us human is not only the larger cerebral substrate with which we operate but the connections within that substrate. These chapters explore pediatric neuropsychiatry from a perspective beyond specific brain regions underlying emotions and behavior. The ongoing refinements that occur in neural circuits are integral to the process of development. When such processes go even slightly awry, the consequences may be profound yet complicated to discern.

For each of the cases in this section, regardless of the specific exposure or the underlying congenital condition, network connectivity and the ability to modulate anxiety, impulsivity, and mood appear to be intimately related. Furthermore, treatment strategies are not specific to neurophysiologic parameters. In each case in this section, a holistic approach is essential to address needs of the individual as well as the family. Psychosocial as well as medical circumstances are equally important. Perhaps the main lesson in this section is that, to address disruptions in widespread neural networks, target symptom driven treatment is insufficient. As is the case in many complex medical conditions, the family structure as a whole is relevant, and treatment including a family focused approach is preferred. The fact that such an approach is meaningful even for marked neuropsychiatric illness is a worthy reminder.

This section begins with the case of a young woman whose neurodevelopmental comorbidities include partial agenesis of the corpus callosum and reveals the complexity of social cognition and communication and the need for cross-referencing between cerebral hemispheres. Anxiety may be a particularly negative influence upon neural connectivity and is explored in the second case. Conversion disorder appears to markedly impair development, magnifying the effects of an underlying genetic disorder. From here begins an exploration of toxic exposures, such as drugs

of abuse and environmental contaminants, during key developmental periods. Although known genetic syndromes affecting neural networks may be rare, prenatal exposures to substances of abuse are common, and network effects may be marked even for seemingly minor exposures. In this series of cases, rather than specific areas being more vulnerable to damage, it appears that widespread regions may be adversely affected and the neurodevelopmental impact of such risk factors is emphasized.

Two Sides to Every Story: Growing Up with Agenesis of the Corpus Callosum

11

Jay A. Salpekar and Aaron J. Hauptman

Case

Shelly is a 16-year-old female with a long history of developmental disabilities. She presented to the outpatient office with impulsive behavior, intrusiveness, and restlessness that had been increasing over the past 6 months. She would verbalize questions in an intense and pressured manner often with increasing loudness in her voice. She also had seemingly spontaneous episodes of yelling and, in the midst of a verbal outburst, would be very difficult to redirect.

She would perseverate, asking questions repeatedly, sometimes in bursts of several questions in a row, over and over requesting the same answer. Examples of questions included, "Am I ok? When are we going home? Where are we going?" She would ask questions and require prompt answers, presumably to receive reassurance, nearly constantly, for hours a day. Caregivers around her would become exhausted with her apparently insatiable perseveration on the same questions over and over, gradually getting more frantic in her verbalization.

Shelly has congenital neurodevelopmental disorder that includes presumed sequelae from partial trisomy 16. In Shelly's case, the trisomy P-16 was a de novo mutation resulting in additional genetic material on the short arm of chromosome 16. Her parents did not have genetic anomalies or any family history of neuropsychiatric illness. She was born in breech position, but at full term and without perinatal complications, although her mother remarked that she did not "turn" while in utero. Early in infancy, she had physical delays including not rolling over until age

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8 months. She was noted to have low muscle tone and neurologic evaluation was done. She received genetic testing as well as a brain MRI which was notable for marked agenesis of the corpus callosum. A subsequent MRI at age 10 confirmed colpocephaly and agenesis of all but a 1.2 cm segment in the midline of the corpus callosum which appeared to be intact. The corpus callosum is typically approximately 10 cm long, meaning that Shelly's represents a near-total agenesis. No other CNS lesions were identified.

Significant gross and fine motor delays persisted. She did not walk until age 2, after which gradually gained reasonable ambulatory stability, and ultimately became right-hand dominant. She began speaking at 1 year, although articulation was problematic. She needed assistance with some activities of daily living, including dressing and toileting, though these improved over the next few years with speech and occupational therapy.

Neuropsychological and developmental evaluations noted consistent delays in cognitive function. At age 5, Vineland Adaptive Scales and Bayley Scales of development showed functionality in the 2–3-year-old age range with some word skills as high as the 4-year-old range. As a preschooler, she was socially very interested though could not always figure out how to play with others. She engaged in parallel play and often watched others, trying to imitate them. By age 7, full scale IQ was reported in the 55–65 range with verbal abilities consistently better than nonverbal abilities.

At age 5 she was noted to have staring spells. An EEG noted right temporal-parietal and left central epileptiform discharges. The spells stabilized with carbamazepine; however, subsequent EEGs continued to show sharp waves bilaterally in anterior regions. Of note, for many years including the present day, she has episodes where she will suddenly look up or have twitches in her face or neck, accompanied by very brief staring.

From ages 5 to 8, epilepsy stabilized, but her behavior and severe anxiety became more problematic. Shelly had always been anxious regarding medical or dental visits, getting haircuts, and in transition times. When anxious, she would raise her voice, cry, repeatedly say "I want to go home," and be difficult to calm down. At this time, Shelly's parents reported that she had a short attention span, requiring repeated directions to accomplish even simple tasks.

In addition to behavioral treatments and individualized educational programming, medication treatment in addition to anticonvulsants was begun. At age 6, a treatment trial of guanfacine was attempted with limited success. Shelly continued to have significant difficulty with hyperactivity and inattention. Her anxiety persisted to such a degree that sertraline was briefly given but discontinued because of vomiting. Because of perseverative and disruptive behavior that severely impacted Shelly's functioning, risperidone was started at age 9. There was some improvement in sleep onset but only slight improvement in anxiety.

Clinical Pearl #1
A challenging aspect of pediatric neuropsychiatry is the dearth of research on the type of patients represented within the clinical population. As a result the typical psychiatric or neurological algorithmic treatment approach is usually fraught with logical confounds. For example, the fact that Shelly responded well to fluoxetine, but not to escitalopram, reflects a common finding in practice. This was a case where the less neurotransmitter-specific or "dirtier" pharmacotherapeutic agent was more effective. Clinical trials do not exist to prove that point; however, given the heterogeneity of child neuropsychiatry cases, often one must wed theoretical approaches with trial and error for optimal outcomes.

At age 11, she was tapered off risperidone as it seemed to have waned in efficacy. Shelly's days were still characterized by emotional "roller coasters." Escitalopram was also attempted presumably to target anxiety but was discontinued after 6 months because of lack of efficacy.

Since age 12, Shelly's physical health and seizure control improved, though she continued to have behavior difficulties, usually related to inattention and anxiety symptoms that led to perseveration about impending events. She did not have compulsive routines, rigidity, or other compulsive behaviors. She demonstrated no dysphoria or hypomania. Sleep, appetite, and energy were intact. She did not have fears or phobias beyond her verbalizations and need for reassurance via responses to her questions. Medication trials subsequently included buspirone and aripiprazole but yielded only moderate improvement.

Behavioral interventions such as precise daily routines and predictable scheduling were quite helpful. Her verbal skills continued to improve, though she was very concrete in her interpretations. For significant periods of time, she thrived in a specialized curriculum emphasizing life skills and directed work activities.

Shelly's acute social sense and intense interest in the feelings of others became gradually more apparent during Shelly's adolescence. Some of her perseverative statements would include repetitively questioning others about their happiness or contentment, with the hope that they were happy and feeling good. She consistently enjoyed watching people and going into public spaces. However, despite her social interest, Shelly still struggled in school and other social settings because of her verbal perseverations and repeated, nearly echolalic phrases. At times she became so agitated and loudly assertive with her verbal queries that she was very difficult to redirect. She continued to exhaust caregivers and peers by her persistent questioning that often superseded personal boundaries and logic.

Because of the extent to which anxiety was considered to be the common thread driving many of the maladaptive behaviors, another course of guanfacine was started. The treatment goal was that the alpha-2 agonist could target impulsivity as well as anxiety and prevent some of the physiologic discomforts associated with her anxiety response. This time, Shelly had reasonable improvement with guanfacine; however, again, the improvement plateaued after about 6 months. She gradually became more frenetic with verbal perseveration to the extent of repeating herself over 100 times in a day, sometimes 100 times an hour. At that point, it was observed that the perseveration and anxiety were disrupting her sustained attention. With this in mind, distractibility was then targeted by a stimulant medicine, dexmethylphenidate.

After about 10 days of treatment, her distractibility improved. She had more prolonged and goal-directed flow of thought though still had pressured speech at times. She continued taking 10 mg of dexmethylphenidate extended release as well as 2.5 mg of immediate release in the afternoon. At that point, the guanfacine was discontinued. She gradually improved in terms of successful social interaction. She made some peer connections and established reasonable relationships with adults in her school setting. She was observed to have more sustained attention in social settings which appeared to mitigate anxiety.

Shelly continued to improve over the next 6 months, though she occasionally had recurrences of frenetic and perseverative statements and a persistence of baseline compulsive behaviors. Her overall gains regarding communication and personal space were to such a degree that the family was able to go on vacations out of town which they would have previously found impossible. After each vacation, in some cases overseas, Shelly seemed to markedly improve in terms of functionality and emotional stability. She appeared to be enthralled by new settings and, ultimately, reached a new level of calm after returning home.

While she had been improving with affective stability and profited from the exercise of "practicing conversations," it did seem that the behavior patterns bordered upon compulsion. At that point, fluoxetine was begun and maintained at 5 mg daily without side effects. The obsessionality improved though she continued speaking somewhat rapidly and at times repeating herself. However, the content was not driven by anxiety but instead reflected intense interest in conversational topics.

At present, Shelly still takes anticonvulsants, but 8 months ago, she discontinued fluoxetine and all other medicines. She has recurring bouts of perseveration and intense questioning, sometimes escalating rapidly and impulsively, but has continued to function reasonably well in most settings. Shelly continues to sustain gains in social relatedness and verbal interaction. She is still very interactive and enjoys social environments. She continues to have anxiety in less structured settings, and these are more routinely characterized by an increase in requests for reassurance. However, since her discontinuation of psychotropic medications, her symptoms have gradually increased over the past several months, with resultant decrease in functionality. At this point, additional treatments or revisiting previous medication treatments are again being considered.

Clinical Pearl #2

Shelly's response to medication was typical of the pattern experienced by many patients. She had gradual improvement in target symptoms over 1–2 weeks, sustained gains for about 6 months, and then gradual return of symptoms. At that point, medications were usually deemed ineffective and discontinued. They were not usually attempted again until approximately 3–4 months elapsed.

It could be considered that a tolerance phenomenon may be occurring with psychotropic medications. However, this is very likely an oversimplification. If tolerance were occurring, then increased dosages would have yielded renewed efficacy. Yet for Shelly, dosage increases did not have increasing efficacy. The fact that medication discontinuation did not result in symptom exacerbation suggests a more complex mechanism as well.

In many pediatric cases, growth and development means that the treatment targets significantly change. New medicines are sometimes necessary to address new neural targets that may not have existed earlier in development. Alternatively, cycling through trials of the same, or related, medicines, as was done with guanfacine and stimulants, may be more effective. Limited caliber evidence exists to guide treatment in pediatric neuropsychiatry, yet an approach to cycling medicine may nonetheless be a novel approach that is warranted in special cases. It may be inaccurate to consider that once a medicine is deemed ineffective, it will never be effective again.

Trisomy p16

Typically, trisomy of chromosome 16 is incompatible with life, but mosaicism or partial trisomy may occur, albeit rarely. The associated medical conditions are quite varied, including pulmonary valve stenosis and renal dysfunction. Because it is generally fatal in utero, very few publications exist on neuropsychiatric effects associated with partial trisomy 16, though like many other genetic disorders, developmental disabilities may be common [1].

Agenesis of the Corpus Callosum

Agenesis of the corpus callosum is uncommon, present in perhaps 1/4000 of the general population. However, in the context of developmental disability, at least partial agenesis may be present in 2–3/100 [2]. The corpus callosum grows from anterior to posterior, so if partial agenesis is present, usually the posterior segment

is absent. The corpus callosum itself contains upward of 200 million axons and is the most important connection between the two cerebral hemispheres. Although in many animals, several million axons cross the midline in white matter bundles, the corpus callosum is considered unique to placental mammals [3].

The corpus callosum has been implicated in several psychiatric illnesses. Differences in the thickness of the corpus callosum have been noted in pediatric bipolar disorder [4] and in Tourette syndrome [5]. Impulsivity and compulsion have also been frequently reported.

Agenesis of the corpus callosum has been associated with a number of genetic syndromes but is ultimately nonspecific [6]. Deficits in social interaction skills as well as altered language processing have been noted, suggesting a diagnostic overlap with autism spectrum disorders [7]. However, many with agenesis of the corpus callosum seem to be quite functional socially, distinctly unlike typical individuals with autism spectrum disorder, suggesting that the clinical significance is likely far more nuanced [8].

Case Reflections

While Shelly is challenged by developmental disability, seizure disorder, as well as likely perceptual or cognitive processing changes related to agenesis of the corpus callosum, much of her disruptive behavior appears to have been anxiety-fueled. She seeks understanding about the world around her with constant questioning, yet her need for reassurance seems nearly impossible to satisfy. She cannot reduce anxiety with self-soothing behavior or with outwardly physical activities. Instead, she wants comfort with words, even though the words seem insufficient. On one hand, she seems to forget that she has been answered, but it may be more accurate to consider that her main difficulty is in fully absorbing and perceiving the verbal information. She seeks reassuring words, but the words do not appear to translate to emotional comfort, and the nonverbal cues also do not seem to be well-perceived.

What is clear is that for Shelly, social sensibility and mitigation of social anxiety depend upon more than just verbal information. Shelly's challenge is not necessarily in perceiving information or even in reading social cues, but it is in correlating the social cues and verbal information. This can be hypothesized to be related to a deficit in integrating information between left- and right-brain-mediated information. Although Shelly's difficulties are heavily anxiety-related, the mismatch between processing capability and interaction between verbal and nonverbal information tend to further perpetuate her anxiety. Her response is then to repeatedly, verbally request reassurance and comfort, though unfortunately, the reassuring words in reply are only briefly effective in reducing her anxiety.

Although some may consider Shelly's psychiatric illness to be generalized anxiety disorder or even obsessive compulsive disorder, she has far too many neurologic and developmental conditions that confound traditional categorical psychiatric diagnoses. Anything beyond an unspecified anxiety diagnosis and attention deficit hyperactivity disorder could not be well established. She has not had additional

OCD symptoms that would affirm this diagnosis, and the time course of symptom exacerbation and remission would have been atypical.

Social sensibility is ultimately a bi-hemispheric phenomenon. Although Shelly has multiple disabilities, including trisomy 16, epilepsy, and motor delays, her functional challenge is most prominently in social interaction. Ironically, that is also her great strength. Perhaps, because she has intrinsic social skills that are advanced as compared to her other abilities, she remains more reliant upon them to interact with the world. Perseveration may have been a logical consequence to her deficits in processing socially-mediated information and observations. The fact that she struggles to apply abstraction to verbal information leads to significant further anxiety. Occasionally she responds to tone of voice with improvement in perseveration; however, that often does not last much longer than the brief period of calm offered by the semantic content of verbal responses to questions.

One social interaction is particularly representative of the unique perceptual challenges faced by Shelly. During a period of relative stability, Shelly and her family were traveling out of state. As was frequently the case, they would engender positive reactions from strangers in response to Shelly's gregarious engagement. Shelly's social skill and pleasant demeanor often shine in such circumstances. She struck up a conversation with a stranger who was nearby and was asked where she was from. Shelly replied, "I'm from Pennsylvania, where are you from? When the other person replied that she was from New York, Shelly was perplexed. She continued to repeat the question over and over again, getting slightly agitated as the person continued to state that she was from New York. Ultimately, Shelly's parents intervened and mitigated the awkward exchange, but the innocent misunderstanding was illustrative.

Shelly understood that she, herself, was traveling from her home and that place was called Pennsylvania. To her, though, the concept of "home" was linked to the word "Pennsylvania." As a result, she expected the stranger, coming from her respective home, to state that she was also from Pennsylvania and the report that she was from New York was conceptually dissonant. She struggled in connecting the abstract concepts with the concrete locations and, so, when unable to rectify these, became perseverative and agitated.

Lessons Learned About Neuropsychiatry

Integration between the two hemispheres appears to be crucial for the complex process of social and emotional functioning. In many cases, we use words either to express or "think through" anxiety-provoking situations. We also incorporate the words spoken to us by others to mitigate and more broadly understand our feelings of anxiety. But we also use those words in context and perceive additional nonverbal feedback to verify that we are safe, to become calm, and to be confidently reassured.

Perhaps the most important lesson that Shelly teaches us is that dramatic improvement is possible. Distinct improvement seemed to occur with antidepressant treatment,

even at low dose. The antidepressant stabilized Shelly in terms of her anxiety and perseveration. However, it seems intuitive that additional connections were made and processing clearly seemed to improve. The antidepressant dose was extremely low, so it is unlikely that the dosage targeted compulsion, as higher SSRI doses are often necessary for obsessive and compulsive symptoms, but instead its utility seemed to be in allowing new and more nuanced thought processing.

It has been theorized that antidepressants work, not necessarily by directly addressing symptoms but by allowing new processing of existing stimuli [9]. In other words, new information is processed in a different light and with a different context. People who have depression or anxiety may respond to any social engagement or new environment with a well-entrenched pattern of melancholy and trepidation, respectively. With antidepressants, the maladaptive patterns of old processing are dispensed, and new ways of processing information can proceed, presumably with a less rigid approach.

Although marked improvement seems related to medication treatment, it is intuitive to consider that enriched experiences also led to significant improvement in Shelly's demeanor and neuropsychiatric symptoms. Her world quite noticeably "grew" when she traveled. She relished the new environments and delighted in the shared experiences with her family. She and her family developed new, often nonverbal, approaches to managing her anxiety. Enriched environments and novel experiences, as can be had with travel, are known to be associated with significant neurogenesis [10].

Observations from Shelly's Family

Shelly's family notes that she still has a repertoire of questions that she asks every morning, and there are good days and bad days. Sometimes Shelly's mother sends a note to school, warning that it may be a bad day, but then often it does not develop as such.

In reviewing details of this chapter, Shelly's mother noted that she was surprised about the emotional reaction she had when reading the report. More than anything, she remembers being isolated from others and feeling alone in managing Shelly's challenging behaviors. She also recalls her own exhaustion as well as that of her husband and of Shelly's typically developing sibling. Overall, she hopes that families in similar situations can find a supportive community, as the isolation was one of the hardest challenges that she and her family faced.

References

1. Benn P. Trisomy 16 and trisomy 16 mosaicism: a review. Am J Med Genet. 1998;79:121–33.
2. Badaruddin DH, Andrews GL, Bolte S, Schilmoeller KJ, Schilmoeller G, Paul LK, Brown WS. Social and behavioral problems of children with agenesis of the corpus callosum. Child Psychiatry Hum Dev. 2007;38:287–302.
3. Palmer EE, Mowat D. Agenesis of the corpus callosum: a clinical approach to diagnosis. Am J Med Genet C: Semin Med Genet. 2014;166C:184–97.

4. Yasar AS, Monkul ES, Sassi RB, Axelson D, Brambilla P, Nicoletti MA, Hatch JP, Keshavan M, Ryan N, Birmaher B, Soares JC. MRI study of corpus callosum in children and adolescents with bipolar disorder. Psychiatry Res. 2006;146:83–5.
5. Plessen KJ, Gruner R, Lundervold A, Hirsch JG, Xu D, Bansal R, Hammar A, Lundervold AJ, Wentzel-Larsen T, Lie SA, Gass A, Peterson BS, Hugdahl K. Reduced white matter connectivity in the corpus callosum of children with Tourette syndrome. J Child Psychol Psychiatry. 2006;47:1013–22.
6. Paul LK. Developmental malformation of the corpus callosum: a review of typical callosal development and examples of developmental disorders with callosal involvement. J Neurodev Disord. 2011;3:3–27.
7. Paul LK, Corsello C, Kennedy DP, Adolphs R. Agenesis of the corpus callosum and autism: a comprehensive comparison. Brain. 2014;137:1813–29.
8. Booth R, Wallace GL, Happe F. Connectivity and the corpus callosum in autism spectrum conditions: insights from comparison of autism and callosal agenesis. Prog Brain Res. 2011;189:303–17.
9. Ma Y. Neuropsychological mechanism underlying antidepressant effect: a systematic meta-analysis. Mol Psychiatry. 2015;20:311–9.
10. Taber KH, Salpekar J, Wong AH, Hurley RA. Developmental origins for neuropsychiatric illness. J Neuropsychiatr Clin Neurosci. 2011;23:1–5.

Developmental Regression: The Power of Anxiety on the Maturing Brain

12

Rebecca Laptook, Matthew Willis, and Kristin Anderson

Case

Connie is a 14-year-old female with a history of typical development and a complex early medical history including idiopathic intracranial hypertension, growth hormone deficiency, and multiple concussions, who began experiencing developmental regression starting at age 7 that was not believed to be causally mediated by any of her underlying diagnosed medical conditions. After thorough neurological, psychiatric, and other medical evaluations, she was diagnosed with conversion disorder and, due to her declining function, was referred to a partial hospital level of care for further assessment and treatment.

Her initial presentation to the partial hospitalization program (PHP) was one of a developmentally regressed child. At the time, she was 13 years old but functioned more like a preschooler and exhibited heightened sensory issues. She made little eye contact, appeared disheveled, would shrug her shoulders in response to questions, was orally fixated on a "chewy stick," her hair, or anything else she could put in her mouth, wore large headphones to block out any sound she perceived as loud, would engage in hand flapping at times, and would mimic other children's behaviors. Despite being able to demonstrate such abilities in first grade, she no longer would recognize or write letters or numbers, sing the ABCs, count or state her age, or show recognition of amounts or time. She would scribble indiscriminately when prompted

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to color and would draw freehand by scribbling rather than drawing an outline of an object and then shading it in. Additionally, upon initial presentation to the PHP, Connie exhibited poor ADLs, including needing parental reminders and assistance to brush her teeth and to wash her hair. She appeared, at times, to have weak muscle tone and poor fine motor skills, as demonstrated by her difficulties engaging in such tasks such as opening food packages or cutting up her food.

Paradoxically, what was most striking about Connie's presentation was both the consistency and inconsistency of her exhibited behaviors. For example, Connie never wavered in her avoidance of showing recognition of anything numerical, whether it was in the context of playing a game, answering questions, identifying her locker key, etc. However, other seemingly cognitive deficits were inconsistent. While Connie reported that she couldn't learn or sing or remember the ABCs, she could watch YouTube videos of other songs, not associated with learning or academics, and memorize and sing them. Connie demonstrated typical abilities with regard to memory and learning unless it was related to a task that she perceived to be associated with formal academics. For example, while in the program, she learned to crochet, played new games, and memorized short stories/word games in the context of interacting casually with peers. She could answer questions and repeat back words when prompted unless she associated these questions and tasks with learning or developmental assessment. For example, if staff said, "My favorite color is pink. What is my favorite color?" Connie would reply "pink." However, if staff said "You are 14 years old. How old are you?" Connie would say "I don't know" or "I don't remember." Additionally, Connie's speech abilities were inconsistent. At times, Connie would be able to engage in discussions around age-appropriate topics; however, other times, she would provide one-word responses, use the wrong tenses of verbs, or say the wrong word (i.e., stating "you're welcome" instead of "thank you" or using "maded" as the past tense for "make").

Clinical Pearl #1

While the *DSM-5* includes conversion disorder and factitious disorder as separate disorders under the larger category of somatic symptom and other related disorders, there is no longer a requirement in *DSM-5* to determine that symptoms are unintentionally produced in order to diagnose conversion disorder. In Connie's case, while some behaviors appear to be volitional and others not, the overall function of her behaviors can be understood in the same way, as they all appear to serve to protect her from her anxieties around growing up and demonstrating independence. Thus, while it is frustrating for her parents and for others to tolerate her behaviors when at times they seem clearly intentional, it is important to remember that they serve the same purpose as her seemingly more unconscious behaviors and can be treated in a similar fashion [1]. Also notably, while one might consider the diagnosis of Ganser syndrome with Connie's presentation, her developmental regression was more expansive and multidimensional than one would anticipate with this syndrome, which typically presents with paralogia (offering "approximate" answers to questions) and is usually associated more clearly with malingering for clear material or procedural secondary gain (e.g., avoidance of legal penalties).

Relevant History and Course

Connie was born at full term with no complications and developed typically in early to mid-childhood, reaching all developmental milestones accordingly. She had a reported mild milk allergy as an infant that she outgrew but continued to experience ongoing constipation issues throughout childhood. Parents describe her as being very stubborn starting as a toddler but functioning well until around first grade. She was able to read at grade level, draw in an age-appropriate manner, retain information, perform simple math tasks, and speak normally. She exhibited some mild academic difficulty around the ages of 6 or 7 that prompted a neuropsychological evaluation, which indicated mild dyslexia and a nonverbal learning disorder. Of note, in first grade, Connie passed vision screenings at school but then went to an ophthalmologist in second grade, and her vision was determined to be very poor and requiring glasses. After results of the neuropsychological evaluation and vision evaluation, an individualized education program (IEP) was implemented at school. However, Connie's functioning began to decline during second and third grades, and, by fourth grade, she had lost almost all of her academic abilities. She could no longer read, write, or do simple math, but she was still able to draw very well. By sixth grade, though, Connie's artistic abilities regressed to scribbling. Between ages 12 and 13, she also exhibited some memory loss, such as not remembering a recent family trip to Disney World. Parents also noted more physical changes as well, including some loss of muscle tone, walking with a different gait, and more physical awkwardness, such as climbing stairs one step at a time instead of alternating her feet.

As Connie's functioning declined over the years, her parents were at first concerned about an underlying neurological or other medical cause, especially in the context of her medical history. Around the time of first grade, for example, Connie was the tallest child in her class, but then stopped growing. There is a family history of growth hormone deficiency, and Connie herself was diagnosed with this condition and subsequently has been followed by an endocrinologist. Additional medical history includes pseudotumor cerebri (otherwise referred to as idiopathic intracranial hypertension) [2] diagnosed at age 11 that has been treated with acetazolamide and followed closely by ophthalmology and neuro-ophthalmology. Connie also notably has a history of sustaining three reported concussions in less than 3 years. In third grade, she fell in the bathroom, hitting her head and breaking her ankle, and was subsequently diagnosed with nerve impingement from her lower extremity cast. She experienced significant hyperalgesia thought to be related to this nerve impingement. She had difficulty tolerating the sensation of a tissue or feather on her leg, requiring a desensitization regimen and a period of time in which she required crutches for ambulation. This lasted for approximately 90 days at which point she was seen by a chiropractor who did several one-time manipulations, after which Connie was able to walk without the crutches. Also of note, Connie's family medical history is notable for confirmed diagnoses of amyotrophic lateral sclerosis (ALS) in two members of the extended family.

Given the complex medical history described above, Connie's parents expressed concern to her multiple medical providers regarding a possible structural and/or otherwise discretely identifiable etiology for the multi-year history of

developmental regression described above. She accordingly underwent an extensive multidisciplinary workup that included MRI studies, an EEG, and a lumbar puncture. Ultimately, she was diagnosed by the outpatient team as having conversion disorder. Of note, while her medical history was certainly complex, her parents received a clear message from this team (and subsequently from her partial hospital team upon her admission to the program) that her history of developmental regression was not explained by the medical issues detailed above and that her ongoing and notably inconsistent cognitive, gross motor, and fine motor regression were best understood in the context of an emotional etiology [3].

Relevant Family Factors and Stressors

Connie lives with her parents and two older brothers. Connie has some social difficulties but overall is interested in peers and tends to gravitate toward younger ones. She also had made some friends in the neighborhood as well as through school and enjoys activities such as making slime and watching age-appropriate television shows such as *Full House* or *Girl Meets World*. She used to be engaged in some more physical activities such as Irish step-dancing, ballet, gymnastics, and softball but has struggled to participate recently given increasing physical coordination difficulties.

In terms of stressors, Connie's parents have noted that her symptoms seemed to coincide with the time when her mother started graduate school and thus was not as present in her daily life. Her mother has a history of attention-deficit hyperactivity disorder and found her program challenging and time-intensive, leading to her feeling as though she was not sufficiently available to assist Connie with her struggles academically or with her vision around the time of first grade. Additionally, around that same time, her older brother was struggling with anxiety and depression and was subsequently admitted to a psychiatric inpatient unit for a week. This appeared to exacerbate some of the existing stress within the parental relationship, and, soon after the hospitalization, Connie's parents separated, with her mother moving out of the home and into an apartment in which she stayed for a few nights each week (the remainder of the time staying in the home with the family). When Connie's parents told her that they were going to separate, they reported a noticeable negative change in her. This living situation lasted for about a year, at which time Connie's mother moved permanently back into the home, and, since then, Connie's parents have functioned more like housemates, living on separate floors of the home but engaging together in family activities while avoiding overt fighting or conflict.

More recent stressors include the impact that Connie's functioning has had over the years on the dynamic at home, notably creating a rift between her and her brothers as they are scared for what will happen to her, embarrassed by her behaviors, and frustrated by her stubbornness and attention-seeking. At school, Connie should be in the eighth grade but performs at a kindergarten level or younger. For a time, she had been placed in an alternative school setting but generally exhibited no improvement in that setting and had started to mimic the developmental level of her cohort, thus exacerbating her regressive behavior. Moreover, Connie is aware of her

academic and social difficulties, which has affected her motivation to be in a school setting with same-aged peers. Furthermore, an additional current family stressor is that a family member has late-stage ALS, and her mother has increasingly needed to travel out of state to help provide care. This has not only been stressful in the context of Connie's desire to have her mother remain close but also in the context of Connie's mother's ability to tolerate Connie's distress as the family tries to push her forward in her treatment.

Discussion

Connie's pattern of symptoms is being conceptualized along the spectrum of conversion disorder, specifically a type of conversion-based developmental regression. Her decline in functioning appears linked to underlying psychiatric symptoms (viz., anxiety) and relevant stressors including the presence of a history of learning/academic disabilities and vision issues, in addition to family/environmental stressors around the time that symptoms began. Additionally, it appears that her symptoms and behavioral patterns were inadvertently reinforced over a period of 5–6 years, thus resulting in more ingrained patterns of responding to her surroundings, as well as her own fixed belief that there is something structurally wrong with her brain. All of the above was also likely further exacerbated by Connie's baseline temperament, as described by her parents, as a child who has always been extremely stubborn and emotionally immature and who now understandably but maladaptively appears to seek "crutches" in her life to hold onto in order to prevent age-appropriate expectations about her functioning.

The theme of all of Connie's symptoms is one that points to her significant anxiety around growing up in the context of her apparent traumatic stressors. This is illustrated by her perceived inability to engage in tasks related to demonstrating growth, whether this be numerically related (e.g., counting, saying her age), academically related (e.g., reading, singing the ABCs), or just the ability to learn in general (e.g., avoidance of acknowledging that her brain "can work"). While there may be components of Connie's behaviors that appear to be more conscious or volitional, her presentation overall is reflective of a conversion spectrum, and a similar treatment approach would be recommended regardless of whether some of her demonstrated behaviors appear to be more in her control than others [1].

Therapy Course

The focus of Connie's treatment in the partial hospital program (PHP) was primarily centered around highlighting two main points: (1) *We know your brain is capable of learning, remembering, and functioning*, and (2) *We know it feels scary to believe that*. Connie continues to maintain very strong fixed beliefs that she was born with something wrong with her brain; that doctors cannot disprove that idea for sure, and thus she cannot learn. Similar to someone with fixed delusional or paranoid thoughts, it has not been helpful to continue to challenge such fixed beliefs, as any evidence

to the contrary can be countered in Connie's mind by her own beliefs. Rather, the approach has been to try to help her acknowledge the emotional basis behind these thoughts and to progressively get her to be more emotionally expressive [3]. This has been done by reframing her statements of "I can't do it" or "There's something wrong with my brain" with "I know it feels scary to do it," "It feels scary so you are choosing not to do it," or "We know your brain can learn, and it feels scary to do so."

During her admission to the PHP, which Connie attended weekdays during school hours, treatment was instilled throughout Connie's day, from the language that was used as described above to the behavioral strategies to guide her treatment forward. Each day, Connie had two layers of behavioral goals on which she was working. First, there was an overarching reinforcement system in which Connie could earn checks on her point card for following directions at each part of the day as well as for "good behavior" which was defined as "putting in appropriate effort, using full sentences to participate in conversation, and engaging in tasks she has shown the ability to do." At the end of each program day, Connie could redeem the checks she earned for different levels of small prizes from the program Point Store. However, an additional layer of goals that she also worked on was to set one daily goal each morning with staff (identified from a list of possible goals) in order to earn a puzzle piece. Once she earned enough puzzle pieces to complete her puzzle (a picture of some bigger reward decided on together by Connie and her parents), her parents rewarded her at home with the actual prize. Her goals included things that were challenging for her as they were all indicative of being able to learn or of growing up (i.e., counting to 10, saying her age, coloring within the lines, opening food packages independently, tracing her name, identifying letters, etc.). If Connie was not able to complete her goal prior to the afternoon activity time, she would sit out of the activity and instead work 1:1 with a staff person on her goal. Once she completed it, she was able to move on with the rest of her day and rejoin the group in addition to having access to her electronics at home that evening or engaging in a fun outing if desired. However, if she wasn't able to complete her goal by the end of the program day, the message to Connie was that she needed to spend more time that day "retraining her brain" and therefore wouldn't have access to electronics at home or doing other fun outings. Instead, her parents would continue to either work with her on the goal in the evening or, if she refused, they could engage her in other activities as long as there was still a focus on "retraining her brain." Instead of playing an easy or preferred game, they would choose something that required counting/numbers, sequencing, or other tasks that she would typically avoid.

Regarding treatment progress, Connie made slow but forward progress during an extended 4-month admission to the PHP. She typically did best when the message that she needed to work on "retraining her brain" was not overly emphasized as she tended to get angry and resistant around continued reminders of what she needed to do. That being said, she did display some motivation to work toward earning the bigger rewards that she set for herself and was successful in completing two puzzles with different sets of goals (about 14 goals each). She typically would struggle for about a week after she completed a puzzle when a new set of goals was introduced. This would manifest as frustration and refusal to work on her goals as well as more tantrums and dysregulated behaviors at home. However, after about a week, with all expectations

and limits remaining consistent, Connie would typically start to make slow progress again. Connie struggled as well when expectations increased to both completing a new goal each day as well as reviewing three goals she had already completed in order to reinforce the need to retain her successes, as she tended to maintain that she couldn't remember how to do things she was successful with the day before.

Clinical Pearl #2

One of the primary treatment strategies for Connie was a behavioral approach that included gradual shaping of age-appropriate behaviors and utilized a contingency management system that included both reinforcers for positive behaviors and negative consequences for others. As with any good behavioral plan, consistency is the key. It is common for parents to become frustrated when they are not seeing forward progress or when problematic behaviors resurface. It is also common for a reward structure to shift over time in order to maintain motivation and incorporate new interests that may become incentives.

With Connie, it was not surprising that each time a new set of goals was introduced, she worsened emotionally and behaviorally for a period of time. In her eyes, she had completed what she needed to do and was upset that more was being asked of her. Parents understandably expressed distress and uncertainty about the plan during times when her behavior would escalate at home. However, with psychoeducation and reassurance, Connie's parents were able to hold steady with expectations and consequences at home, and, inevitably, Connie's behavior would deescalate after a period of time and she would start to show progress again. This serves to highlight how important consistency is when using a behavioral treatment approach rather than letting a child's behavior dictate when to make changes in the plan.

Despite the slower progress in working on these more "academic" goals, Connie overall made significant progress in areas such as acting more socially appropriate and engaged (especially in the context of being in a milieu with same-age and typically developing peers), doing more of her ADLs independently, caring more about her appearance such as wanting to brush her hair and showing interest in makeup, and participating more appropriately throughout the day in activities and conversations with staff and peers. Notably, Connie happened to start her menses for the first time while admitted to the PHP. Despite her clear angst and avoidance of acknowledging her age at the start of her admission, her reaction to this normative developmental milestone was surprising in that she handled it quite well, possibly a reflection of some of her growth in the area of becoming more comfortable with herself and having the desire to be more like her peers. Toward the end of her admission, Connie also seemed to be a little more connected with her emotions, voicing more concerns around feelings of anxiety and depression and wanting to address this. However, she continued to prefer to only talk to her mother and not open up emotionally when prompted, and, at times, it appeared that her desire to focus on emotions was in part her way to deflect attention from needing to also work on "retraining her brain."

Another major theme of therapeutic work with Connie over the course of her admission included "disproving" her worry that her parents might one day cease to provide her with emotional and social support when she makes a certain amount of developmental/cognitive progress. As she made steps toward progress, Connie was able to eventually acknowledge that her parents continued to provide her with support, and her parents expressed to her that they would continue to do so throughout her life and, in fact, would never anticipate a time in Connie's life when she would not need their support in the future, thus allaying part of her anxiety that she would be "on her own."

Medical Course

In addition to the behavioral therapeutic and family work during Connie's admission, treatment also included adjustments in her psychiatric medication regimen. Upon her admission to the PHP, Connie was being prescribed fluoxetine 50 mg daily and bupropion 150 mg daily. Her parents shared at the time that Connie had no clear past or present therapeutic response to fluoxetine, particularly in the realm of anxiety, and had differing opinions as to any positive mood response to the addition of the bupropion. Given the lack of any clear treatment response to fluoxetine, the decision was made to discontinue it within the first week of her admission. Lorazepam was started as a standing medication and eventually increased to 0.5 mg twice daily in order to address how Connie would get "stuck" and perseverate on not being able to work on her goals. Upon review of the pharmacogenomics testing previously obtained by Connie's outpatient psychiatrist, folic acid was also discontinued and l-methylfolate was initiated in its place based on Connie's documented methylenetetrahydrofolate reductase (MTHFR) enzyme deficiency.

Clinical Pearl #3

The methylenetetrahydrofolate reductase (MTHFR) enzyme converts synthetic folic acid and dietary folate into l-methylfolate, the active form that crosses the blood-brain barrier and plays a critical role in neurotransmitter synthesis. Individuals who are heterozygous for a mutation at the C677T SNP of the MTHFR gene exhibit 45% reduction in enzyme activity, while the same homozygous mutation carries a 70% reduction in enzyme activity. Patients with such deficiency seem to produce fewer peptide precursors for important neurotransmitters, which may in turn negatively impact responsiveness to psychiatric medications. As such, supplementation with l-methylfolate can serve to optimize the efficacy of psychiatric medications in such patients [4–6].

Also of note, a course of sertraline was also initiated in particular to target what was formulated by Connie's PHP treatment team as an anxiety-based regressive pull to avoid moving into adolescence. Based on Connie being an extensive metabolizer

in the c19 cytochrome p450 pathway – the primary pathway for sertraline metabolism – it was agreed that dosing of sertraline would need to be higher than what might be typical for Connie's age. Over the course of her admission, the dose was titrated to 100 mg daily, which Connie tolerated well. Additionally, in the context of lack of a clear historical response to bupropion, this medication was eventually weaned to discontinuation concomitant with sertraline titration.

Over time, it appeared that while Connie benefited intermittently from as needed lorazepam for acute agitation and/or anxiety, she did not appear to have benefited overall from her standing dosages. This medication was thus weaned to discontinuation, and a decision was made to replace it with standing aripiprazole, both as an adjunctive medication for her anxiety and mood as well as to help address significant behavioral impulsivity when emotionally distressed. Connie notably benefited behaviorally and emotionally from the initiation of this medication, with her parents reporting significant improvement at home in particular. She did gain approximately 17 lbs over the following 6 weeks after initiation of aripiprazole, prompting a decrease from 2.5 to 1 mg daily. However, Connie's behavioral and emotional dysregulation worsened significantly over the following week even with this modest decrease, prompting an increase to a dose of 2 mg. Of note, a baseline fasting metabolic panel done prior to initiating aripiprazole demonstrated a mildly elevated fasting glucose level of 103 and a normal hemoglobin A1C. Due to her weight gain as well as treatment with rhGH and aripiprazole, Connie will require regular monitoring for glucose intolerance and diabetes [7].

As noted above, Connie's weight gain was considered secondary to aripiprazole as well as her consistent pattern of sedentary behavior. With the implementation of a daily exercise routine including 30–60 min walking on the treadmill as well as implementation of dietary recommendations, her weight stabilized in the final 2 weeks of her admission. She continued to be followed by her outpatient ophthalmology team for her diagnosis of pseudotumor cerebri as well as by her outpatient endocrine team for her diagnosis of growth hormone deficiency. As noted above, while these medical issues were significant, they were assessed not to explain or directly relate to her developmental regression by both the PHP team and the multidisciplinary outpatient team that evaluated Connie prior to her PHP admission. Also of note, given the extensive medical workup that Connie underwent prior to the PHP admission and the clearly prominent role of the complex emotional factors noted above in driving her symptoms, Connie did not undergo further medical workup for her developmental regression during the PHP stay, which enabled the treatment to remain focused on her complex behavioral plan and family-based therapy.

Next Steps

After thorough consideration of academic placement options, it was ultimately decided that Connie would do best returning to her regular middle school with certain accommodations in place. First, she needs to continue to have a structured school day but would do best with one that is weighted toward being able to participate in nonacademic subjects with her peers. This would include electives such as

art, music, photography, gym, etc. The idea would be for Connie to have a period of structured time in a school setting where she is with similar aged/developed peers and engaging in age-appropriate activities. Second, while Connie needs to participate in some academic blocks, it would be counterproductive for her to sit in regular classes where she is not going to be able to participate. Instead, these would be times when Connie could continue to work 1:1 in the school setting on similar academic/cognitive goals to what she was working on at the PHP. This 1:1 time would be seen more as behavioral/therapeutic tutoring that could continue to focus on consistent expectations around moving forward with goals as well as maintaining consistency with consequences for refusing to do work and ongoing communication and collaboration with Connie's parents and outpatient providers. Third, Connie's school schedule should also include other therapeutic opportunities such as meeting with a support person such as the school psychologist or social worker or taking part in a social skills lunch club. Fourth, Connie would continue to receive PT and OT services in the school setting which could continue to work with her on skills such as writing, ADLs, muscle tone, and physical coordination. Fifth, outside of the school day, Connie would continue to see an outpatient psychiatrist as well as an outpatient therapist skilled in principles of cognitive behavioral therapy and parenting/family work in order to continue to work with Connie and her family in a similar manner to the treatment approach she had been engaged in at the PHP.

Lessons Learned About Neuropsychiatry

What could be so powerful so as to disrupt development, lead to a regression in emotions and behaviors, and keep a child "stuck" in a maladaptive pattern of functioning? The answer is anxiety. While anxiety is a normative emotion and an essential one to survival, excessive anxiety can be debilitating. Treating anxiety is even more complicated when the person experiencing it isn't even aware of this emotional experience. In cases like Connie's, the root of anxiety likely took hold when she was 5 or 6 years old and she began to internalize stressors such as changes in the dynamics at home and struggles in school. Connie's way of coping with this anxiety seemed to be to unconsciously create a world in which she needed to be cared for as she showed that she could no longer do things for herself that she used to do. The thought of demonstrating skills and growth was threatening in that it would mean that she needed less attention, care, or love from those closest to her, and she would effectively be on her own. The anxiety and internal stress that this seemingly created was powerful enough and remained fixed for such a long period of time that this became Connie's world. Her beliefs that there was something wrong with her brain and that she couldn't learn became her reality. No matter what physical or biological evidence to the contrary was presented, Connie's anxiety was more powerful.

The mind-body connection is a fascinating relationship, and some facets of it are easy to conceptualize than others. For example, most people are familiar

with the notion that when someone says they feel like they have butterflies in their stomach, they are referring to the fact that they feel nervous, and that sensation is felt physically in their stomach. However, when talking about more unusual symptoms, namely, neurological ones, it's often harder for people to accept the mind-body connection. For example, how can someone's emotions or stress lead to physical manifestations such as seizure activity, paralysis, dysphonia, or blindness? This speaks to an important lesson in the power of emotions, namely, stress and anxiety, to supersede many aspects of brain function as it did with Connie.

Brain regions currently implicated in the precipitation and perpetuation of conversion disorder currently include the amygdala, striatum, precuneus, dorsolateral and ventromedial prefrontal cortices, dorsal anterior cingulate, supplementary motor complex, and temporoparietal junction. For a comprehensive summary of the known underlying pathophysiology of functional neurological disorders, please see the publication by Voon et al. [8] in the Journal of Neuropsychiatry and Clinical Neurosciences. As more becomes understood about the structural and physiological etiologies and correlates of anxiety, the ability to explain some of this underlying pathophysiology in biological terms will hopefully serve to reinforce the connectedness of anxiety and neurological symptoms for patients and families, thereby destigmatizing and demystifying this connection.

Family Reflections

In trying to understand Connie's struggles over the years, her parents have been able to see the stressors that were occurring around the time when her symptoms started as playing a role in what happened but have struggled to explain how her behaviors became so severe given the seemingly "low" level of trauma they created compared to more significant traumatic events that families could experience. They ultimately have viewed Connie as, at baseline, a very emotionally immature and very strong-willed/stubborn child who seemed to find any way to establish "crutches" in her life to hold on to so that she doesn't have to grow up and function independently.

Throughout Connie's lengthy admission to the PHP, Connie's mother was able to be very open and honest around how draining this whole process has been, especially in the context of other major family stressors, including caring for her own dying mother. There were times when parental frustration would come out in a way that Connie would internalize as her mother not caring about her (i.e., if mom made a statement such as "I'm done with this"). While the family was able to address these themes in family sessions, they described how it remained very difficult to balance the needs of the whole family. However, Connie's parents remained generally committed to the treatment strategies and course as they recognized that they have already spent years letting Connie direct her own course and pace, which had not resulted in any forward progress.

References

1. Martin P, Schroeder R. Challenges in assessing and managing malingering, factitious disorder, and related somatic disorders. Psychiatric Times. 2015;22:11–3.
2. Friedman D. The pseudotumor cerebri syndrome. Neurol Clin. 2014;32:363–96.
3. Williams C, Carson A, Smith S, Sharpe M, Cavanagh J, Kent C. Overcoming functional neurological symptoms: a five areas approach. Boca Raton: CRC Press; 2011.
4. Nazki FH, et al. Folate: metabolism, genes, polymorphisms and the associated diseases. Gene. 2014;533:11–20.
5. Nelson JC. The evolving story of folate in depression. Am J Psychiatr. 2012;169(12):1223–5.
6. Stahl S. Novel therapeutics for depression: l-methylfolate as a trimonoamine modulator and antidepressant-augmenting agent. CNS Spectr. 2007;12(10):739–44.
7. Richmond E, Rogol A. Treatment of growth hormone deficiency in children, adolescents, and at the transitional age. Best Pract Res Clin Endocrinol Metab. 2016;30:749–55.
8. Voon, et al. Functional neuroanatomy and neurophysiology of functional neurological disorders (conversion disorder). J Neuropsychiatr Clin Neurosci. 2016;28:168–90.

Assessment and Treatment of Prenatally Exposed Infants and Children

13

Amanda Lowell and Linda Mayes

Case 1: Opioids

Benjamin is a 3-year-old male with a history of prenatal exposure to opioids. He appears to demonstrate delays in both verbal and motor domains and has been followed by the newborn follow-up clinic associated with the hospital where he was born. His face is also slightly dysmorphic, with wide-set exotropic eyes. There were concerns about whether Benjamin's exposure to opioids in utero might have affected his brain development and subsequent developmental difficulties.

In cases of prenatal substance exposure, it is ideal for a multidisciplinary team to provide assessments of developmental functioning at regular intervals throughout early childhood. As part of this process, it is of paramount importance to obtain a thorough prenatal, postnatal, and developmental history given that the timing and type of substance(s) to which the fetus was exposed may impact development. Understanding that substance use is often associated with profound family and parental stress, it is also important to obtain a detailed family and social history.

According to Benjamin's mother, she had used methamphetamine throughout her 20s before initiating opioid use in her 30s. Like many individuals who become opioid-dependent, Benjamin's mother initially gained access to opioid prescription painkillers after a medical procedure. At age 31, she was in a minor car accident requiring a subsequent hand surgery, at which time she was treated with oxycodone. She reported that these pain pills helped with her physical pain as well as the emotional pain she was experiencing secondary to her stressful circumstances at the

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time and her history of childhood adversity. Specifically, Benjamin's mother had witnessed domestic violence and experienced physical and emotional abuse throughout her childhood. Given the relief she found through opioid use, she continued to endorse physical pain to various doctors in order to obtain oxycodone prescriptions. She transitioned to using heroin almost exclusively about 1 year later at age 32, citing that it was cheaper and easier to access than prescription pain pills. She met her current partner, Benjamin's father, through a group of individuals who were buying, using, and selling opioids in the local community. His history was positive for witnessing domestic violence, as well as parental substance use, and emotional neglect. Benjamin's parents began dating about 3 months after meeting, and Benjamin's mother became pregnant at age 33.

Upon learning of her pregnancy, Benjamin's mother was using only opioids. At the beginning of her second trimester of pregnancy (around 14 weeks' gestation), she entered residential substance use treatment at a facility for pregnant and parenting women. There, she received individual and group substance use counseling, began taking methadone, and stopped using heroin and prescription pain pills. Throughout her pregnancy, Benjamin's mother did well in treatment, did not relapse into illicit drug use, and did not drink alcohol; however, she continued to use tobacco. She remained in a relationship with Benjamin's father, who entered outpatient substance use treatment. Benjamin's father moved in with his parents who had a history of substance use, though they were not actively using at this time.

Benjamin was born prematurely at 36 weeks, as is the case with up to 30% of opioid-exposed infants [1]. However, given that Benjamin's mother (like many methadone-maintained mothers) experienced high levels of stress during pregnancy, it is likely that Benjamin's early birth may have been caused in part by stress during pregnancy. Given that opioids including methadone and buprenorphine cross the placental barrier and enter the fetus' bloodstream [2], Benjamin also tested positive for opioids in his system at birth as confirmed by urine and meconium analysis [3]. He experienced some perinatal health complications associated with neonatal abstinence syndrome (NAS) including low birth weight, loose stools, poor feeding, vomiting, nasal stuffiness, and moderate tremors.

Multipronged non-pharmacological intervention is now considered the standard of care for all prenatally exposed infants. Non-pharmacological intervention was initiated for Benjamin and his mother in the nursery in order to address the effects of NAS via the promotion of maternal responsiveness and nurturance, dyadic bonding, and infant self-regulation and self-organization [4]. Interventions for dyads like Benjamin and his mother should be individualized based on the infant's neurobehavioral profile as well as the mother's strengths and weaknesses.

Although the standard of care for prenatally exposed infants has shifted from pharmacological treatment to non-pharmacological care, evidence-based evaluation and pharmacologic management is still used with some infants [5]. The Finnegan

Neonatal Abstinence Scoring System [6] initially placed Benjamin in Category IV of NAS severity and he was placed in the NICU for stabilization. After stabilization, he was treated in the nursery and his symptoms were monitored every 4 h using the Finnegan system. He was treated pharmacologically with an alcohol-free oral morphine sulfate preparation (0.4 mg/mL) and was fully weaned from an initial dose of 0.16 mg over the course of 3 weeks in the hospital.

Benjamin's sensory reactivity, behavioral states and state regulation, motor and tone control, and autonomic signs of stress (e.g., tachypnea, yawning, sighing, sweating, sneezing, hiccups, gagging, spitting up, frequent bowel movements, color changes, mottling) were used to guide his individualized non-pharmacological treatment [4]. In terms of sensory processing, Benjamin became easily overwhelmed by sound and touch as evidenced by becoming visibly agitated. Benjamin's apparent overresponsiveness was characterized by crying, vocalizing, closing his eyes, having erratic limb movements, spitting up, hiccupping, and even having bowel movements. As a result, care was taken to ensure a quiet, dimly lit environment in the nursery. This also helped address Benjamin's dysregulated sleep-wake states. Benjamin's impaired motor control was evident in tremors, problematic feeding, and inability to latch to breast or bottle. These issues were addressed with the use of swaddling, light tactile pressure, a pacifier, and small frequent high-calorie meals.

Additionally, treatment for NAS requires educational and psychological intervention aimed at improving the mother's responsiveness to the infant's needs [4]. A key feature of this approach centers around building the mother's confidence and ensuring that she does not misinterpret or internalize the infant's dysregulated behaviors. Nurses taught Benjamin's mother about the importance of providing a calm, non-overwhelming environment for him due to his sensory sensitivities. They also showed her specific holding and swaddling techniques that worked well for Benjamin in the nursery and allowed her to practice and master these before discharge. She was encouraged to continue participation in the group parenting intervention program, *Circle of Security (CoS)*, that she was already enrolled in at the residential substance use treatment facility [7]. She was also referred to individual parenting intervention, *Mothering from the Inside Out (MIO)*, targeting the neural stress and reward circuitry of mothers in substance use recovery [8]. Given that high emotional arousal triggers craving responses in addicted individuals, MIO aims to reduce emotional arousal in the caregiver through a process called *mentalization* (i.e., understanding behavior by examining one's own and others' underlying thoughts and feelings). MIO thus helped Benjamin's mother to understand her own emotional states and become regulated, thus expanding her ability to mentalize for her son and allowing her to experience the reward of parenting him [8]. The intervention team also worked with Benjamin's mother around her expectations for her parenting role and her worries about the impact of her drug use on her son.

Research Pearl #1: Maternal Responsiveness as an Important Consideration for Prenatally Exposed Infants

In addition to the physiological effects of prenatal substance exposure, child development is also shaped by maternal/adult responsiveness, which can be hampered by substance use as well. First, substance use alters the *stress and reward systems* in the brain. When infants cry, for example, these cues are experienced as more stressful to mothers with substance use disorders compared to mothers who do not use substances. For nonaddicted mothers, an infant cry triggers a caregiving response, and the process of soothing the infant is experienced as rewarding. In contrast, for mothers with substance use disorders, infant cries trigger a craving response, and the use of substances to regulate in the face of stress is experienced as rewarding [9].

Second, mothers' *internal working models* (i.e., mental representations) of their infants begin to take shape during pregnancy [10] and have a strong influence on mother-child attachment. Risk factors such as substance use can affect the formation of these internal working models [11], which can also disrupt maternal responsiveness, negatively impact bonding between mother and child, and increase the risk of insecure attachment relationships. As we know from decades of attachment research, insecure relationships formed very early in life often have long-lasting consequences including dissociation, anxiety, conduct problems, and substance use [12]. As a result, maternal responsiveness is a key point of intervention for this population and can be addressed via treatments that target internal representations of infants and/or neural stress and reward circuitry. One such empirically supported treatment that specifically targets mothers in recovery from substance use problems is *Mothering from the Inside Out* [8]. This treatment works to enhance mothers' own stress-regulatory capacities via mentalization, with the goal of helping mothers achieve more balanced mental representations of their children, thereby improving their responsiveness, the reward they experience from parenting their children, and the overall quality of the parent-child relationship.

Benjamin's mother visited him daily in the nursery. With pharmacological [5] and non-pharmacological intervention [4], Benjamin's central and autonomic nervous systems became more regulated. His feeding and elimination improved, weight increased, vomiting and tremors stopped, and overall irritability dissipated.

Upon discharge Benjamin came to live with his mother at the women's residential substance use treatment facility. They remained at this facility for the first 8 months of Benjamin's life, where they were provided with a safe, substance-free, low stress environment in which they were able to form a healthy bond. This

approach reflects optimal care, which is unfortunately quite rare for most opioid-exposed mother-child dyads. Afterward, Benjamin and his mother moved into the paternal grandparents' home. Benjamin and both biological parents moved to the local homeless shelter when Benjamin was approximately 2 years old due to the paternal grandparents' financial hardships (i.e., foreclosure) and his parents' difficulty finding employment. They continue to reside at the homeless shelter presently.

Benjamin's mother reported that he was a happy and social baby throughout infancy. After overcoming NAS fully, he was easy to soothe, cried infrequently, and was relatively quiet. He continues to be very friendly and smiles often at others despite little familiarity with them. He demonstrates appropriate eye contact, though this is impacted somewhat by exotropia (i.e., divergent strabismus), a condition that is ten times more likely to occur in prenatally exposed children than in the general population [13, 14]. He tends to withdraw and close his eyes when faced with loud noises or bright lights. Despite his interest in others, his verbal communication is still limited to only a few short phrases at 3 years of age. He communicates mostly in two-word utterances. His language delay is likely multi-determined, caused in part by the direct effects of prenatal exposure on brain development, as well as other factors often associated with prenatal exposure (e.g., poverty, living in a high stress environment at the homeless shelter, low levels of parental education and literacy, and his parents' continued methadone maintenance treatment which could have dampened their responsiveness and engagement with him) all of which are known factors in language acquisition [15, 16].

With regard to motor delays, Benjamin's gross and fine motor skills have been slow to develop. At birth, he had difficulty latching which affected his feeding. As an infant, he did not show much interest in physically exploring his environment and was content to remain seated. Unlike many infants with NAS, Benjamin did not exhibit hypertonia. Rather, his lack of motor control was apparent as he did not frequently reach for objects, and when others attempted to hand him items, he often did not grab or hold them successfully. He took his first steps around 15 months of age and began walking independently at 16 months. His gait continues to be clumsy at present, and he often is transported by his mother in a stroller. He does not fuss or protest when placed in his stroller and he easily tolerates being strapped in. In fact, he becomes calm when he experiences the tactile sensory input and light pressure across his chest provided by the straps of his stroller.

Given his history of NAS and related stay in the NICU, Benjamin has been continuously followed by a multidisciplinary medical and developmental follow-up program associated with the hospital. Benjamin was assessed at 6, 9, 12, 18, 24, and 36 months of age. This is yet another example of the optimal care that was provided to Benjamin and that not every prenatally exposed infant is fortunate enough to receive. The Bayley Scales of Infant Development-Third Edition (Bayley-III; [17]) have been used to assess Benjamin's development in the domains of cognitive, language, and motor skills.

Clinical Pearl #1: NICU Follow-Up Clinics
In keeping with best practice guidelines, high-risk infants like Benjamin benefit from follow-up by multidisciplinary teams consisting of individuals in the fields of neonatology, neuropsychiatry, clinical psychology, developmental behavioral pediatrics, occupational therapy, nutrition, nursing, and social work. These professionals collaborate to generate a comprehensive conceptualization of the infant in order to inform recommendations that will increase the infant's chances of positive developmental outcomes. These teams also track the infant's development in many domains in addition to cognitive, language, and motor skills. These assessments aid in determining if interventions are needed or are working. They can also detect any regressions in development that may be signs of more serious problems. Although ideal, this model has unfortunately not yet been adopted as the current standard of care in all hospitals. Funding for this type of care is relatively limited, and when it is available, parents with substance use problems often face issues with accessing such care. For example, parents of prenatally exposed infants may be experiencing psychosocial stressors that make it difficult to attend appointments. They may also face issues with accessing care due to the stigma surrounding substance use during pregnancy or due to their fear of judgment from health professionals [18].

Benjamin's cognitive abilities have remained relatively stable over time and have rated within the average range at each of his follow-up assessment visits. Although research studies on the effects of prenatal opioid exposure on cognitive development have revealed inconsistent results [1], Benjamin's case supports findings suggesting minimal impact on intellectual functioning [19, 20].

In contrast, Benjamin's language skills placed within the low average range initially. Within this domain, however, there was significant variability. Upon further analysis, it was evident that his receptive communication abilities fell within the average range and were significantly stronger than his expressive communication abilities which fell within the extremely low range. Social work facilitated a referral to a local early intervention agency, and home-based speech-language services began when Benjamin was approximately 12 months of age. His expressive language skills have improved over time with intervention, though he still struggles somewhat in this area. His most recent assessment of language skills at 36 months revealed that his receptive communication continues to be in the average range and his expressive communication abilities are now within the high end of the borderline range.

Benjamin's motor skills also began in the borderline range initially, with his gross and fine motor abilities being similarly developed. When Benjamin began speech-language services, he also began home-based occupational therapy

through the same early intervention organization. These services targeted fine motor skills such as reaching, grasping, and feeding, as well as gross motor skills such as walking and standing up from a seated position. He has made progress in both areas, and his most recent assessment of motor skills at 36 months revealed that both his gross and fine motor skills now fall within the low average range.

Overall, the importance of early and continuous follow-up and intervention cannot be stressed enough in cases like Benjamin's. Although he still exhibits some delays in language and motor skills, his abilities in these domains have improved with the interventions that were made possible by the initial identification of his delays and by the multidisciplinary follow-up program. In addition, Benjamin's positive developmental trajectory was also impacted greatly by the pharmacological and non-pharmacological treatment of his NAS in the hospital nursery. As his medical team determined what worked best to address his symptoms, his mother observed and learned techniques to soothe and bond with him. Benjamin's mother's involvement in mentalization-based intervention geared specifically toward mothers in recovery from substance use disorders [8] also has proven to be integral for bolstering the parent-child relationship and buffering against the effects of his prenatal exposure. Her ability to respond to him successfully will likely continue to shape a positive path for Benjamin as he continues to develop. In this spirit, given Benjamin's family history of substance use and current stressors of poverty, homelessness, and trauma recovery, other supports will continue to be necessary to help his parents remain as stable caregivers for him. For example, participation in relapse prevention services, recovery support groups, and individual trauma-focused treatment will be integral in maintaining their own mental health. Further, supports such as case management, vocational training, and supportive housing would be beneficial to address their more concrete needs. Overall, the ultimate goal of each of these supports is to halt the intergenerational cycle of substance use and stress for Benjamin.

Finally, it is worth noting that Benjamin's needs may not be solely associated with prenatal opioid exposure, but rather a combination of early life stress and drug effects. As a result, as Benjamin matures, he will likely benefit from other services aimed at addressing his experience of early life stress such as frequent transitions and moves, homelessness, poverty, and his parents' continued need for methadone maintenance. For example, participation in *Child Parent Psychotherapy (CPP)* with his mother and/or father would serve to help the family process Benjamin's stressful experiences, understand and organize his emotions, develop regulatory capacities, and further strengthen their safe relationships with one another [21]. It will remain to be seen if Benjamin will need further services when he is older, though it is hoped that with each of the services the family has received thus far, his likelihood of a positive developmental trajectory has increased dramatically.

Case 2: Cocaine

Tasha is a 9-year-old female with a history of prenatal cocaine exposure. Her biological mother became pregnant unexpectedly with an individual with whom she was not in a relationship. She discovered she was pregnant at 6 weeks, and at that time she made efforts to eat healthier, discontinued alcohol use, and decreased her cocaine use to some extent; however, she continued using cocaine and smoking cigarettes throughout her entire pregnancy. After Tasha was born, she experienced postpartum depression and resumed heavy use of cocaine throughout Tasha's infancy and toddlerhood. As a result, Tasha's maternal aunt has been involved as a support since her birth. She assumed full guardianship when Tasha was 18 months of age given that Tasha's biological mother's addiction had worsened and she was unable to care for herself or Tasha. It is presumed that Tasha's first 18 months were characterized by emotional and physical neglect. Per the maternal aunt's report, Tasha's biological mother was frequently consumed with various romantic relationships with men who were violent and sold drugs. She also reportedly spent much of her time either high or engaging in efforts to obtain drugs, often dropping Tasha off with her aunt or other family members for days at a time without a diaper bag, extra clothing, or other supplies needed for her care.

Despite this early life stress and disruption in her placement, Tasha bonded well with her aunt, and each of her developmental milestones was met within normal limits. Similar to many children who were exposed prenatally to cocaine, Tasha presented with executive functioning deficits [22–24] such as inattention, impulsivity, and hyperactivity, as well as symptoms of anxiety [25] and dysregulated arousal [26, 27]. At home, her aunt reported that she does not pay attention when being spoken to, frequently daydreams, often acts before thinking, is constantly moving, and appears tense and worried much of the time. At school, she has difficulty remaining seated, following directions, and distracting her classmates. Her school performance is also notable for long-standing learning difficulties and poor grades in reading and writing.

Given her academic underperformance, Tasha participated in psychoeducational testing at her school in the first grade when she was 6 years of age. The Wechsler Preschool and Primary Scale of Intelligence-Fourth Edition (WPPSI-IV; [28]) revealed low average overall intellectual functioning. Specifically, Tasha exhibited average verbal comprehension, very low fluid reasoning, low average working memory, and low average processing speed. The Wechsler Individual Achievement Test-Third Edition (WIAT-III) revealed average oral language skills, very low early reading skills, low average written expression skills, and very low math skills. These results prompted accommodations including extended time and preferential seating. Tasha also began receiving special education intervention to improve her reading, writing, and mathematics performance. Despite intervention and her average cognitive skills in the verbal comprehension domain, Tasha's grades continued to suffer.

Research Pearl #2: Cognitive Development and Learning Following Prenatal Cocaine Exposure

Overall, research suggests that prenatal cocaine exposure is related to subtle but persistent differences in children's brains, effects on their cognitive functioning, and especially on their stress-regulatory capacities [29]. Tasha's cognitive profile is remarkably similar to findings suggesting that cocaine-exposed youth suffer from deficits in perceptual reasoning, fluid reasoning, and problem-solving skills but have relatively unaffected cognitive abilities in the domains of verbal comprehension and memory [30, 31]. Despite average verbal skills and memory, we might expect Tasha to exhibit academic underperformance due to the impact that altered stress reactivity has on learning and cognition [32]. In other words, when cognitive resources are more quickly allotted to stress regulation due to prenatal cocaine exposure, the brain is less able to use resources for learning or attending to material presented in school.

Because of continued scholastic difficulties as well as caregiver and teacher reports of symptoms of inattention, hyperactivity, and impulsivity, at age 7 Tasha was further evaluated using the Quotient ADHD System, a computerized objective test of inattention and motor movement. Tasha's performance provided evidence of significant inattention as well as hyperactivity and impulsivity. Tasha fell below the 16th percentile on most measures of inattention (e.g., accuracy, omission errors, variability, distractibility) and hyperactivity/impulsivity (e.g., head movements, head immobility duration, and area of movement). What providers failed to appreciate at the time, however, was Tasha's history of prenatal cocaine exposure. Consistent with literature suggesting elevated likelihood of ADHD diagnosis for children prenatally exposed to cocaine [33] and tobacco [34], she was diagnosed with ADHD.

Tasha was subsequently treated for ADHD with methylphenidate 18 mg extended release for approximately 6 months. Her executive dysfunction continued, as did her anxiety. Her aunt found it difficult to communicate her ongoing symptoms to doctors who simply encouraged her to engage in more consistent parent management and advocate for improved school programming.

At age 7.5, Tasha moved with her aunt to a different city in the same state. Her inattentive, hyperactive, and impulsive symptoms persisted. This prompted a referral by her new pediatrician for evaluation, management, and psychotherapy at an outpatient psychiatric clinic in their new city, where she continues to receive services presently. Tasha's new psychiatrist initially increased her dose of methylphenidate extended release to 36 mg to determine if her previous dose was simply insufficient. This was trialed for approximately 1 month with little benefit. In addition, her symptoms of anxiety increased.

In response, guanfacine 1 mg immediate release was added to her medication regimen in the evenings. The family was instructed to continue methylphenidate in the morning as well. Within a few days, Tasha exhibited fewer executive functioning difficulties; however, her anxiety and general emotional arousal persisted. Methylphenidate was removed 1 month later, and Tasha continued taking guanfacine 1 mg. With this adjustment, her executive functioning remained improved, with better ability to focus, follow directions, and inhibit impulses. Her anxiety, reactivity to stress, and emotional arousal also decreased when methylphenidate was removed.

Neuroscientific research [27] suggests that for all individuals, during calm times (i.e., at moderate levels of stimulation and arousal), alpha-2 systems are regulating prefrontal cortical activity with the functional result of optimal attention and executive control functioning. As arousal increases with stress or overstimulation, alpha-1 systems predominate with the resulting downregulation of prefrontal cortical systems and upregulation of more posterior cortical, automatic response systems. The threshold of stimulation at which an individual's alpha-1 systems take over is often referred to as the *neurochemical switch*, and this varies across individuals to a certain degree. It is hypothesized that prenatal cocaine exposure (and also excessive prenatal stress) can shift this neurochemical switch to activate alpha-1 systems too early, which is behaviorally displayed as impaired executive functioning, poor behavioral inhibition, difficulty with attentional shifting, and faster fight-or-flight response. Therefore, it is understandable that guanfacine, an alpha-2 adrenergic agonist, would help to regulate Tasha's arousal by reducing alpha-1 activation thus improving Tasha's symptoms of anxiety and her executive functioning. In addition, Tasha's positive response to guanfacine is noteworthy and corroborates findings that such medication improves executive functioning in cocaine-dependent women following stressful, anxiety-provoking stimuli [35].

Throughout this time, Tasha was engaged in outpatient clinical services that included executive functioning coaching. For example, Tasha learned techniques for self-monitoring her attention so she could begin to refocus upon noticing she had become off-task. Notably, executive functioning skills and strategies were taught separately from challenging academic material and before being applied to current coursework. Once Tasha learned these strategies, she was then taught when to apply them. She was provided with a visual "cheat sheet" listing these skills to remind herself of them until they became more automatic. In addition, Tasha was provided with a small electronic timer to remind her to engage in period self-monitoring of her on-/off-task behavior and attention at timed intervals (e.g., once every 15 min). Simply by tracking her performance/behavior, Tasha increased her awareness not only of the expectations but also of her ability to meet the expectations. Over time, tracking of behavior and increased self-monitoring abilities led to improvement in her performance.

Tasha's anxiety was targeted via cognitive behavioral therapy. This treatment included psychoeducation regarding the relationships between thoughts, emotions, and behaviors, as well as techniques regarding how to challenge negative automatic thoughts with evidence that supports more rational beliefs. Her overall level of

heightened arousal and reactivity to stressful stimuli was addressed through the training of relaxation strategies such as deep breathing, progressive muscle relaxation, and guided imagery.

Parent management intervention was also employed as part of Tasha's outpatient treatment. Her aunt was taught behavioral strategies to reward Tasha for on-task behavior, following directions, and inhibiting impulses. She also was taught Tasha's newly learned executive functioning strategies so she could help Tasha employ them at home during homework time, for example. Finally, the aunt learned the same relaxation techniques and CBT skills so she could help Tasha practice at home and encourage use of these strategies when needed during times of distress.

Overall, Tasha's grades improved with better executive functioning and lower levels of anxiety. She also had better relationships with her aunt and with her teachers, who no longer struggled to constantly redirect Tasha's attention and prompt her to follow directions. It was evident that when her providers appreciated the impact of her prenatal exposure to cocaine, the approach to treatment and the combination of pharmacological and non-pharmacological intervention benefited Tasha and her family greatly.

Lessons Learned About Neuropsychiatry

Although quite different, Benjamin's and Tasha's cases collectively have much to teach us about neuropsychiatry and the complex interaction of environmental stress and the biologic impact of exposure to psychotropic drugs in pregnancy. First and foremost, Benjamin and Tasha both demonstrate the fact that parental substance use and prenatal substance exposure do not occur in a vacuum. Rather these problems very often co-occur with other psychosocial stressors. In Benjamin's case, prenatal opioid exposure was one piece of a puzzle that also involved poverty, homelessness, many years of parental substance use, and parents who continued to need opioid maintenance therapy. In Tasha's case, prenatal cocaine exposure occurred in conjunction with tobacco and alcohol, exposure to violent relationships throughout infancy and toddlerhood, experience of early emotional and physical neglect, and her mother's continued substance use which led to their early separation and loss of contact.

Given that these risk factors so often co-occur, it can be difficult for the practitioner to tease apart the direct neurological effects of exposure from those caused by prematurity, low birth weight, continued parental substance use, chronic psychosocial stress, inconsistent caregiving, low socioeconomic status, trauma, and neglect [1, 36, 37]. Prenatal exposure also increases children's vulnerability to the effects of psychosocial stressors, leading to poorer outcomes than those of children who are prenatally exposed only or those with psychosocial stressors only [38]. Further, researchers have begun to demonstrate that there are likely epigenetic effects from the environmental stressors accompanying substance use and prenatal exposure that in turn may also impact children's development [39, 40].

Through these cases, we have also learned that different classes of substances affect the developing brain differently and lead to varying outcomes. Tasha's executive functioning deficits can be explained in part by corticolimbic changes in the prefrontal cortex due to prenatal exposure to cocaine. For example, research demonstrates reduced gray matter in the prefrontal and frontal brain regions in children with prenatal cocaine exposure [41]. In contrast, in utero opioid exposure impacts the fetus' developing brain diffusely, potentially impacting several brain regions and resulting in unpredictable neurobehavioral outcomes and various developmental deficits [42]. For example, research has shown that opioids interfere with the myelination process [43], which potentially played a role in Benjamin's language and motor delays [44].

Finally, the reality is that the majority of substance-exposed infants are polydrug-exposed and endure the aftereffects from in utero exposure to multiple potentially harmful agents [5]. Therefore, although studies have identified the specific effects of individual substances, the pediatric neuropsychiatrist should be prepared to encounter patients with a variety of symptom constellations following prenatal exposure. By understanding the neurobehavioral effects of the substance(s) to which a patient has been exposed, the practitioner will surely be better equipped to address his or her deficits successfully and with less guesswork. But above all, the practitioner is best served by understanding that prenatal exposure especially to illicit drugs involves complex interactions with environmental stress and disruption and thus, understanding and working with the family is a necessary part of treatment interventions.

References

1. Konijnenberg C, Melinder A. Prenatal exposure to methadone and buprenorphine: a review of the potential effects on cognitive development. Child Neuropsychol. 2011;17(5):495–519.
2. Nekhayeva I, Nanovskaya T, Deshmukh S, Zharikova O, Hankins G, Ahmed M. Bidirectional transfer of methadone across human placenta. Biochem Pharmacol [serial online]. 2005;69(1):187–97.
3. Kocherlakota P. Neonatal abstinence syndrome. Pediatrics. 2014;134(2):547–61.
4. Velez M, Jansson L. The opioid dependent mother and newborn dyad: non-pharmacologic care. J Addict Med. 2008;2(3):113–20.
5. Jansson L, Velez M, Harrow C. The opioid-exposed newborn: assessment and pharmacologic management. J Opioid Manag. 2009;5(1):47–55.
6. Finnegan L, Connaughton JFJ, Kron R, Emich J. Neonatal abstinence syndrome: assessment and management. Addict Dis. 1975;2(1):141–58.
7. Powell B, Cooper G, Hoffman K, Marvin B. The circle of security intervention: enhancing attachment in early parent-child relationships, vol. 2014. New York: Guilford Press; 2014.
8. Suchman N. Mothering from the inside out. Zero Three. 2017;37(3):35–40.
9. Rutherford H, Potenza M, Mayes L. The neurobiology of addiction and attachment. In: Parenting and substance abuse: developmental approaches to intervention. New York: Oxford University Press; 2013. p. 3–23.
10. Innamorati M, Sarracino D, Dazzi N. Motherhood constellation and representational change in pregnancy. Infant Ment Health J. 2010;31(4):379–96.

11. Vreeswijk C, Rijk C, Maas A, Bakel H. Fathers' and mothers' representations of the infant: associations with prenatal risk factors. Infant Ment Health J. 2015;36(6):599–612.
12. Sroufe L. Attachment and development: a prospective, longitudinal study from birth to adulthood. Attach Hum Dev. 2005;7(4):349–67.
13. Firth A. Ocular sequelae from the illicit use of class a drugs. Br J Orthoptics. 2004;1:10–8.
14. Gill A, Oei J, Lewis N, Younan N, Kennedy I, Lui K. Strabismus in infants of opiate-dependent mothers. Acta Paediatr. 2003;92(3):379.
15. Perkins SC, Finegood ED, Swain JE. Poverty and language development: roles of parenting and stress. Innov Clin Neurosci. 2013;10(4):10–9.
16. Tamis-LeMonda C, Bornstein M, Baumwell L. Maternal responsiveness and children's achievement of language milestones. Child Dev. 2001;72(3):748.
17. Bayley N. Bayley scales of infant and toddler development. 3rd ed. Minneapolis: Pearson Assessments; 2005.
18. Van Scoyoc A, Harrison J, Fisher P. Beliefs and behaviors of pregnant women with addictions awaiting treatment initiation. Child Adolesc Soc Work J. 2017;34(1):65–79.
19. Nygaard E, Slinning K, Moe V, Walhovd K. Cognitive function of youths born to mothers with opioid and poly-substance abuse problems during pregnancy. Child Neuropsychol. 2017;23(2):159–87.
20. Pulsifer M, Radonovich K, Belcher H, Butz A. Intelligence and school readiness in preschool children with prenatal drug exposure. Child Neuropsychol. 2004;10(2):89–101.
21. Lieberman A, Ghosh Ippen C, Van Horn P. Child-parent psychotherapy: 6-month follow-up of a randomized controlled trial. J Am Acad Child Adolesc Psychiatry. 2006;45(8):913–8.
22. Beeghly M, Rose-Jacobs R, Martin B, Cabral H, Heeren T, Frank D. Level of intrauterine cocaine exposure and neuropsychological test scores in preadolescence: subtle effects on auditory attention and narrative memory. Neurotoxicol Teratol. 2014;45:1–17.
23. Bridgett D, Mayes L. Development of inhibitory control among prenatally cocaine exposed and non-cocaine exposed youths from late childhood to early adolescence: the effects of gender and risk and subsequent aggressive behavior. Neurotoxicol Teratol. 2011;33(1):47–60.
24. Rose-Jacobs R, Waber D, Frank D, et al. Intrauterine cocaine exposure and executive functioning in middle childhood. Neurotoxicol Teratol. 2009;31:159–68.
25. Chaplin T, Visconti K, Mayes L, et al. Prenatal cocaine exposure differentially affects stress responses in girls and boys: associations with future substance use. Dev Psychopathol. 2014;27(1):163–80.
26. Chaplin T, Fahy T, Sinha R, Mayes L. Emotional arousal in cocaine exposed toddlers: prediction of behavior problems. Neurotoxicol Teratol. 2009;31:275–82.
27. Mayes L. A behavioral teratogenic model of the impact of prenatal cocaine exposure on arousal regulatory systems. Neurotoxicol Teratol [serial online]. 2002;24(3):385–95. Available from: PsycINFO, Ipswich, MA. Accessed 4 Jan 2018.
28. Wechsler D. Wechsler preschool and primary scale of intelligence. 4th ed. Minneapolis: Pearson Assessments; 2012.
29. Gautam P, Warner T, Kan E, Sowell E. Executive function and cortical thickness in youths prenatally exposed to cocaine, alcohol and tobacco. Dev Cogn Neurosci. 2015;16:155–65.
30. Richardson G, Goldschmidt L, Larkby C, Day N. Effects of prenatal cocaine exposure on adolescent development. Neurotoxicol Teratol. 2015;49:41–8.
31. Singer L, Nelson S, Minnes S, et al. Prenatal cocaine exposure: drug and environmental effects at 9 years. J Pediatr. 2008;153(1):105–11.
32. Blair C, Raver CC. School readiness and self-regulation: a developmental psychobiological approach. Annu Rev Psychol. 2015;66:711–31.
33. Morrow C, Accornero V, Bandstra E, et al. Estimated risk of developing selected DSM-IV disorders among 5-year-old children with prenatal cocaine exposure. J Child Fam Stud. 2009;18(3):356–64.

34. Nomura Y, Marks DJ, Halperin JM. Prenatal exposure to maternal and paternal smoking on attention deficit hyperactivity disorders symptoms and diagnosis in offspring. J Nerv Ment Dis. 2010;198(9):672–8.
35. Milivojevic V, Fox H, Jayaram-Lindstrom N, Hermes G, Sinha R. Sex differences in guanfacine effects on stress-induced Stroop performance in cocaine dependence. Drug Alcohol Depend. 2017;179:275–9.
36. Konijnenberg C, Melinder A. Executive function in preschool children prenatally exposed to methadone or buprenorphine. Child Neuropsychol. 2015;21(5):570–85.
37. Konijnenberg C, Lund I, Melinder A. Behavioural outcomes of four-year-old children prenatally exposed to methadone or buprenorphine: a test of three risk models. Early Child Dev Care. 2015;185(10):1641–57.
38. Hans S. Developmental consequences of prenatal exposure to methadone. Ann N Y Acad Sci. 1989;562:195–207.
39. Gartstein M, Skinner M. Prenatal influences on temperament development: the role of environmental epigenetics. Dev Psychopathol. 2017;1:1–35.
40. Murgatroyd C, Spengler D. Epigenetics of early child development. Front Psychol. 2011;2:1–15.
41. Grewen K, Burchinal M, Gerig G, et al. Prenatal cocaine effects on brain structure in early infancy. NeuroImage. 2014;101:114–23.
42. Yanai J, Huleihel R, Yaniv S, et al. Functional changes after prenatal opiate exposure related to opiate receptors' regulated alterations in cholinergic innervation. Int J Neuropsychopharmacol. 2003;6(3):253–65.
43. Vestal-Laborde A, Eschenroeder A, Bigbee J, Robinson S, Sato-Bigbee C. The opioid system and brain development: effects of methadone on the oligodendrocyte lineage and the early stages of myelination. Dev Neurosci. 2014;36(5):409–21.
44. Pujol J, López-Sala A, Sans A, et al. Delayed myelination in children with developmental delay detected by volumetric MRI. NeuroImage. 2004;22:897–903.

A Diagnosis of Exclusion: Demystifying Neurodevelopmental Disorder Associated with Prenatal Alcohol Exposure

14

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Case

Jacob is an 8-year-old Russian-born adopted boy presenting for a consultation for mood outbursts and aggressive behavior at home, school, and in the community. From his appearance, Jacob did not fit the textbook criteria of a frail child with "dysmorphic" facial features of prenatal alcohol exposure. Since the features change through development, his parents brought a picture of him as a baby just after being adopted. The picture showed a stark contrast. He appeared to have lonely, distant eyes and was barely fitting into 6-month clothing at 18 months. Since that time, he ate well and gained weight rapidly and was well-developed by the time of his visit.

Perceptive, comfortable, and open yet cautious at times, his favorite activities during psychotherapeutic sessions were toys, art supplies and doll house, moon sand, building blocks, farm animal figures, and army men. He often asked off-topic questions such as "What's your favorite sports hero?" Jacob was concrete, conversant, spontaneous, funny, and light-hearted with 4-year-old bathroom humor scattered throughout the discussions. His face lit up as he asked, "Do you help kids that pee on them self? Or can't sit still?" He skirted around any direct references to himself, changing the subject or distracting himself further in the play activity. When asked directly why he was there, he jumped up and scattered a handful of sand and army men, shoved an oversized chair out from the wall, and climbed behind it. He spent most of the session crouched under a makeshift tent from a quilt draped over the chair, vacillating between sucking his thumb and yelling, "I hate this place! I'm going to break this house! I want to go home!"

Jacob had experienced low frustration tolerance and an easily triggered flash point from an early age. He was in a Russian "baby home" from birth, having been placed there because his alcoholic mother was found unfit by the

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government child welfare agency. When he was adopted at 15 months, he was the size of a 6-month-old baby. He was found to have had a number of medical issues, prematurity, low birth weight, failure to thrive, and developmental delay which was said to be due to lack of stimulation. He was left in the crib for such extended periods of time that he developed torticollis, a chronic muscle spasm of the neck causing his head to tilt to one side. After arriving in the USA, he began to receive occupational therapy though with limited improvement. He attended a private day care and preschool program but had to repeat kindergarten and was failing first grade by the time of his evaluation. Though he struggled on a number of different levels, his school said that he was capable of grade-level work.

Transitions had always been hard for Jacob, especially around loud noises and in crowded settings. Seemingly minor triggers tended to unravel Jacob, leading him to "fight or flee" to get out of the situation. He also had difficulty appreciating the boundaries of personal space, at times leading to others getting hurt. For example, swinging his book bag around at the bus stop may lead to him accidentally hitting another child. Peers and teachers often thought he did it on purpose, and he would be scolded. Jacob would feel so anxious and ashamed that he would have a meltdown when he got home that day.

Since Jacob is a very sensitive and perceptive boy who is eager to please his parents and other adults, their reprimands led to him feeling "bad" and different from other kids his age. On some occasions, his parents would get a glimpse into his internal conflict. He would say, "I like Miss A, she helps me learn…I like reading, science, math, art, music, or gym…I don't like getting in trouble, but when I get mad, I can't control myself…I know it's my fault when I get in trouble…I want to have a good day…I want to be with my sister and go to [aftercare]…"

At school, Jacob had become physically aggressive toward himself, teachers, and classmates, quickly escalating and becoming defiant and disrespectful. Often, this oppositionality would lead to loud, verbal confrontations with the teacher in which Jacob would rip up his work, draw on his desk, and shout "I'm stupid!" or "I'm a baby!" He would begin scratching his arms, face, and forehead. He made frequent, threatening statements – "I will push [item] off your desk!" "You need to shut your mouth and quit talking!" "I am going to scratch my face!" "I am going to the lunchroom and start a food fight."

At home, he would demonstrate physically regressive behaviors, curling up in a ball on the floor in a fetal position, kicking to the point of his shoes coming off, and disregarding others who were speaking to him. Jacob's mood shifted, switching from "attentive to disruptive in a flash." He would also say things like "I want to turn into a giant and crush the school and burn it down!" These periods of upset would require anywhere from 30 to 40 min to de-escalate. He often would complain afterward, "my head hurts" and "I can't control how I act." His behaviors transformed into whining, making crying noises, and even farting in the aftermath of one of these explosive episodes. Despite the intensity of the incident, he rarely would apologize for his behaviors and would move on as though nothing had happened. His family

members and anyone around him would feel terrified during the events and traumatized afterward. He often confabulated to others that his parents would lock him out of the house or physically harm him by kicking or slapping, often acting out the action to whomever was listening.

Based on school reports and discussions with teachers and administrators, Jacob was performing on grade level and therefore did not qualify for extra services at school. However, he was perceptive enough to recognize that other children finished assignments much faster than he did and were reading and completing math problems accurately. Jacob felt uncomfortable, frustrated, and misunderstood at school and unable to please his parents at home. Daily negative reports from school and his out-of-control behavior at home left his parents feeling inept and hopeless. At a crossroads in understanding his challenges, they began to lower their own expectations for him emotionally and academically, recognizing that they needed different strategies to parent.

Diagnostic Assessment

Jacob was assessed to have neurodevelopmental disorder associated with prenatal alcohol exposure (ND-PAE) under other specified neurodevelopmental disorder (ICD-10 Code F88). The Diagnostic and Statistical Manual 5th Edition lists ND-PAE as a diagnosis to explain the complex neuropsychiatric, cognitive, behavioral, social, language, communication, and other multisensory deficits associated with maternal alcohol use during pregnancy. Like autistic disorder, symptoms mimic a myriad of neuropsychiatric conditions [1].

Evaluation included a 24-h EEG which showed nonspecific background abnormalities and an MRI which showed thinning of the corpus callosum. He was started on lamotrigine and clonidine to help control impulsivity and hyperactivity. Ultimately, Jacob was hospitalized in a specialty neurobehavioral unit specializing in children and adolescents with neurodevelopmental issues such as ND-PAE. Eventually, after several failed attempts to place Jacob in a variety of public school settings, he was placed in a therapeutic residential school.

Just prior to his admission to the residential school, Jacob quickly began telling about the many things he hoped would be there, a go cart track, a Native American campsite and tool-making center, a tree house, and on and on. Paradoxically, Jacob, who had been so out of control, was able to sit calmly drawing and labeling his vision of the "blueprint" for the school that he was excited to attend.

Adaptive functioning continued to be problematic and was a focus of his comprehensive treatment approach in the residential setting. Activities of daily life including bathing and hygiene were still challenging, and he was socially immature compared to his peers. He had difficulty understanding nonverbal cues and struggled with being gullible and easily influenced by others. Academically, by this point, he was found to be far behind his peers in math, writing, and reading and was found to have an FSIQ rating of 56.

Clinical Pearl
Infants who are poorly regulated in their sleep/wake cycle, are difficult to soothe or comfort, or have hyper- or hyposensitivity to light, sound, taste, temperature, textures, or other experiences often have underlying neurodevelopmental issues. It is common for children with undiagnosed ND-PAE to have been expelled from preschool more than once, to be labeled with "behavioral issues" in elementary school, to get into fights with peers and have oppositional behaviors over homework or chores, and to have academic failure or juvenile delinquency. Externalizing, defensive, oppositional, defiant, maladaptive, and acting-out behaviors may occur, particularly when the child is frustrated, conflicted, indecisive, or confronted with a difficult task. For patients presenting with such a complex array of issues, ND-PAE should be high on the differential diagnoses.

Neurodevelopmental Sequelae of Fetal Alcohol Spectrum Disorder (FASD)

By some estimates, up to 10% of US grade school children have FASD/ND-PAE [2]; clearly many more children are affected than are diagnosed. The main reasons that children like Jacob are not identified with ND-PAE are that the birth history is unknown or that mothers may not admit use during early stages of pregnancy. Like other individuals with ND-PAE, Jacob likely had brain damage from prenatal alcohol exposure given his mother's history of heavy drinking during pregnancy.

The degree of effects of ND-PAE depends upon a mother's nutrition status, genetic predisposition, other lifestyle behaviors (e.g., smoking cigarettes, recreational/illicit substance use), stress level, and medical issues. The timing, duration, frequency, and maternal alcohol concentration also contribute to the range and degree of deficits, with earlier and binge exposures possibly associated with worse outcomes. Extrinsic factors, such as witnessing or experiencing abuse, neglect, loss, and other trauma may further impact neurodevelopment, increasing vulnerability to "fight or flight" reactions.

Prenatal alcohol exposure likely caused Jacob's brain to be "wired differently" as compared to a typically developing child. One way to understand this altered connectivity is to consider renovation of an old 1800 era manor house with electricity installed in the late 1930s. The electric wires will likely need to be routed in different directions because of the placement of support walls that were never intended to be hollowed with cables passing through them. Jacob's brain had connections that were affected by switches not biologically programmed to control those areas. During their migration in early pregnancy, brain cells lost their ability to plot their course and steer in the right direction, leaving them in places they were never intended to develop.

Jacob's poorly wired nervous system impaired his ability to function in a world tolerable to most 6- to 8-year-old children. His low frustration tolerance, lack of social skills, limited cognitive abilities, and hypersensitivities to noise, smells, and textures left gaps in his basic life skills. His emotional, cognitive, language, and social skills were more consistent with a 2- to 3-year-old child than an 8-year-old child.

Reflections from the Family

Until school age, Jacob's parents were unaware of the degree of his disability, having been told when they adopted him that he was growth deficient and had health problems because he had been in an orphanage for the first 15 months of life. The adoption agency said he would "catch up" on his milestones and gain weight once he had gotten proper love and nutrition. They believed that their son was a survivor, possibly more resilient than most other children, and they were determined to help him thrive by giving him a loving, nurturing home environment as they had been told would help him overcome his harsh beginnings.

The family has vivid memories of bringing Jacob home with legs so weak he could not stand at 15 months and of being too small for size 6 months baby clothes. They also remember his anxious feeding habits, gulping down mouthfuls of food as though he would not have another meal.

Jacob's mother vividly remembers the intensity of his violent rages, uncontrollable crying spells, and other significant emotional problems during his early years. Jacob's current living situation in a pastoral environment learning life skills rather than being in a diploma track school setting appears to be much better suited to his neurodevelopmental level. He is proud of working in the cafeteria where he is learning to assist the staff with preparing simple meals, setting the tables, prepping vegetables, and doing minimal chores in lieu of the pressure toward high level math or reading novels.

Four-Domain Model of ND-PAE

A four-domain model of ND-PAE depicted in Fig. 14.1 provides a structure to understand the complex array of neurodevelopmental issues potentially affected by prenatal alcohol exposure: emotional regulation, social communication, neurocognitive functioning, and motor/coordination/sensory function. The overlapping areas indicate that individuals with prenatal alcohol exposure can have one or more domains of impairment.

Using this approach, individuals suspected of ND-PAE would be referred for the following assessments: neuropsychological testing to rule out neurocognitive issues, speech/language screening to understand their social communication problems, and occupational/physical therapy to identify and treat underlying fine/gross motor

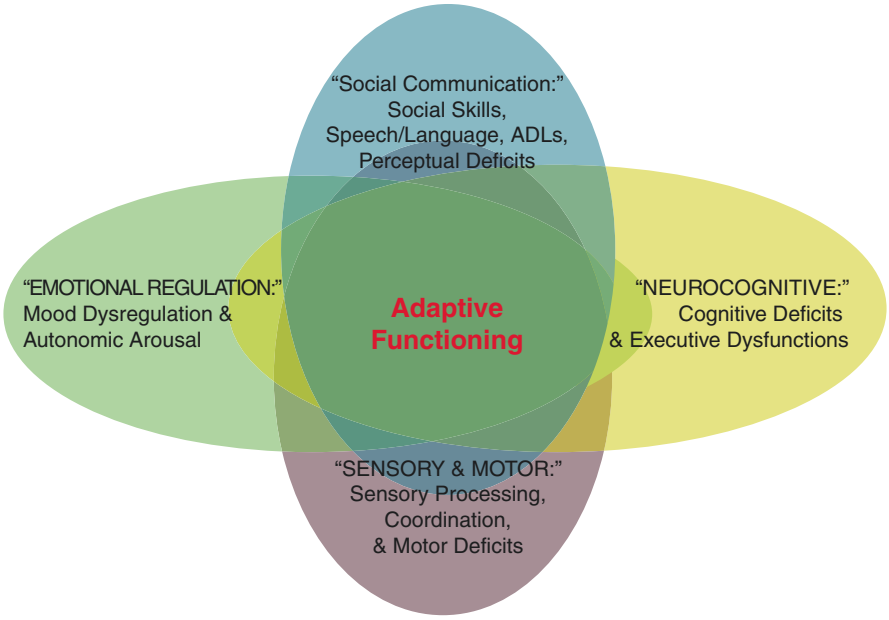

Fig. 14.1 Domains of ND-PAE for Treatment Planning

deficits or other functional issues. Mood regulation and autonomic arousal would ideally be assessed by a physician. This team of professionals would work with the individual and family to develop a comprehensive treatment plan to enhance strengths and build vocational skills and self-esteem through mentoring, apprenticeships, and experiential learning.

Emotional Regulation: Mood Dysregulation and Autonomic Arousal

Children with ND-PAE, compared with neurotypical children, may be less able to adapt to their surroundings, accept responsibility, identify social cues, demonstrate appropriate behavior, and bond with peers. Given the nature of their impairments, they may lack self-discipline, be short-sighted and impulsive, easily be swayed by peers, and overreact to stressors. Described by their parents and caretakers as "moral chameleons," it is no wonder that 60% of children with FASD ultimately encounter legal trouble [3].

Often, the effects of alcohol on the central nervous system (CNS) produce a highly mood-dysregulated child, having seemingly random or easily provoked episodes of frustration, irritability, aggression, and anger. Infants and toddlers with ND-PAE can present with Regulatory Disorder Type I, II, or III [4]. This may lead to infants and toddlers seeming to be easily agitated, overstimulated, and hyperaroused. This leads to impulsive aggression and physically lashing out during stressful or emotionally charged situations.

Many are prone to mood dysregulation that, on the face of it, may appear to mimic bipolar disorder and be characterized by intermittent explosive outbursts and episodes of rage triggered by the slightest insult, sideways glance, or annoyance. As a result, they are often more vulnerable to emotional overreaction, poor frustration tolerance, hypersensitivity to criticism, and suspicion about both positive and negative stimuli and may be overwhelmed by apparently minimal life stressors.

Such altered "arousal patterns" are associated with difficulties settling to sleep. Altered or disrupted sleep has been described by many parents and caregivers of children with ND-PAE. At the same time, few studies have been conducted to tease out the differences between typically developing children's sleep disorders and those of children with ND-PAE [5]. In animal models, prenatal alcohol affects the circadian rhythm in the hypothalamus by changing the metabolism in pro-opiomelanocortin (POMC)-producing neurons as well as the expression of "clock regulatory genes" [6].

Neurocognitive: Cognitive and Executive Dysfunctions

Individuals with ND-PAE may have deficits in a variety of cognitive domains, including but not limited to fronto-executive dysfunction (organization, concentration, processing speed, working memory, problem solving, attention, impulse control, etc.), intellectual disability, or specific learning disabilities. These disruptions in cognitive functioning often lead to a failure to understand consequences and limited insight.

Social Communication: Language, Social Skills, and Perceptual Deficits

A variety of speech and language and related socialization disabilities can also be seen in individuals with ND-PAE. The misuse of language integral to social cognition and communication are quite common problems in adolescents or young adults with ND-PAE. At times, these patients are misdiagnosed with autistic spectrum disorder or Asperger's syndrome [7]. Individuals with ND-PAE may have indiscriminate or immature behaviors. Behavior problems range from silly or irritating socially inappropriate behaviors to overtly aggressive and sometimes risky behaviors.

Sensory and Motor Processing and Coordination Issues

Many patients with ND-PAE have sensory integration (also known as "sensory processing") issues, including hypo- or hypersensitivities to noise, touch, proprioceptive stimuli, smells, tastes, and/or visual stimuli. As infants, they are often difficult to soothe, may not seem to enjoy their caregivers, and can suffer from a range of

other regulatory problems. As toddlers and young children, they frequently are sensitive to environmental sounds, lights, and fans and may be easily irritated by loud voices or music. Older children, adolescents, and adults may cope by avoiding situations or environments which provoke their sensitivities.

Lessons Learned About Neuropsychiatry

Because effects of prenatal alcohol exposure can mimic a variety of psychiatric disorders, it is important to accurately diagnose the condition in order to develop the most appropriate treatment plan. Moderate to heavy prenatal alcohol exposure can cause a wide range of deficits in children that are somewhat resistant to standard techniques of treatment. Children may have underlying cardiac defects, conduction anomalies, or arrhythmias associated with prenatal alcohol exposure, so it is important to rule out underlying heart conditions prior to beginning treatment with stimulants. Additionally, leptomeningeal heterotopias and other brain anomalies caused by prenatal alcohol exposure can be linked with seizure disorders. Medications that lower the seizure threshold can sometimes unmask such conditions (e.g., bupropion).

Additionally, traditional psychotherapy, cognitive and behavioral approaches, and other forms of non-pharmacological treatment should take into account subtle receptive and/or expressive language deficits, nonverbal learning disorders, social pragmatic challenges, or other communication issues. Other children may have auditory processing issues, cognitive or executive functioning problems, or difficulties interfering with their ability to benefit from traditional behavioral management.

References

1. Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5). American Psychiatric Association; 2013.
2. May PA, et al. Prevalence of fetal alcohol spectrum disorders in 4 US communities. JAMA. 2018;319(5):474–82.
3. Streissguth AP, Bookstein FL, Barr HM, et al. Risk factors for adverse life outcomes in fetal alcohol syndrome and fetal alcohol effects. J Dev Behav Pediatr. 2004;25(4):228–38.
4. Diagnostic Classification of Mental Health and Developmental Disorders of Infancy and Early Childhood, Revised (DC:0-3R). 2005.
5. Chen ML, Olson HC, Picciano JF, Starr JR, Owens J. Sleep problems in children with fetal alcohol spectrum disorders. J Clin Sleep Med. 2012;8(4):421–9. https://doi.org/10.5664/jcsm.2038.
6. Agapito MA, Zhang C, Murugan S, Sarkar DK. Fetal alcohol exposure disrupts metabolic signaling in hypothalamic proopiomelanocortin neurons via a circadian mechanism in male mice. Endocrinology. 2014;155(7):2578–88. https://doi.org/10.1210/en.2013-2030.
7. O'Malley KD, Rich SD. Chapter 20: Clinical implications of a link between Fetal Alcohol Spectrum Disorders (FASD) and Autism or Asperger's Disorder – a neurodevelopmental frame for helping understanding and management. In: Fitzgerald M, editor. Recent advances in autism spectrum disorders – Volume I; 2013.

Accounting for Childhood Lead Exposure: New Directives Around an Old Problem

15

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Case

John is a 6-year-old boy with a prior diagnosis of autism spectrum disorder (ASD) who presents for evaluation of inattention and hyperactivity. He was diagnosed with ASD when he was 2.5 years old and has engaged in evidence-based treatment for ASD since that time, including applied behavioral analysis, speech therapy, occupational therapy, and the integration of these therapies into his school day with an active behavioral plan. Recently, the family has become concerned about increasing aggression, destruction of property, and severe tantrums. This is occurring in both the home and school setting with evidence of increasing impulsivity. The family reports that historically John has always been "on the go." Currently, he cannot sit still during dinner and has a difficult time during seated activities at school. John moves quickly from task to task and cannot sustain attention on activities aside from video games for more than 2–3 min. He is physically intrusive and has a difficult time waiting his turn and following directions.

Otherwise, John is physically healthy. His pregnancy was complicated by fetal alcohol exposure during the first and second trimesters. No other intrauterine chemical exposures were reported. Delivery was uncomplicated at 37 weeks gestational age via normal spontaneous vaginal delivery. John has no other medical diagnoses

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or hospitalizations. He met initial milestones during the first few months of life except for delays with social smile and social reciprocity. John later developed mild fine motor delay and moderate communication delay, with atypical social interactions. Family history is significant for learning disability in mother and attention deficit hyperactivity disorder (ADHD) in father. Family history is otherwise unremarkable for other psychopathology, physical disease, or developmental concerns.

John is currently in the first grade and has an established Individualized Education Plan (IEP). He lives with his father and stepmother, one biological brother, and two half sisters. He has limited contact with his biological mother. The community that the family lives in is relatively safe and there is no apparent violence in the home. There is a history of significant high expressed emotion in the biological mother's home, where John lived from birth to 3 years old. There is no history of physical or sexual abuse. Current stressors include marital conflict and father's ongoing unemployment. The family's apartment complex is in an urban area and was built in 1982. The local water has recently been tested and found to have elevated levels of lead (32 parts per billion). The family is currently replacing their pipes and has switched to bottled water for drinking and food preparation.

On physical exam, John is afebrile with stable vitals for age. He is thin and well appearing. John is a short, quiet boy with a flat affect. He has a smooth philtrum, flat upper lip, and small eyes. He is difficult to redirect at times. The rest of his exam is normal including no other evident focal neurologic findings, no rash or other neurocutaneous findings, and no evidence of physical injury or trauma. Neurobehavioral observations reveal that John is very active, playing with the exam table paper and the otoscope and frequently moving around the room. He is difficult to engage and to redirect. His gross motor skills are appropriate for his age. John demonstrates spontaneous phrase speech but fails to respond to several bids for reciprocal communication. He has inconsistent eye contact.

Evaluation

Developmental testing is completed. John's verbal IQ is 76, nonverbal IQ is 90, and full-scale IQ is 84. Beery Visual Motor Integration standard score is 62, demonstrating a relative fine motor delay. Lab studies include a complete blood count (CBC) and a blood lead level. CBC is within normal limits and the lead level is 3 μg/dL. Conner's rating scales are obtained and are consistent with a diagnosis of ADHD, combined subtype. John had a diagnosis of fetal alcohol spectrum disorder (FASD) made early in childhood based on restricted growth, full facial features, and confirmed prenatal exposure to alcohol, though the quantity could not be well verified.

Diagnoses

Autism spectrum disorder, fetal alcohol syndrome disorder, ADHD, lead exposure

Treatment and Follow-Up

Given John's low blood lead level, treatment of the lead exposure specifically (e.g., by means of chelation therapy) was not pursued. Instead, the focus of treatment was on reducing future lead exposure and managing other diagnoses and symptoms of concern. John received a complete neuropsychological evaluation to identify strengths and vulnerabilities relevant to his learning and to inform his individualized educational and behavioral plan. He was connected with a community behavioral therapist to work on impulsivity, pro-social habits, and emotional regulation, in addition to ongoing applied behavioral analysis. John was started on short-acting guanfacine for his impulsivity, agitation, inattention, and hyperactivity. The dose was titrated to efficacy over 3 months and verified by reduced scores on the clinical attention problem scales (CAPS).

At 6-month follow-up, John was taking guanfacine extended release 3 mg daily. His inattention and hyperactivity symptoms improved with CAPS scores changing from mostly 2s to mostly 1s, but symptoms continued to interfere with his functioning at home and school on a weekly basis. John also exhibited difficulties with aggression and emotion regulation. The family had struggled to attend therapy and continued to be concerned about the impact of lead exposure on the patient's behaviors and potential. A clinic social worker was consulted to assist the family with transportation and resources in order to attend therapy. The family was counseled about the critical importance of therapy, to avoid lead in the environment, and to optimize nutrition. Guanfacine was continued at the current dose with consideration of titration to 4 mg daily if he continued to be symptomatic. If an adequate trial of behavioral therapy was completed and significant aggression continued in multiple settings, a second-generation neuroleptic could be added to John's treatment plan, along with obtaining baseline metabolic screening in anticipation of this change to his psychotropic management.

Discussion

Scope of Lead Exposure

Lead is one of the oldest known toxic agents and lead exposure continues to be an important pediatric environmental health problem. Costs associated with lead-related morbidity exceed 40 billion dollars annually while not fully accounting for the tremendous additional costs of low-level lead exposure and related subclinical neurologic, cognitive, behavioral, and emotional deficits [1–3]. Great strides have been made in primary prevention, early identification, and rapid management of childhood lead exposure, owing to efforts in education, screening, public health intervention, and policy change. Despite this, children of underrepresented minorities, immigrant backgrounds, lower socioeconomic status (SES), and with developmental disability are disproportionately affected by lead exposure [2–4]. The case

above highlights the complexity of evaluating and managing lead exposure and its effects on patients, families, and communities. It also highlights the challenges of addressing lower lead level exposure or lead exposure less than 10 μg/dl.

Lead absorption typically occurs via inhalation or ingestion. Common current sources of lead exposure in the United States have been related to international trade, including Chinese-made toys with lead paint, imported foods from Mexico, and traditional medicines and spices from India [1–3, 5–6]. Soil is another potential source with an estimated 4–5 million tons of lead deposited in soil throughout the United States via leaded gasoline and related fume emissions [3]. Drinking water has been an increasingly recognized source of lead exposure in the United States, owing in part to the nationally publicized man-made disaster in Flint, Michigan, in 2014, with lead leaching into drinking water from pipes and water storage systems [6].

Absorbed lead is excreted renally and nonabsorbed lead is excreted in feces [3, 7]. Lead is carried predominantly by erythrocytes, with 5% being available freely in plasma [7]. Lead permeates all organs. Serum lead levels capture acute lead toxicity, but do not capture prolonged lead deposition seen commonly in the brain and bone. Reservoirs in the brain and bone can be mobilized and result in prolonged systemic exposure. The developing child's brain is particularly sensitive to the effects of lead, due to significant neuronal proliferation, differentiation, periods of synaptic pruning, and anatomic organization [3]. Children are also vulnerable due to increased gastrointestinal absorption, a more porous blood-brain barrier (BBB), greater deposition of lead into soft tissues rather than bone, and increased circulating serum lead levels relative to adults [3–4]. Children under 5 years old are especially affected due to significant penetration of serum lead into the developing brain [2].

Impact of Lead Toxicity

Children with the same blood lead level should not be assumed to carry equal neurodevelopmental risk [2, 8]. Each child has unique physiologic and environmental factors influencing susceptibility to the effects of lead. Consequently, evaluation of each child's unique presentation, course, source(s) of exposure over time, and response to lead exposure is needed, with management tailored accordingly.

Currently, the Centers for Disease Control and Prevention (CDC) advises the actionable level of serum lead exposure is ≥10 μg/dl. This threshold was intended to provide guidance for risk management and intervention but is often misinterpreted as a "safety" threshold [2, 4]. Current evidence indicates there is no lead exposure level that is "safe" for children [1–4, 7–9]. Emerging evidence suggests reducing the cutoff for management and intervention from 10 to 2 μg/dl [1, 2, 8]. However, the CDC does not plan to change the guidelines, citing the lack of clear evidence of a threshold below which adverse effects are not experienced, a lack of interventions demonstrated as efficacious below the current cutoff, and uncertain benefits from reducing the cutoff [1, 2].

Low-level lead exposure remains neurotoxic in children and presents with less overt, yet equally important, clinical changes [3, 7–9]. Low-level lead exposure is

associated with decrements in IQ, with an inverse relationship between serum lead levels and global IQ [1–3, 7–9]. IQ scores can decline 2–3 points per 10 μg/dL of exposure, with the rate of IQ decline being greatest at serum lead levels below 10 μg/dl [1, 3, 9]. At this low level, lead-sensitive neurotoxic pathways are rapidly saturated, which can have significant influence on word recognition, reading comprehension, listening comprehension, math reasoning, and math calculation [1, 3]. Neuropsychological examination similarly reveals deficits to verbal learning and processing, language, executive functioning, visuomotor processing, fine and gross motor functioning, memory, information processing, and reaction time [1, 7–8].

Lead also has a considerable impact on the emotional, behavioral, and social well-being of children [8]. Lead can directly modulate social/emotional and behavioral regulation as early as a few years of age, with deficits seen in orientation-engagement and emotion regulation [7, 9]. Lead exposure, at times in a dose-dependent manner, increases the occurrence of depression, anxiety, ADHD, somatization, and irritability [1, 3, 7–9]. Higher prenatal lead exposure has also been associated with increased risk of schizophrenia [1, 3]. Aggression is also directly tied to increasing levels of lead exposure and can be seen with levels of 15 μg/dl or lower [1, 7, 9]. Similarly, lead has been linked to juvenile delinquency and antisocial behavior, even when adjusting for medical, birth-related, and socioeconomic factors [1, 7, 9]. Cognitive limitations associated with childhood lead exposure include poor frustration tolerance, difficulty adapting to stressors, low self-esteem, poor social development, and diminished capacity to manage complex thoughts and emotions [1, 7, 9].

Although many neurocognitive effects are identified at low levels of lead exposure, effects tend to be idiosyncratic. Consequently, low-level lead exposure is more common than overt toxicity, yet the clinically associated sequelae are more elusive. Limited recognition of the time, duration, and source of exposure further reduces identification. Children with lead exposure also disproportionately experience reduced access to educational supports and high-quality schooling and an increased incidence of adverse childhood experiences and reside in lower socioeconomic status (SES) settings. Many of these environmental factors result in greater environmental exposures to lead via paint in older homes, water-based lead exposure, and nutritional deficiencies in calcium, iron, zinc, or protein [3, 4, 7]. Furthermore, lower SES directly increases susceptibility to the toxic effects of lead while reducing the likelihood of improvement after removal of lead exposure [4]. SES appears to interact with the neurotoxic effects of lead to further impact visual-motor integration and reaction time [5, 7]. Children from lower SES backgrounds have been shown to perform significantly worse on cognitive testing relative to children from higher SES backgrounds with the same level of lead exposure [5, 7].

Clinical manifestations of lead are broad, diverse, and can impact a variety of organ systems. Thus, the astute clinician should always have a high suspicion of lead exposure as a contributing factor when neurocognitive and behavioral disturbances are present. Such difficulties may present across academic, behavioral, interpersonal, and developmental domains.

Mechanisms of Lead Toxicity in the Central Nervous System
• Replacement of calcium and zinc in cellular function and signaling
• Impact on calcium release, regulation, and homeostasis
• Neuronal apoptosis and excitotoxicity
• Reduced cellular energy metabolism
• Altered neurotransmitter release
• Altered genetic transcription and regulation
• Direct damage to mitochondria and mitochondrial membranes
• Effects on oxidative metabolism and anti-oxidative enzymes
• Disruption to lipid metabolism and peroxidation
• Accumulation in astrocytes within the brain
• Aberrant oligodendrocyte development and functioning with abnormal myelin production
• Sequestration in tissues and bone with systemic penetration over time
• More porous blood brain barrier
• Long half-life in the central nervous system with slow accumulation and chronic effects

Fig. 15.1 Mechanisms of lead toxicity in the central nervous system

Neuroanatomy and Pathophysiology

Lead has no biological function within the human body and acts only as a toxin [6]. The direct toxic effects on cellular health are broad and include apoptosis, excitotoxicity, mitochondrial damage, disruption of intracellular messaging, and altered neurotransmitter storage and release (Fig. 15.1) [1, 7]. Primary targets include cerebrovascular endothelial cells, astrocytes, and oligodendrocytes, cells that are critical for neuronal transmission, oxidative metabolism, lipid peroxidation, and brain homeostasis [1, 7].

Lead principally has two major neurotoxic effects: (1) neurodevelopmental effects on the differentiation and connectivity of the brain and (2) neurotransmission effects on ion-based mechanisms and neurotransmitter function. One of the common mechanisms leading to the neurotoxic effects of lead is the ability to supplant calcium (Ca) and zinc (Zn) in cellular interactions [7].

Cellular Regulation and Neurotransmission

Lead can impact intra- and intercellular messaging through its substitution for Ca in Ca-mediated messaging. This influences intracellular Ca homeostasis, which can have wide effects on cellular functioning and signaling including impacts on cell proliferation, plasticity, and differentiation [6]. Lead can dampen Ca-dependent release of acetylcholine, dopamine, and amino acid neurotransmitters, through presynaptic

Ca channels and increasing the pool of vesicles at the presynaptic neuron [7]. At the same time, lead increases basal release of these neurotransmitters. This can affect neurotransmitter storage and release, as well as neurotransmitter receptor density and functioning [6–7]. Chronic lead exposure can impact N-methyl-D-aspartate (NMDA) receptor regulation, leading to increased proliferation of the NMDA receptor. This can have downstream effects on glutamatergic regulation at the level of the hippocampus, impacting learning, memory, and neuronal plasticity [6].

Lead also displaces Zn, having particular effects on intracellular genetic transcription. It can deposit into the cellular nuclei and associate with nuclear proteins and chromatin thereby effecting gene regulatory proteins [7]. Zn finger proteins can also be impacted, resulting in disruptions of gene expression, chromosomal structure, signal transduction, cell growth, cell differentiation, and cell proliferation [7].

Even at chronically low levels, lead can trigger apoptosis in dopamine-producing cells. It can have significant effects on dopaminergic receptor function, particularly D1 and D2 receptors, in the striatum and nucleus accumbens with an apparent vulnerability of the D2 receptors to chronic low lead exposure [7]. Dopaminergic disruptions can effect motor development, attention, memory, and executive functioning. GABA-mediated neurotransmission can be inhibited by lead through inhibition of GABA release and competition with GABA at receptor binding sites [7].

Lead can have significant toxic effects on oligodendrocytes and astrocytes. Oligodendrocytes are more vulnerable with lead exposure resulting in abnormalities of maturation and function. The process of myelination can be disrupted, a key function of oligodendrocytes, resulting in abnormal myelin morphology, hypomyelination, and demyelination [7]. Lead also has direct toxic effects on Schwann cells in the peripheral nervous system [7]. Astrocytes are more susceptible to the effects of lead early in maturation with disruptions to differentiation. In the mature state, astrocytes can initially protect against the neurotoxic effects of lead by serving as repositories for lead deposition [7]. However, over time this lead can be released into the brain and eventually serve as a source for ongoing lead transmission [7]. Astroglial function can be altered resulting in reduced glutamine synthetase activity, a key enzyme that converts glutamate to glutamine [6]. In the presence of lead, less glutamate is converted to glutamine, subsequently increasing neuronal excitotoxicity.

Pregnancy and Fetal Development

Mothers with a history of chronic lead exposure or lead toxicity can directly transmit lead to the developing fetus. Lead transmission can involve exogenous and endogenous sources, with the primary endogenous source being bone lead deposition [7]. Lead is also present in maternal breast milk with concentrations being dependent on maternal serum lead levels. Increased maternal calcium intake can mitigate this effect by decreasing lead bone resorption and bone demineralization [7]. These findings are particularly concerning as the immature fetal and early infant brain are highly sensitive to the effects of lead exposure, including low-level

exposure [3]. The exposure to lead is unidirectional, with the fetus being at risk for significantly higher lead exposure than the mother due to direct transmission across the placenta [3].

Treatment Strategies

Unfortunately, prospective studies demonstrate little evidence that neurodevelopmental deficits associated with early lead exposure resolve over time [1, 3]. Chelation therapy, the mainstay of treatment for lead levels >20 μg/dl, can improve neuromotor outcomes, such as balance, fine motor, and gross motor deficits, yet does not prevent or reverse cognitive deficits in children [1, 3, 4]. Evidence does not support benefits of chelation therapy for low-level lead exposure [1].

The best approach to managing lead exposure is prevention [2, 3]. Prevention is predicated on avoidance of lead sources including exposure to lead-based paints, lead-based fuels, and soils laden with lead [2]. Risk factors include housing built before 1978 (particularly if undergoing renovation), children living near smelting, processing or battery disposal plants, children whose parents work in a lead-related field, children whose family or peers were recently diagnosed with lead toxicity, and children who recently immigrated from countries where lead toxicity is endemic [3]. Prevention also includes access to safe water and nutrition supplementation to prevent water-based exposure and to mitigate the effects of historic exposure [3, 6].

It is also important that children receive regular screening and monitoring by their primary care provider. The primary care provider can be instrumental in raising awareness of public health resources related to lead exposure within a given community. The CDC recommends screening all Medicaid-eligible children, children living in high-risk areas, and children at high risk due to underlying risk factors [3].

Management includes addressing environmental, social, psychological, cognitive, and behavioral sequelae of lead exposure using evidence-based management strategies (Fig. 15.2) [2, 8]. No single non-pharmacologic approach universally

Management Strategies for the Management of Low Level Lead Exposure
• Preventing exposure to lead-based paints, gasoline, soil, and other products
• Access to clean water with replacement of lead piping or lead water storage systems
• Adequate nutritional intake including sources high in calcium, iron, and Vitamin C
• Frequent hand washing, particularly in environments with high risk of lead exposure
• Regular lead screening and clinical assessment by primary care provider
• Referral to Educational Specialist for academic supports and interventions
• Referral to Neuropsychology for neuropsychological assessment
• Referral to Psychology or Social Work for psychotherapy
• Referral to Child and Adolescent Psychiatry for management of comorbid psychopathology

Fig. 15.2 Management strategies for the management of low-level lead exposure

addresses lead-based neurodevelopmental effects. This may be due in part to the heterogeneous effects of lead on neurodevelopment and the context in which lead exposure occurs [5, 8, 10]. Therefore, an individualized approach to intervention should be undertaken that targets the primary neuropsychiatric and/or neurocognitive problems of a given child and utilizes the most evidence-based interventions to address them accordingly.

Interventions utilized to address functional impairments in individuals with brain injuries are more likely to improve outcomes than those used with otherwise typically developing children that exhibit learning or cognitive difficulties [8]. One such intervention, cognitive rehabilitation, entails training children to rely upon intact cognitive abilities to compensate for relative deficits. Another non-pharmacologic intervention, behavioral modification, aims to modify the environment around children in a manner that accommodates areas of reduced cognitive function while maximizing areas of cognitive strength. For example, in a child with significant attention-related deficiencies, behavioral modifications may include preferential classroom seating, prompts for on-task behavior at pre-specified intervals, and periodic breaks. In addition, activities aimed at developmental and environmental enrichment may also be of benefit to reducing the neurodevelopmental/neuropsychiatric effects of lead exposure [1, 6]. Enrichment activities, such as early parenting education to support nurturing parent-child interactions or early exposure to books to promote stimulation, have the potential to mitigate lead effects.

Clinical Pearls

This case highlights that there is no safe lead level. Neurocognitive effects from lead exposure can be detected at serum levels as low as 3 μg/dl [10]. Children in economically disadvantaged settings and those with developmental delays remain at an increased risk relative to the general population. Compounding ongoing risk of exposure for certain vulnerable populations is the occurrence of lead exposure via plumbing and water. Water-based lead exposure is a relatively new phenomenon, and primary prevention strategies are emerging.

Until primary prevention strategies are in place for water-based lead exposure, secondary and tertiary prevention efforts are needed. Secondary prevention efforts include routine screening for lead exposure risk, counseling families on lead exposure prevention, and utilizing established blood lead screening guidelines [2]. When risk for lead exposure is high, more frequent screening and referral to developmental specialists, where available, is encouraged. Developmental enrichment, nutritional supplementation, and access to clean water are also essential. Once exposure is identified, individualized management should target the unique constellation of neurocognitive and neuropsychiatric difficulties encountered.

Another key point exemplified within this case is that lead exposure can complicate the treatment of neurodevelopmental diseases in two key ways: (a)

decreasing clarity around diagnosis and (b) decreasing the effectiveness of standard treatment for neurodevelopmental disease. When diagnostic clarity is reduced, ambiguity surrounding an explanatory model for difficulties and contributing factors increases. This leaves parents and other caregivers understandably anxious and seeking answers. Consequently, in an effort to resolve uncertainties and address possible contributing factors, parents and families can expend energy and resources in directions that are less helpful (e.g., completion of unnecessary labs, invasive procedures, imaging). Similarly, when standard treatments fail to produce expected outcomes, parents and providers must identify alternative strategies for maximizing outcomes, a common occurrence when lead exposure occurs in a child with pre-existing neurodevelopmental difficulties.

Lessons Learned About Neuropsychiatry

Owing to the complex neuropathophysiology of lead exposure and its synergistic interaction with a myriad of co-occurring factors (e.g., environmental, developmental, psychiatric), determining the relative contribution of lead exposure to a given child's presentation is challenging. Conducting a comprehensive evaluation and adopting a measured conceptualization and management approach that considers potential co-occurring factors along a biopsychosocial continuum can be helpful. Once complete, communicating the multifactorial nature of a child's presentation to families, while emphasizing the needed for an equally multifaceted, multidisciplinary management approach, can reduce ambiguity considerably.

Families will often understandably seek swift resolution to their child's difficulties at which point education on the value of behavioral modification, cognitive and emotional rehabilitation, and developmental supports is of benefit. Pharmacology may be helpful in some cases to target particular symptoms, such as impulsivity or inattention, or to reduce symptom burden in children with severe and impairing symptoms. Additional research exploring standard treatments for neurodevelopmental difficulties in the context of lead exposure, examining evidence-based treatments for children with brain injuries, and investigating novel approaches to treatment for children with lead exposure is sorely needed.

The assumptions should always be that (1) there is no safe level of lead exposure, (2) lead exposure should be considered in a broad range of presentations, (3) efforts should be made to mitigate and reduce exposure to lead, and the presentation is often not simply related only to lead exposure but to multiple factors interacting within a given child; otherwise effective treatments may not have the same effect. Lead impacts neuronal growth, functioning, and differentiation in multiple ways and affects multiple interrelated intercellular and intracellular pathways that it can be challenging to tease out the effects of lead exposure from other comorbid clinical and environmental factors. In the absence of alternative interventions, families and

providers must utilize existing interventions while attempting to adapt these interventions to the patient's unique needs. The care team must be mindful of the potential reduced effect of intervention secondary to comorbid lead exposure and counsel families accordingly.

References

1. Bellinger DC. Very low lead exposures and children's neurodevelopment. Curr Opin Pediatr. 2008;20(2):172–7.
2. Binns HJ, Campbell C, Brown MJ, Centers for Disease Control and Prevention Advisory Committee on Childhood Lead Poisoning Prevention. Interpreting and managing blood lead levels of less than 10 microg/dL in children and reducing childhood exposure to lead: recommendations of the Centers for Disease Control and Prevention Advisory Committee on Childhood Lead Poisoning Prevention. Pediatrics. 2007;120(5):e1285–98.
3. Woolf AD, Goldman R, Bellinger DC. Update on the clinical management of childhood lead poisoning. Pediatr Clin N Am. 2007;54(2):271–94.
4. Bellinger DC. Lead. Pediatrics. 2004;113(3):1016–22.
5. Bellinger DC. Lead neurotoxicity and socioeconomic status: conceptual and analytical issues. Neurotoxicology. 2008;29(5):823–32.
6. Toscano CD, Guilarte TR. Lead neurotoxicity: from exposure to molecular effects. Brain Res Rev. 2005;49(3):529–54.
7. Lidsky TI, Schneider JS. Lead neurotoxicity in children: basic mechanisms and clinical correlates. Brain. 2003;126(Pt 1):5–19.
8. Lidsky TI, Schneider JS. Adverse effects of childhood lead poisoning: the clinical neuropsychological perspective. Environ Res. 2006;100:284–93.
9. Chen A, Caj B, Dietrich KN, Radcliffe J, Rogan WJ. Lead exposure, IQ, and behavior in urban 5-to 7-year-olds: does lead affect behavior only by lowering IQ? Pediatrics. 2007;119(3):e650–8.
10. Chiodo LM, Jacobson SW, Jacobson JL. Neurodevelopmental effects of postnatal lead exposure at very low levels. Neurotoxicol Teratol. 2004;26:359–71.

Part IV

Epilepsy

Introduction

> Melancholics ordinarily become epileptics, and epileptics melancholics: what determines the preference is the direction the malady takes. If it bears upon the body, epilepsy, if upon the intelligence, melancholy.
>
> Hippocrates

This section explores a broad range of pediatric neuropsychiatric topics in epilepsy and psychogenic non-epileptic seizures (PNES). Epilepsy has been a source of neuropsychiatric intrigue among clinicians for millennia yet has also captured the interest of the lay public given that epilepsy has affected the lives, and sometimes the work, of writers, performers, and artists as diverse as Dostoevsky, Lil' Wayne, Neil Young, and Prince. Epilepsy is a quintessential neuropsychiatric illness given that behavioral, cognitive, and emotional comorbidities are vastly overrepresented as compared to other chronic illnesses. Historical assessments by two neurologists, Jean-Martin Charcot and Sigmund Freud, of what was then termed "hysteria," might now be called psychogenic non-epileptic seizures (PNES) and led to the founding tenets of psychoanalysis. Thus, epilepsy and the differentiation of psychic conflicts leading to PNES ultimately defined psychiatry in ways that have been indelible.

There is a vast literature on the management of pediatric epilepsy in the neurological and pediatric literature. Because of this, the focus in this section, rather than addressing core diagnostic and treatment aspects of pediatric epilepsy, is to explore neuropsychiatric interface and emphasize the way in which neurological and psychiatric management overlap in complex cases.

The section begins with an exploration of the complicated, but nonetheless common, presentation of non-epileptic events in the setting of epilepsy. The second case explores the challenging management of epilepsy with mood, cognitive, and emotional sequelae and the intriguing subject of hemispheric lateralization. The next case explores management of common epilepsy sequelae using a multidisciplinary, integrated approach utilizing complementary and alternative techniques as part of

comprehensive neuropsychiatric management. Finally, the devastating and important subject of treatment refractory epileptic encephalopathy is discussed as the final case of the section. Epilepsy engenders personal insight into states of consciousness in so many ways. In that light, families in this section have made notable contributions to the discussion. Their insight is precious and more articulate and meaningful than could be expressed by clinician voices alone.

Psychogenic Nonepileptic Seizures and Comorbid Epilepsy in an Adolescent

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Sigita Plioplys and Amandeep Jutla

Case

Kim is a 16-year-old girl with a history of epilepsy (Jeavons syndrome) since age 5 and mood and anxiety symptoms since early adolescence.

At age 13, Kim experienced stress at school and started having more frequent seizures despite having been seizure-free for about 1 year with ethosuximide. Levetiracetam was added to further control the seizures. It was ineffective, and Kim developed panic attacks, so levetiracetam was discontinued. Kim continued to have frequent, treatment-resistant seizures that became more prolonged over time and changed in presentation. Kim's typical epileptic seizures had always been characterized by stereotypic eye blinking or brief periods of staring. The new seizure-like episodes were different; they could either start unexpectedly or be provoked by intense emotions, stressful situations, strong smells, or changes in lighting. The episodes occurred four to five times weekly and they lasted from a few seconds to an hour. Occasionally, Kim had a premonitory sensation that her body was about to "go limp in an unnatural way." Often, she would become "unconscious," limp, and unable to move. Sometimes her arms and legs would "float" up to the ceiling; sometimes they would spasm. She would make many facial expressions and her eyes would flicker. At times she appeared to be vomiting, choking, or gasping for air. According to Kim's father, during the episodes, "she was a different person: her voice changed, her way of inhabiting her body changed... she really embodied a

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very scared little girl, but in a way that didn't look like [Kim] being scared but someone else being scared." During the episodes Kim often felt unable to move or speak, and she often had unusual sensory experiences, such as a sense of physical pressure on her shoulders and chest or a bright flashing white light that seemed to be within her head. She could not hear her mother talking but could hear her singing. Kim also had various mental images of herself "stuck going around on a track" or of "everything being navy blue." Following the episodes, Kim often reported prolonged periods of memory loss (3–4 h) during which she did not know where she was and could not recognize herself or family members. Sometimes she would have nightmares about killing her older sisters.

Clinical Pearl 1

Psychogenic non-epileptic seizure (PNES) events are non-stereotypic and episodic, with anatomically unexplainable cognitive, sensory, and motor symptoms. Changes in cognitive functioning may occur before, during, or after an event. Patients often look confused, disoriented, unresponsive, or unconscious and may have memory loss. Patients may appear to be "coming in and out of unresponsiveness" during the event, especially if it is prolonged. Events may be brief or may last several hours. Sensory experiences may be complex and multisensory. Motor behaviors may present with a broad range of movements such as loss of function (not able to move or stand), hyperkinetic movements (tremors, shaking, convulsing, rolling), or both. Vocalizations are common. Salivation (foaming) and urinary incontinence may also be present.

Kim underwent extensive medical and neurological evaluations that included electroencephalographic (EEG) testing. At first, her EEG demonstrated baseline epileptiform abnormalities with generalized spike, polyspike, and wave discharges, but over the next 2 years, her EEG showed normal background and resolved previous ictal abnormalities. Despite a normalized EEG and treatment with valproate, Kim continued to have ongoing paroxysmal seizure-like episodes that were treated as electrical seizures. Conversion disorder (PNES) was diagnosed about 2 years later, when several typical paroxysmal events were captured on video EEG and no associated ictal EEG abnormalities were identified.

Kim began to have panic attacks at age 12. Initially, panic attacks were thought to represent a side effect from levetiracetam; however, they persisted even after levetiracetam was discontinued. Kim described the panic attacks as unprovoked and typically beginning with a feeling of "intense shame" or extreme fear, a sense of onrushing dread, and hyperacusis. During an attack, she felt nausea, vertigo, and a burning sensation in her gut. Her limbs would shake and she would hyperventilate, but she would not lose consciousness. Following a panic attack, she would experience a headache. Kim reflected that panic attacks and PNES felt fundamentally different.

Kim first felt depressed in fourth grade, when her friends were forming cliques and she felt lonely and rejected. Her mood worsened over the years. In eighth grade, she began struggling with social and academic activities that she had historically enjoyed and found easy. Her eating patterns changed and she had a 20 lb weight gain. Kim described anergia, irritability, difficulty falling asleep, and hypersomnia. She felt unmotivated and disinterested in recreational activities: she went from going to karate two or three times a week to only going twice a month. She began to frequently refuse to attend school and she withdrew from friends and social contacts. Kim had some fleeting, passive thoughts of death (if she "did not exist, it might be easier"), but she denied suicidal ideation. Kim felt worthless, hopeless, and guilty for burdening family members with her medical problems. She reflected that sometimes her guilt and shame were "strange" in that they were associated with not feeling "the right emotion" for particular situations (e.g., feeling that she had not been sufficiently sad after learning about the death of a neighbor).

Clinical Pearl 2
Comorbid psychopathology is common in youth with PNES, as 42–84% of them have at least one psychiatric diagnosis (not including conversion disorder) [1, 2]. Most common are internalizing disorders; 7–41% of PNES youth have anxiety, 19–32% have depression, and 2–8% have PTSD [3]. Among PNES youth with anxiety disorders, separation anxiety and school phobia are more common than panic disorder, generalized anxiety disorder, or posttraumatic stress disorder [3, 4]. Notably, relative to their unaffected siblings, PNES youth have been found to have a significantly greater tendency to interpret anxiety-related bodily sensations as dangerous ("anxiety sensitivity"), more somatization symptoms and are significantly more likely to have a passive "venting" coping style.

Psychiatric History

Kim has been in psychiatric treatment on and off since middle school. First she was given an ADHD diagnosis, but when additional educational interventions were implemented, symptoms improved. In middle school, Kim received 6 months of cognitive behavioral therapy for panic attacks but discontinued treatment because she felt it was not helpful. Subsequently, Kim was admitted to an inpatient psychiatric unit for ongoing, recurrent, intrusive PNES. She then entered a partial hospitalization program but was discharged after 2 days, as ongoing PNES interfered with her participation. She was referred to an intensive outpatient program which she completed successfully.

At the time of her presentation, she was taking quetiapine 125 mg every night at bedtime as prescribed for treatment of PNES. For depression and anxiety, she was taking sertraline 50 mg every morning.

Psychological and Developmental Profile

In early life, Kim was an overactive child with mild sensory issues. She didn't like wearing pants around her waist and preferred not wearing clothes at all. She did not have excessive fears or worries in early childhood. In fact her father described her as "the farthest thing from an anxious or fearful child." Kim did have "an active sense of shame" and was often concerned about whether she had "done something wrong." She has always been perfectionistic, compelled to please others, and an emotionally sensitive person, prone to having her feelings hurt easily. Her therapist noted that some of Kim's perfectionism seemed to be driven by a fear of failure; she often compared herself to her parents and siblings, all of whom were highly accomplished, driven, and educated individuals. Her two older sisters, both intellectually gifted, even at a young age had a broad range of interests and major academic and personal accomplishments. As the youngest sibling, Kim looked up to and adored her sisters, but she also felt competitive with them and was prone to worry that she would not live up to the high standard they had set in the family.

Kim has always been a highly creative, enthusiastic, curious, excitable, and energetic individual. She had a "quirky" way of thinking that could be expressed in elaborate, evocative ways, often through writing plays and books. She could have "many movies (dozens) playing in her head at the same time," as though there are "many worlds in her mind, all going on at once." Her therapist described this as a "fascinating but overwhelming" internal world. She could work on projects for long periods of time (12 h) without sleep, though afterward she would "crash" and feel very tired.

Although intellectually gifted, Kim had difficulty with mathematics in elementary school and required assistance in finding specific ways to learn the material using visual aids. Also, she had some difficulty with rote memorization (such as with spelling), though generally had excellent memory and was able to memorize poems and book chapters.

Although Kim and her parents were concerned about epilepsy, it did not seem to limit the family's everyday life. Kim always had a typical schedule and multiple social and recreational activities; thus epilepsy was not considered to be a burden to the patient and her family.

Kim had been enrolled at a selective high school where she did very well for the first 2 months of the freshman year. She stopped attending school in the middle of her freshman year and instead began taking online classes, though was only able to take one class at a time and even that she found very stressful.

Medical History

Kim had frequent ear infections in infancy and toddlerhood. She first experienced epileptic seizures at age 5, in the form of brief (1–2-sec-long) episodes of speech arrest and rapid eye blinking. Her family initially thought these episodes were tics; ultimately, when she was about 11, she was diagnosed with absence seizures. Later,

Table 16.1 Jeavons syndrome

Description	An idiopathic generalized epilepsy syndrome characterized by (1) eyelid myoclonia (with or without absences), (2) eye closure-induced seizures/EEG paroxysms, and (3) photosensitivity [5]. Motor symptoms (such as leg twitching) are not typical of this syndrome
Epidemiology	Childhood onset; typical age range 2–14 years; twice as common in girls; 3% of all epilepsy [6]
Treatment	Avoid photic triggers; AEDs (levetiracetam, valproate, ethosuximide) [7]
Neuropsychiatric comorbidities	Associated with impairment in rote, verbal learning, sustained attention, and processing speed [7]. To our knowledge no studies have examined comorbid psychopathology in youth with Jeavons syndrome. It has, however, been our clinical experience and impression that many youth with Jeavons syndrome experience comorbid anxiety and learning difficulties
Overview of Jeavons syndrome	

she developed additional motor symptoms (leg twitching), which led to the diagnosis of Jeavons syndrome (see Table 16.1). At the time of presentation, Kim was taking divalproex 1000 mg twice a day, but previous trials included ethosuximide, levetiracetam, and zonisamide. She did not have a witnessed seizure since starting divalproex.

One year prior to developing new seizure-like episodes, Kim had a prolonged period (5 months) of medically resistant headaches for which she underwent extensive neurological evaluations and was not able to attend school for several months. Medical workup was found to be negative. She ultimately disclosed that she had fabricated the headaches to avoid going to school.

Clinical Pearl 3

Epilepsy is present in 30% of youth with PNES [4]. The following "red flags" may suggest PNES in children with epilepsy: (1) changes in typical seizure presentation, despite previously stable course of illness and effective treatment; (2) the "rule of 2" (at least two seizure-like events per week, refractory to at least two antiepileptic drugs, and at least two EEGs without epileptiform activity); (3) family, interpersonal, and learning problems; (4) developmental milestones (middle school, high school, college); and (5) loss or trauma.

The gold standard approach for diagnosing PNES includes a detailed history, a psychiatric assessment, and a video-EEG recording of the paroxysmal event in question that demonstrates no associated epileptiform activity before, during, or after the event. This approach is particularly important in patients with comorbid epilepsy and background epileptiform discharges. As differentiation of paroxysmal seizure-like episodes from epileptic seizures may be complicated, it is helpful to have a good description and video recordings of all paroxysmal events provided by parents. Additional testing of ictal prolactin, heart variability, oximetry, and cognitive and psychological functioning can be used as supplemental (but not diagnostic) tests.

Table 16.2 Diagnostic levels of certainty for psychogenic nonepileptic seizures

Level of certainty	History consistent with PNES	Witnessed event	EEG
Possible	+	By witness or self-report/ description	No epileptiform activity in routine or sleep-deprived interictal EEG
Probable	+	By clinician who reviewed video recording or in person showing semiology typical of PNES	No epileptiform activity in routine or sleep-deprived interictal EEG
Clinically established	+	By clinician experienced in diagnosis of seizure disorders (on video or in person), showing semiology typical of PNES, while not on EEG	No epileptiform activity in routine or ambulatory ictal EEG during a typical ictus/event in which the semiology would make ictal epileptiform EEG activity expectable during equivalent epileptic seizures
Documented	+	By clinician experienced in diagnosis of seizure disorders, showing semiology typical of PNES, while on video-EEG	No epileptiform activity immediately before, during, or after ictus captured on ictal video-EEG with typical PNES semiology

Adapted from LaFrance et al. [1]

The requirements described in Table 16.2 can help guide the PNES diagnosis.

Treatment

After Kim received a documented PNES diagnosis, she continued weekly individual and family therapy along with taking sertraline 50 mg, quetiapine 150 mg, and divalproex 1000 mg twice a day. Over the next few months, quetiapine was discontinued.

Psychiatric treatment was provided by a team of a child psychiatrist and a child psychologist experienced in treating youth with conversion and anxiety disorders. Both mental health clinicians were in frequent communication about overall treatment progress. Treatment goals included focusing on both PNES and Kim's comorbid psychopathology. Kim's neurologist also collaborated with her mental health providers regarding general treatment goals and, specifically, management of divalproex for treatment of epilepsy.

Initial PNES treatment goals included resolution of PNES episodes using individual behavioral interventions and parent training. During weekly individual therapy, Kim learned to identify stressors and understand the body-mind connection. She learned how to more effectively communicate her negative emotions and recognize associated body changes.

Simultaneously, the team worked with Kim's parents on how to decrease their focus on Kim's somatic complaints and acknowledge her emotional distress while

setting realistic expectations for her return to normal daily functioning. Kim's family and the treatment team have worked closely with the school and developed an IEP that included transitional plan for her return to school. She restarted ninth grade and transitioned gradually to a full-time school schedule over a 3-month period. Once this was accomplished, the next step was to address Kim's perfectionistic tendencies, unspoken fear of disappointing her family, competitiveness with older siblings, and improving her communication of emotional distress.

Though enthusiastic about returning to school and being free from PNES, Kim developed new somatic symptoms (vertigo, nausea, fatigue, sleep problems) that interfered with her transition to school. She also experienced panic attacks at school and other social, athletic, or competitive performance settings. The panic attacks were triggered by her feeling overwhelmed, "out of control," and unable to communicate her needs. Notably, she continued to be highly sensitive to bodily sensations (high anxiety sensitivity) and continued to have a tendency to present with medical symptoms and "short-lived" medical illnesses when experiencing stress. As she progressed in treatment, she was better able to identify depressed and anxious feelings, including being able to clearly describe panic or anxiety attacks, but she still had tremendous difficulty recognizing and acknowledging the multiple somatic symptoms related to her psychological distress.

As her depression subsided and resolved, treatment focused on Kim setting realistic goals for her daily functioning, mastering problem solving and verbal communication of her needs and difficulties, continuing to explore the mind and body connection, and using relaxation techniques when anxious.

Kim has been free from her typical PNES episodes for about 9 months.

Lessons Learned About Neuropsychiatry

Conversion disorder, also called functional neurological symptom disorder, is a somatic symptom disorder described by DSM-5. For a diagnosis of conversion disorder, 4 sets of criteria are necessary: alteration in voluntary motor or sensory function, symptoms not compatible with recognized medical illness, presentation not better explained by alternative conditions, and symptoms cause significant distress [8]. Psychogenic nonepileptic seizures are considered a type of conversion disorder (specifically, "conversion disorder with attacks or seizures").

Although the clinical presentation of PNES events is similar regardless of age, the typical psychosocial risk factors for the disorder are different in youth and adults with. In particular, while PNES in adults is often thought to be associated with a history of sexual abuse, that specific association has not been found in pediatric studies, although generally speaking children and adolescents with PNES report more lifetime adversities than their unaffected siblings [9].

Pediatric PNES is complex and multifactorial, and it requires comprehensive multidisciplinary evaluation and treatment. Psychiatric and neurological symptoms have to be thoroughly considered in the diagnosis and treatment along with psychosocial factors. The dynamic interaction between all these variables plays a

role in the development of PNES. Kim's nonepileptic seizures are best understood as the maladaptive expression of underlying psychological distress from the challenges of normal psychosocial development. Although Kim did not appear to be "an anxious person" and did not experience any traumatic events, she had several other important PNES vulnerability factors. She had a complex early medical history and high sensitivity to bodily sensations (sensory integration problems) as a toddler. Though intellectually gifted, she had ongoing subtle learning problems that at first may have been associated with underlying epilepsy and treatment with divalproex, though later may have been a function of her depression. Kim's high sensitivity to perceived failure, perfectionism, and unspoken worries about living up to the standards of her sisters led her to believe that she was a disappointment to her parents. This conviction may have further impaired her ability to recognize and effectively articulate her negative emotions, distress, and developmental struggles. She developed somatization that, along with her existing experience of having epileptic seizures, may have unconsciously contributed to the manifestation of PNES.

Reflections from Kim, a Patient with PNES

To me conversion disorder really felt like being broken, for two reasons:

One, it took a long time and a lot of therapy before I could trust myself to know what in various circumstances was wrong with me. (…) To start saying to myself I have a migraine, something must be distressing me emotionally or psychologically. What is it? instead of thinking I have a migraine. I have overexerted myself I must be sick, I can't go to school – I have to sleep. …And before I knew I had conversion the uncertainty of everything that was happening to me, wondering constantly if I was just depressed and had migraines and anxiety or if I had a brain tumor that for some reason caused me to be in excruciating pain, and incredibly tired, and nauseous, faint, shake, have panic attacks, hyperventilate, lose control of my limbs and have them "float," vertigo, and recurring violent nightmares that I acted out in my sleep about the torture of my older sister. All this made me feel helpless.

Two, the "symptoms" themselves. If I tried to push or force myself, my body would shut down and physically render me incapable. It was as if some evil part of my not- so- subconscious kept popping up and saying "hey remember who's in charge! I decide everything" I wasn't in control of my own body. I felt broken.

Conversion disorder also confused me and made me feel misunderstood. I became angry with everyone especially my parents. When after complaining or seeking help because of a physical symptom, they would ask and push me to consider the "real problem" or they would tell me to focus on getting over it as my headache, nausea, vertigo, whatever it was wasn't real. Finally, they learned that my symptoms were real. I was actually having a migraine and feeling the pain and everything but the solution was psychological, emotional not physical. However,

even as they adjusted the way they phrased "focus on the real problem" it still felt as though they were telling me what I felt wasn't real. I was faking it. I needed to stop it, just like that. I would feel the need to faint or something. I was addicted to being sick.

Message from the Parent of a Child with PNES

I would say that there were three main things that made caring for a child with PNES particularly hard and stressful.

First, it is not a well-known condition, even in the medical community that falls in a kind of crack between disciplinary specialties. As a result, it took a long time to get a definite diagnosis and even longer to find someone with experience in treating it. For a long time, it felt as if the various doctors we saw (neurologists, psychologists, psychiatrists, our GP, ER doctors) would treat one part of what was going on and then declare some other part out of their specialty. Our daughter has epilepsy as well, and that also complicated the process. As her life slowly unraveled, it often felt like there was no doctor who had the whole picture in view, and so that put more pressure on us to try to not only coordinate care but see what it seemed the various specialists were not seeing. It was a bit like the old tale about the seven blind men and the elephant: one grabs the tail and thinks it is a rope, another the leg and thinks it is a tree, and so forth. We didn't know it was an elephant, but knew it wasn't just a rope or a tree or a rope and a tree.

Also, because it is not a well-known condition, even when we had a diagnosis, we would have to explain it to medical professionals: EMTs and ER doctors, for instance. In the final phases of her illness, our daughter would repeatedly pass out during an episode and occasionally suffer total memory loss (including not knowing who she was). If she did this when out of the house (at school, walking along the street, at the DMV), we would find ourselves trying to convince the EMTs who would arrive when a concerned person called 9-1-1 that, no, we didn't need to go to the hospital, that her being passed out was a routine occurrence and it wasn't a sign of a catastrophic physical problem. When we nevertheless ended up at the ER, we would have to convince the doctors that we didn't need to stay overnight for evaluation, that, OK, if they really felt they needed to run some tests before we left, I guess they could do that, but that, no, the fact that our daughter kept repeatedly passing out was not something for which they could provide medical help.

Of course, and this is the second thing, because the nature of her episodes evolved over time, it wasn't always clear to us that an episode was actually a PNES episode and not, in fact, a purely physical problem, and the trips to the ER were not so routine as all that. The first several times your child faints, you are very glad when the ambulance shows up, and you are happy they will run lots of tests at the hospital. And even the 100th time she faints, part of you worries that, what if this time it isn't just psychogenic? Am I really going to not seek medical help as my child goes into spasms or keeps passing out, and remains unresponsive for 10…20…30…40 minutes? And this is harder when you are in public. I have sat at a baseball game next

to my daughter as she passed out, came to, passed out, came to, and tried to reassure the people sitting around us that there was no cause for alarm: "She does this sometimes. It'll be alright." (Eventually, we called the medics over, and eventually spent the night at the hospital. I have crouched over her as she lay on a sidewalk unresponsive and waved concerned passers-by away telling them it was ok. Someone eventually called an ambulance.) So you stop going out in the world.

But it is also that a lot of the things that happened, the first time they happened, were genuinely terrifying: shaking fits that lasted 30 minutes, sudden piercing headaches and stabs of pain, a sudden a complete shutting off, a fast evolving amnesia that felt like her mind was slowly being erased. And each time this happened for the first time, having wonderful, competent, caring doctors and medical professionals not be able to say, "Oh yes, I know what this is. Here is what we can do about it…" just added despair to the terror. Well, until one finally did say, "I think I know what is going on and I can help."

The third tricky thing is that even when you have a diagnosis and are getting treatment, each physical symptom your child manifests is open for interpretation: does she have a stomach bug or is she somatizing her anxiety? Is she dizzy because she didn't drink enough or because of the math test that didn't go so well? That makes the work of responding to it in the moment much harder and leaves you less certain as a parent that you are doing the right thing. And it leaves you arguing with your sick child about what is going on, and searching for ways to suggest that maybe this is psychogenic while not denying that it is real or important.

I don't see clearly yet through all that has happened. When I pause and try to conjure up the totality of the last few years, I only see a set of paradoxes. The first one has to do with a perception of us, of me: are we now members of this sad club no one ever wants to join, the one that binds together all the poor parents who have gone through a lot, *the worst thing that can happen* (short of losing your kid)? Yes, certainly, but at the same time, no! No, really, it wasn't that bad. Or was it?

Another paradox has to do with the intensity of the experience: that for 2 years, even more, this is all that there was, this is all that we were: on call 24/7, every day managing doctors' appointments and calls to insurers, providers, calls to the pharmacy to change or tweak a prescription yet again? Were we not always both fearing and expecting the daily call from the school nurse or the vice-principal to drop everything and come get our fainted/ panicked/choking/vomiting/shaking and now barely coherent daughter—yet again? Yes, I would say that. After all, that is really what happened. *This is all that we were*. Caregivers. Managers. Worriers. Advocates. Night and day. Day and night. Lots of nights.

I suspect that her having a mental illness—as opposed to something easily isolated to a physical source or symptom, like an illness of vital organs, of cells, of bones—is responsible for my contradictory emotions. The child I love was very sick yet physically unchanged. And, now and again, for a few hours (or sometimes even many), the child was the same as she was "before." We were constantly reminded of what "normal" looks like, feels like. It didn't let itself be completely forgotten. I don't think there will be an "after" when all is forgotten and has completely gone back to "normal."

I fear our child with conversion disorder will never stop needing us. I find this thought hard to digest. It pains me; it freaks me out. I feel I will never be "liberated"

of my parenting duties and worries. Sure, our daughter will eventually want to leave the coop, fly away—she certainly has all the intellectual talents of her two siblings—but she will nevertheless need to remain connected to us. She will need us to remain forever the guardians not so much of her medical records but of her medical story. Part of who she is will forever be encompassed in a narrative that will slowly vanish beyond the reach of her own memory—while continuing to define her, explain this "emotional handicap" her IEP says she has. Because her sickness goes so far back we, the parents, are its memory, the depository of facts needed to describe and understand it. We are the ones she may need to question. Mostly though, we are the ones she knows she can forever count on. Because even though our daughter is on the whole much, much better, I don't think she is cured; I don't think she will ever be cured. At least, that's not what it looks like or feels like to me. I feel that she will forever live on the crack between two tectonic plates. The fact that she is doing well today but wasn't feeling well at all yesterday, for instance, tells me nothing about how things will be tomorrow. Tomorrow, she could continue to "cruise" or she could get worse, maybe even worse than yesterday. Perhaps she will be paralyzed by a panic attack or what she calls a migraine—which is one of the ways her body now shuts down so it can get away from the world for a few hours or for a day, sometimes two. How well or poorly she will sleep on a given night (bad nights often lead to days where she can't function) is still completely unpredictable and determines much of what the following day will be.

I think that no one fully understands how a happy, bright child with a mild seizure disorder became depressed and anxious to the point of completely dissociating for minutes, hours at a time. Neither can anyone explain how, after months of meandering through specialists and ERs, some basic old-fashioned talk therapy, a bit of Zoloft (sertraline), and a knowledgeable and charismatic neuro-psychiatrist were able to prevent the dissociative episodes from happening every day, the anxiety to be manageable, the depression to quiet down. All I know, what I will know forever, is that this difficult health crisis happened here, to us and that I now live with the fear that it could happen again.

I hope I am wrong. I hope there will be a time when I believe we are truly giving our daughter the proverbial last push across the pond. But what her conversion disorder and all its weird manifestations, especially these years of what felt like progress but ultimately wasn't have taught me is to keep my hopes in check. If I have joined any club, it's one for people whose lives are forever a little sadder even after the right diagnosis, the right doctor and the right regimen of treatments and therapies have been found.

References

1. LaFrance WC, Baker GA, Duncan R, Goldstein LH, Reuber M. Minimum requirements for the diagnosis of psychogenic nonepileptic seizures: a staged approach. Epilepsia. 2013;54(11):2005–18.
2. Verrotti A, Agostinelli S, Mohn A, et al. Clinical features of psychogenic non-epileptic seizures in prepubertal and pubertal patients with idiopathic epilepsy. Neurol Sci. 2009;30(4):319–23. https://doi.org/10.1007/s10072-009-0107-x.

3. Reilly C, Menlove L, Fenton V, Das KB. Psychogenic nonepileptic seizures in children: a review. Epilepsia. 2013;54(10):1715–24. https://doi.org/10.1111/epi.12336.
4. Plioplys S, Doss J, Siddarth P, et al. A multisite controlled study of risk factors in pediatric psychogenic nonepileptic seizures. Epilepsia. 2014;55(11):1739–47. https://doi.org/10.1111/epi.12773.
5. Viravan S, Go C, Ochi A, Akiyama T, Carter Snead O, Otsubo H. Jeavons syndrome existing as occipital cortex initiating generalized epilepsy. Epilepsia. 2011;52(7):1273–9.
6. Fournier-Goodnight AS, Gabriel M, Perry MS. Preliminary neurocognitive outcomes in Jeavons syndrome. Epilepsy Behav. 2015;52:260–3.
7. Striano P, Sofia V, Capovilla G, et al. A pilot trial of levetiracetam in eyelid myoclonia with absences (Jeavons syndrome). Epilepsia. 2008;49(3):425–30.
8. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5. 5th ed. Arlington: American Psychiatric Association; 2013. p. 318–9.
9. Doss JL, Plioplys S. Pediatric psychogenic nonepileptic seizures: a concise review. Child Adolesc Psychiatric Clin. 2018;27(1):53–61. https://doi.org/10.1016/j.chc.2017.08.007.

Further Reading

10. Caplan R, Doss J, Plioplys S, Jones JE. Pediatric psychogenic non-epileptic seizures. Cham: Springer; 2017.

Switching Sides: A Case of Sepsis, Seizures, and Shifting Hemispheric Dominance

17

Anupriya Razdan, Cynthia Salorio, Sarah Kelley, and Jay A. Salpekar

Case

Robert is a right-handed 14-year-old male with a complex history of medically intractable focal epilepsy and GI disease as well as unspecified mood and anxiety disorder with impulsivity. He was first seen for neuropsychiatric evaluation at age 11 for assessment of behavior and learning difficulties in the context of complex neuropsychiatric illness.

Robert was the product of an uncomplicated 38-week pregnancy and weighed 4 pounds and 15 ounces at birth. He had a pneumothorax that resolved spontaneously after birth with no intervention and was discharged after 3 days. He achieved his developmental milestones on time. Medical and developmental histories were otherwise unremarkable. Educationally, Robert was always known to be a very bright child and highly capable academically. Testing done through the school at age 4 resulted in Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III) scores of 137 verbal and 116 performance, with 102 processing speed. He played the piano and was active socially.

Robert was in his usual state of health until age 8 when he developed appendicitis and his appendix unexpectedly and rapidly ruptured. He subsequently developed sepsis and was hospitalized for 4 weeks requiring ventilator support. His first seizure was witnessed during that time. Eventually, Robert recovered medically but started having frequent episodes of gagging and vomiting the following year. He

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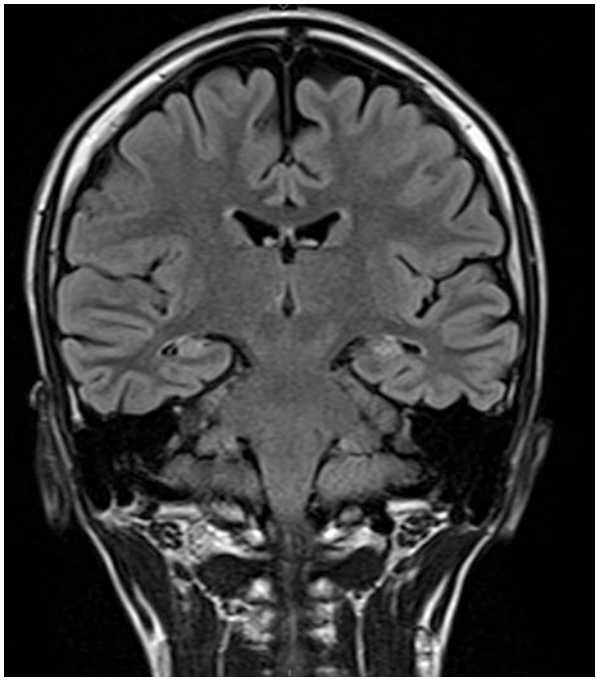

Fig. 17.1 MRI scan showing bilateral hippocampal sclerosis

was diagnosed with eosinophilic esophagitis and, after a difficult early course, slowly improved with treatment.

Gradually developing from that time, Robert started having recurrent seizures. His semiology consisted of behavior arrest and eye and head deviation to the right with occasional tonic activity or loss of muscle tone. His parents also reported that occasionally during these events, he would attempt to climb on top of furniture. He would not usually be successful, but still had the physical drive to do so during the initial phases of the seizure. He would routinely have altered awareness and no memory of the events. An initial electroencephalogram (EEG) showed bilateral spikes with left temporal slowing. Robert was prescribed oxcarbazepine to which he initially responded. However, the seizures continued, and lamotrigine was added and then changed to divalproex sodium a year later. During an initial admission to the epilepsy monitoring unit, Robert's EEG demonstrated left temporal slowing and left anterior temporal sharp waves that evolved into high-voltage rhythmic 4 Hz activity over the left hemisphere with some spread to the right. A follow-up EEG done later that year showed intermittent left temporal sharp waves with focal slowing over bitemporal head regions, left more than right. An MRI showed bilateral hippocampal sclerosis, left worse than right. See MRI images in Fig. 17.1.

Later that year, Robert accidently hit his head on a doorframe, and although he did not lose consciousness, he started having multiple episodes of vomiting along with headaches, dizziness, and weakness in his legs, affecting his mobility. Robert was hospitalized again on the epilepsy monitoring unit to evaluate periods of being unable to ambulate and episodes of becoming unresponsive for 30 s to 1 min. These episodes were accompanied by periods of intermittent crying, eye rolling, and falling backward, with return to baseline in between the episodes. Extensive workup

did not find a clear physiologic cause for these episodes. The EEG did not show an epileptiform correlated with the clinical events. Psychiatry consultants diagnosed Robert with unspecified anxiety and depression.

Clinical Pearl 1
Many clinicians react with frustration to non-epileptic events; however, in many cases, including for Robert, he also had epilepsy. Clinicians still need to have a high index of suspicion for true electrical seizures, even when EEG monitoring proves to be negative. In this circumstance, the identification of anxiety and mood issues were important and required clinical attention in addition to the persisting epilepsy.

Over the following year, Robert became increasingly anxious, at times with panic. He reacted impulsively and when frustrated or in an argument would attempt to run out of the room or even the house. Although he was more medically stable and was able to return to school, he experienced increasing anxiety relating to the return. A decline in his academic performance was noted with his teachers noticing difficulties with sustained attention, organization, and difficulty completing homework. This was initially attributed to his missing a considerable amount of school due to medical reasons. However, later it became clear that language processing abilities were markedly impaired. He also had unsuitable social behaviors, making odd noises or facial grimaces in social situations, presumably as attempts to engage on some level with peers. Despite efforts to redirect, he was seemingly unable to modulate this behavior.

Cognitive Sequelae

Robert's academic difficulty was a puzzle, given that his premorbid function was exceptional. It was common for him to forget entire events and have difficulty planning ahead, organizing his thoughts and activities, and sequencing events. Memory was particularly problematic. After a period of weeks, he would have no recollection of significant events such as visits with relatives or family vacations. He reportedly zoned out when not engaged in a task, yet also resisted being told what to do or how to do things (e.g., showing his work on math problems). He had particular difficulty with writing his thoughts on paper, sometimes being unable to write a single word for an hour.

Psychological testing done at age 12 showed an overall intellectual functioning still in the superior range (WASI-II = 122), with a relative strength in vocabulary skills when compared to nonverbal reasoning skills. These scores were almost identical to previous testing done a year earlier, suggesting stability (and appropriate development) of skills over the past year. Additionally, Robert performed within age expectations for motor sequencing tasks, complex receptive language, cognitive flexibility, and academic fluency.

However, Robert demonstrated slowed processing speed and weaknesses in visual selective attention as well as for sustained and divided attention. His ability to learn and recall verbal contextual material was intact, while his ability to recall

non-contextual verbal information was significantly weaker, and he did not appear to benefit from information presented in a recognition format. For visual memory, his ability to immediately recall designs was in the low average range. An apparent conundrum was present in that he tested well in terms of intellectual ability, but his performance in a school setting was still markedly impaired.

At the same time, Robert had many successful pursuits. He was particularly skilled musically, with an uncanny ability to learn new music on the piano, and had a good sense of rhythm. He also developed new physical interests. Prior to his sepsis episode, he was not particularly physically active, but afterward he had a voracious inner drive to climb trees which he did whenever possible. He also had marked interest in fine motor activities. He had an ability to construct origami figures, creating complex three-dimensional figures with great skill. Sometimes in the waiting room, he would lead groups of kids in constructing origami, teaching them how to make simple designs.

Treatment Course

At 12.5 years old, and over the subsequent few months, his seizure control improved moderately but gradually his mood worsened. He started becoming increasingly irritable and overwhelmed at school and home even in the face of relatively minor frustrations. He reported having dissociative phenomena, feeling that he was losing track of time, and he was increasingly frustrated with interpersonal relationships. Of note, his intellectual ability appeared to remain in the well above average range, but his processing speed and efficiency, especially for verbal information, continued to be markedly impaired. Although he still performed adequately in accelerated math classes, a modified curriculum with flexibility in completing writing assignments in English or Social Studies was begun.

Robert received a speech and language evaluation for continuing problems with word finding and difficulties with verbal formulation of thoughts. He was observed to have a halting rhythm to his speech that was difficult for others to follow and frustrating for him in trying to be understood. Part of his educational accommodations included telling instructors to be very patient, while Robert formulated verbal responses. Sometimes it would take up to 30 seconds of waiting for Robert to come up with a verbal response, but that process would be necessary to allow a full response to occur.

Illustrative of Robert's unusual speech patterns is that he commonly would speak in puns and rhymes that were nonsensical at times but eloquent in terms of plays on words or ironic meaning. He delighted in such word play, sometimes engaging in that type of discourse to the exclusion of other verbal output. In response to a phrase such as "That's a good point," he would say, "but the point is blunt," in a manner alternatively playful or sullen, depending upon his mood. He would sometimes respond with rhymes, not in a clanging manner, but in terms of associating sounds that were alliterative, even poetic.

Aggressive treatment with medications proceeded over the next year to address impulsivity, mood lability, as well as seizures that were quiescent for a period of time but then reemerged on a weekly basis. Another inpatient epilepsy monitoring unit evaluation revealed bilateral temporal ictal onset zones, eliminating resective surgery as a possible treatment option. At that time, divalproex sodium was replaced with levetiracetam to try and improve seizure control.

Robert was consistently frustrated with his functionality but in the next months had additional affective symptoms that emerged. Because of his ongoing affective symptoms, he was started on citalopram, but it was stopped within 2 weeks because of apparent activation. Robert gradually experienced increasing dysphoria, mood lability, feelings of guilt, and hopelessness relating to his past medical experience, and his current quality of life. Eventually he was hospitalized for worsening of mood and suicidal ideations. During this time, Robert was started on sertraline for anxiety and depression and transitioned from levetiracetam to clobazam for seizure control. He gradually stabilized but only briefly and continued having very strong depressive symptoms that were very difficult to redirect even with intensive psychotherapy. Over the next 6 months, he had three additional psychiatric hospitalizations for ongoing mood symptoms and suicidal ideations.

Ultimately, clobazam was discontinued and divalproex was restarted for mood stabilization and seizure control. Lacosamide was also added with reasonable response. His mood and anxiety improved with increasing doses of sertraline, and impulsivity and inattention also improved with guanfacine. Over the next year, from ages 13 to 14, Robert continued to take this medication regimen though still had seizures every 1–2 weeks. He tried the modified Atkins diet (MAD) and cannabidiol oil (CBD) for treatment of his seizures. MAD was partially effective in improving his seizure frequency but ultimately led to stress due to food restriction. Relapses were common whenever carbohydrates were accidentally or even purposefully consumed. CBD has led to some improvement in seizure control, though only moderately at best.

At age 14, Robert switched to a different academic setting that was more flexible in terms of tailoring educational strategies to his abilities. He improved overall but continued to have intermittent anxiety in the context of schoolwork. He stopped doing origami but instead became very active with crochet. He was successful in crocheting handbags and scarfs with different patterns and weights of yarn. He even started a website to display his products and sold some on occasion. He was frequently observed to be carrying a bag of yarn and to be engaged in crochet at various points through the day.

Over the past year, Robert's medical course has stabilized, with baseline seizure frequency of 2–3 per month. His neuropsychiatric course has markedly improved. His mood has stabilized with current anticonvulsants and adjunct medications. Occasional mood relapses are very responsive to slight increases in sertraline dosages. He continues to improve in terms of being socially related, though is still somewhat impulsive in social settings. His rhyming or pressure to speak in puns has been less prominent and his efficiency and ability to express himself has markedly improved.

Clinical Pearl 2
Robert had significantly negative mood reactions following treatment with levetiracetam and with clobazam. Although irritability and depression have been observed with levetiracetam, specific risks of vulnerability are not well elucidated. In some cases, levetiracetam may improve mood. Vitamin B6 supplementation may mitigate mood effects in some cases, but this was not helpful for Robert. Clobazam has been effectively used for anxiety control but also seemed to be associated with depressed mood. Although many anticonvulsants may improve mood, it is equally important to consider potential adverse mood effects [1, 2].

Diagnostic Considerations

Robert's neuropsychiatric condition has proven to be exceedingly complex. At its basis, the illness represents a true blend between epilepsy and associated mood disorder. His mood symptoms were mostly characterized by dysphoria and ideations of self-harm but also included intrusive thoughts and impulsivity. His sleep and appetite were irregular, but it was very difficult to isolate these symptoms from the timing of seizure episodes. Still, the depressive symptoms were very strong and may have been amplified by adverse reactions to some anticonvulsants. Yet the symptoms were also very responsive to even small sertraline dosage increases.

Robert has marked bilateral hippocampal sclerosis, and it is known that the mesial temporal lobes are closely involved with pathophysiology of depression [3, 4]. A neurologic pathway that involves caudate nucleus, amygdala, and cortical regions may be involved in at least the perpetuation of depressive symptoms [5–7]. For Robert, having significant pathology in this circuit would correlate with known neurologic bases for depression. It may also be no surprise that given the refractory nature of his seizures, the associated ongoing pathologic processes in this part of the brain could yield recurring depressive symptoms as well.

Despite this marked pathology, Robert has managed to improve in terms of cognitive development, even while his seizure control has not improved beyond his baseline frequency of approximately every 2 weeks. This fact suggests that at least some improvement in his neurologic status has occurred. An additional evaluation that included language mapping via functional MRI studies is enlightening. The result of this study was that he was deemed to be right hemisphere dominant for language. This fact would be very unusual given his history of being strongly right handed, and also being particularly skilled with mathematical analytics, even in the throes of his most impaired cognitive state.

The shift in hemispheric dominance may explain a great deal in Robert's progress to recovery. Robert gravitated toward creative pursuits where he had not done so to the same extent in the past. Although hemispheric shift is not unique, the course of improvement in cognition has been dramatic and may reflect additional

connectivity that developed. Robert benefitted from a combination of medicines that addressed seizure control as well as depression and impulse control. He has been responsive to medication adjustments, but it must be considered that brain growth and maturity have also played a large role. We expect that he will continue to improve, though the course of development is long and impulse control may continue to be challenging given his neuropsychiatric illness. Still, the past is a strong predictor, and we consider that past success for tells a brighter future for Robert.

Lessons from Robert About Neuropsychiatry

Despite the marked cognitive challenges, and medically intractable seizure disorder, Robert has made amazing gains in his academic function and ability to sustain attention and process information logically. He has improved his ability to formulate thoughts and is now much more efficient in terms of communication. While these areas have improved, he still has difficulties with mood regulation, dysphoria, and anxiety that can be overwhelming.

The persisting depression reflects the powerful role that mesial temporal lobe pathology has upon mood, especially with a left-sided focus. It is reasonable to wonder how his symptom profile may have differed if his hemispheric pathology was reversed; that is, if he was originally right dominant and then became left dominant or if his hippocampal sclerosis pattern was reversed. Seizure foci in the temporal lobes are gradually becoming recognized as marked risk factors for depression comorbidity [6]. Robert's very powerful symptoms of dysphoria and hopelessness strongly reinforce the role of temporal lobe neurologic instability in depression, possibly magnified by the additional presence of seizure foci in this region.

Robert has improved in terms of verbal expression, but his relative strength now seems to be in nonverbal abilities. It could be understood that the switch of hemispheric dominance has changed how he perceives information and has also changed his cognitive strengths in many ways. Early in his recovery, he gravitated toward speaking in puns and rhymes. These may be inherently "right-brained" ways of speaking, less concrete and sequential and, instead, more impressionistic or artistic. While such notions may be oversimplifications, Robert's unique patterns of verbal discourse cannot be ignored. That prosodic word play came so easily to him, while sequential logical patterns of discourse as required for writing or oral presentations were so difficult, affirmed the apparent shift in hemispheric dominance for language.

In addition to the language processing issues representing a hemispheric shift, the fact that Robert so strongly gravitated toward crochet may not be an accident. He was able to combine his interests in crochet with mathematical concepts as well. One of his crochet creations was a hyperbolic plane, shown in Fig. 17.2. Hyperbolic planes are surfaces with negative curvature throughout, and while they cannot be represented by mathematical equations, they can be constructed and visualized using crochet. Robert discovered some geometric insight while engaged in the craft

Fig. 17.2 Robert's crochet of a hyperbolic plane

and was able to identify the relationship between crochet stitches in successive rows that could lead to a negative curvature in the developed surface.

While speculative, he may have been driven to engage in this craft in order to "activate" neurons that needed to connect or repair in some way. Such phenomenology would not be unprecedented. This interest developed when Robert was a young adolescent, an age where lots of brain growth is happening. Typically developing children will seek activities that are consistent with principles of experience-dependent development, that is, brain growth will occur if specialized neurons are readily engaged [8]. For example, infants are fascinated with mobiles or other moving objects because they are driven to develop visual networks involved in tracking objects. Young children will favor repetitive songs or stories in order to gain a sense of sequence or cause and effect.

Much brain development may be underpinned by critical periods of brain growth that occur for sensory development, best characterized in the visual or auditory system [9]. If appropriate visual stimulation does not occur within a critical window of development, then the underlying neural networks may not develop at all, even if the stimulus occurs later. It may be intuitive to consider that complex human functions such as emotional control, impulse control, mood regulation, and communication may also have sensitive or critical periods of development [10]. Social function depends in large part upon interhemispheric connections, which are particularly well developed in humans.

In that way, Robert's interest in crochet may have been a way to build connections, not necessarily for social purposes, but to fine-tune the white matter apparatus involved in possibly peripherally related cognitive processes [11]. Just as motor development often precedes cognitive development in infants, a dual process of motor and cognitive development may require a framework to process others sorts of information. Robert's seemingly spontaneous drive to pursue activities to improve his motor and visual spatial skills may in some way have concurrently improved his verbal skills and efficiency of thought processing.

Reflections from Robert's Family

Surviving sepsis and its many complications at age 8 was a life-changing event for the whole family. There were some dark days in the intensive care unit when he was on the ventilator and receiving intensive supportive care; there were at least a few days when we thought that he was not coming back home.

Over the next several years, continued seizures, GI issues, ongoing anxiety, compromised memory, and difficulties with school and socialization have cast a long shadow that we live under daily, but we habitually contrast our challenges today with the memories of the darker moments and challenges already overcome. Then the daily struggles and challenges of life seem smaller in comparison and more manageable.

Coping with seizures and anxiety, achieving stability in behavior, and improving learning and socialization are all ongoing challenges for Robert and by extension for the family. Some days are draining on us as a whole. But our ability to recover from difficult days and renew our efforts has improved over the years. Robert's younger brother has also shown high maturity and empathy from a young age in supporting his brother.

Robert has shown strong determination and works hard to counter the frustrations and despair he experiences. At times, his memory problems prevent him from internalizing his successes that would ordinarily improve his own self-esteem. Repetition is needed to shore up positive reinforcement and learning.

The entire experience has rearranged our mental furniture significantly. We succeed when we focus on immediate concrete steps and actions that can be taken to improve the situation in the moment. Allowing anxieties about future prospects or frustrations of the past to occupy one's attention in the moment degrades the quality of attention that we can give to issues of the present. When we remember this and act accordingly, we cope well; when we forget this, we suffer.

Overall, we know that our son has many gifts and strengths that help him compensate and work around his challenges. He is highly intelligent, has a good sense of humor, loves nature and animals, and enjoys learning and tinkering with mechanical gadgets and science experiments. He has immense potential even as he faces significant challenges. We are hopeful that he will find his own unique path to lead a happy and productive life.

References

1. Salpekar JA, Mishra G, Hauptman AJ. Key issues in addressing the comorbidity of depression and pediatric epilepsy. Epilepsy Behav. 2015;46:12–8.
2. Salpekar J. Mood disorders in epilepsy. Focus. 2016;14:465–72.
3. Hecimovic H, Goldstein JD, Sheline YI, Gilliam FG. Mechanisms of depression in epilepsy from a clinical perspective. Epilepsy Behav. 2003;4(Suppl 3):S25–30.
4. Drevets WC. Neuroimaging abnormalities in the amygdala in mood disorders. Ann N Y Acad Sci. 2003;985:420–44.
5. Hastings RS, Parsey RV, Oquendo MA, Arango V, Mann JJ. Volumetric analysis of the prefrontal cortex, amygdala, and hippocampus in major depression. Neuropsychopharmacology. 2004;29:952–9.

6. Valente KD, Busatto Filho G. Depression and temporal lobe epilepsy represent an epiphenomenon sharing similar neural networks: clinical and brain structural evidences. Arq Neuropsiquiatr. 2013;71:183–90.
7. Richardson EJ, Griffith HR, Martin RC, Paige AL, Stewart CC, Jones J, Hermann BP, Seidenberg M. Structural and functional neuroimaging correlates of depression in temporal lobe epilepsy. Epilepsy Behav. 2007;10:242–9.
8. Gunnar MR, Fisher PA. Bringing basic research on early experience and stress neurobiology to bear on preventive interventions for neglected and maltreated children. Dev Psychopathol. 2006;18:651–77.
9. Rice D, Barone S Jr. Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. Environ Health Perspect. 2000;108(Suppl 3):511–33.
10. Ismail FY, Fatemi A, Johnston MV. Cerebral plasticity: windows of opportunity in the developing brain. Eur J Paediatr Neurol. 2017;21:23–48.
11. Marsh R, Gerber AJ, Peterson BS. Neuroimaging studies of normal brain development and their relevance for understanding childhood neuropsychiatric disorders. J Am Acad Child Adolesc Psychiatry. 2008;47:1233–51.

18 Epilepsy and Behavior: Response to an Integrative Treatment Paradigm Highlighting Complementary and Alternative Medicine

V. Misra, V. G. Srivatsa, and E. S. Krishnamoorthy

Case

Mahesh an 18-year-old male, first presented at age 15, with persistent childhood onset seizures from the age of 11 months. He had persistent electrophysiological abnormalities, even in the absence of clinical seizures for varying periods of time. A slow learner, he had significant social and pervasive anxiety having faced adverse childhood experiences in the form of bullying in school, with poor scholastic performance and residual speech difficulties.

Like many patients with chronic disease in India, Mahesh had consulted multiple specialists in the period before his initial presentation, and there had been no obvious continuity of care except in one instance. The history detailed below was gleaned from the available medical reports, prescription records, and from the parent reports.

Mahesh was born at full term, with uncomplicated delivery, the second of two children born to non-consanguineous parents, the sibling being typically developing, with no relevant neuropsychiatric history in either parental dyad. He achieved normal developmental milestones until the age of 11 months. At the age of 11 months, acute onset of repetitive jerky movements of the limbs with head nodding (diagnosed as infantile spasms) were evident, which on electrophysiological studies revealed a modified hypsarrhythmia pattern showing right frontal lobe seizure onset with secondary generalization. MRI of the brain was unremarkable. He displayed symptoms consistent with infantile spasms, also called West syndrome, which are characterized by the triad of infantile spasms, intellectual disability, and hypsarrhythmia on electroencephalogram (EEG).

From that time, Mahesh has been evaluated and treated by a range of neurologists and epileptologists across institutions. His progress in clinical evaluation and

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care is detailed in Table 18.1. He has never really become seizure-free for any significant length of time except for one phase at age 12.

Mahesh has had unusual responses to several antiepileptic drugs (AEDs) that have been attempted over time. His seizure frequency improves transiently when a drug is introduced only to relapse soon afterward. Any dose escalation on the assumption of an impending relapse only results in seizure worsening. Throughout his treatment history, positive responses occurred only within narrow therapeutic windows, with presumed tolerance developing at lower doses and paradoxical increase in seizure events with higher doses. This response has been noted with sodium valproate, ACTH, levetiracetam, clobazam, and vigabatrin, among others. He has also experienced adverse reactions to other psychotropic drugs like methylphenidate.

By the time he presented at age 15, Mahesh had a number of other associated problems – cognitive, behavioral, and psychosocial – that impeded his normal functioning. Falling grades, school refusal, depression, and social anxiety with phobic avoidance were all part of his clinical profile. Indeed the level of functional impairment he suffered from was way markedly in excess of that explained attributable to his seizure severity or neurodevelopmental disability.

Table 18.1 The longitudinal disease course and treatment summary

Year (Age)	Clinical events	Investigation results	Drugs used	Response
0–1	Infantile spasms presenting with head nodding and myoclonic jerks	Modified hypsarrhythmia showing right frontal lobe seizure onset	Sodium valproate	Initial improvement not sustained
		Normal MRI No hematologic or biochemical abnormalities of note	ACTH	Improved but with prolonged use developed hypertension, hence withdrawn
1	As above	NA	Clobazam	Significant reduction in clinical events
2	As above/ delay in speech initiation	Persistent EEG changes	Reintroduction of sodium valproate that had been stopped; increase in clobazam	Seizure freedom was probable
2–4	As above/ started speaking/ hyperactivity noted	Persistent EEG changes	Sodium valproate continued; problems with higher dose noted and maintained at 500 mg/day	Significant drowsiness resulting in reduction of both medication doses
			Vigabatrin 500 mg and methylphenidate 5 mg twice daily introduced	

Table 18.1 (continued)

Year (Age)	Clinical events	Investigation results	Drugs used	Response
5–9	As above/ attained other milestones/ slow learner with speech difficulties	Persistent EEG changes	Treated with biotin 10 mg	Increase of clobazam dosage with subsequent tapering due to inadequate response
		MRI reported to show flattened hippocampi with reduction in volume	Clobazam increased to 20 mg and tapered to 7.5 mg	
		Normal tandem MS C50II at 0.63, a high normal biotinidase activity at 3, and he was screen negative for urinary organic compounds	Sodium valproate and clobazam tapered and stopped; levetiracetam introduced	Change to levetiracetam due to inadequate response to both valproate and clobazam
9–11	As above/one episode of shivering in both lower limbs reported	EEG and MRI done with identical results as reported above	Levetiracetam dose optimized	No significant interval changes noted
12	Generalized involuntary movements without LOC reported	EEG as above	Levetiracetam increased and pyridoxine added	Events settled with this treatment
13	Change in the character of events reported; absence-like episodes supervened. Head nodding episodes continued	Head up tilt test conducted/positive for vasopressor syncope	Lamotrigine 50 mg/day introduced/ levetiracetam 1 g per day continued	Minor events continued
14–15	Recurrence of absence-like episodes; very poor academic and social functioning with inability to progress in school	Persistent EEG changes	Sodium valproate restarted and replaced levetiracetam	Reduction in absence-like episodes
		Diagnosed also to have learning disability, social anxiety, and impaired social cognition	Lamotrigine introduced and dosage built-up	
			Clobazam reintroduced	
		Also identified to have a neurodevelopmental disability profile, clumsy, poor fine motor coordination, poor handwriting	Citalopram	
			Zonisamide trial/ not well tolerated with seizure worsening when dose of 100 mg per day achieved	

(continued)

Table 18.1 (continued)

Year (Age)	Clinical events	Investigation results	Drugs used	Response
18	Gradual reduction in absence-like episodes; when they occur they are fleeting	Pharmacogenetic studies discussed separately	Sodium valproate Lamotrigine Phenobarbitone	Seizure events are fleeting and well tolerated by patient and family
	Occasional head nodding noted in association with the spells	EEG findings as above	Clonazepam	
	Reduction in anxiety, improved mood, improved social functioning, improved academic performance	Evaluated for a range of metabolic conditions including Wilson's disease, NMDAR antibody syndrome, metabolic syndromes	Citalopram	
	Significant academic and social milestones achieved		Multivitamins and multimineral supplements An integrated care and rehabilitation approach using a range of non-pharmacological therapies described in detail herein	Cognitive, behavioral, and psychosocial functioning has improved considerably; more coordinated, able to play sports, improved handwriting and fine motor coordination; near normal for a late adolescent in his age group

Disease Course

Diagnostic Impression

Mahesh was evaluated and treated by our multidisciplinary team: neuropsychiatrist, neuropsychologist, counseling psychologist, physical and neurodevelopmental therapists, CAM (complementary and alternative medicine) physicians with Ayurveda/naturopathy, and yoga specialization among others. Details of his evaluation are summarized in Table 18.2.

Table 18.2 Details of multidisciplinary evaluation and treatment approach

Department	Tests performed at intake	Key findings	Treatments offered	Response
Neuropsychiatry	Clinical evaluation using a standard protocol	Intractable seizures (2 variants – infantile spasms/salaam seizures and absence-like spells) Unusual AED response Abnormal EEG Cognitive, behavioral and psychosocial aspects	Drug optimization	Reduction in seizure frequency
				Reduction in disability due to seizures
			Integrated care and rehabilitation program under the neuropsychiatrist's supervision	Improved cognitive, behavioral, and psychosocial functioning
Psychologists (neuropsychologist and counseling psychologist)	Detailed psychological interview	Intellectual impairment (IQ = 61) Learning disability Internalizing syndrome with significant social anxiety Skill deficits Fluctuating attention and vigilance Reduced ability of abstraction Poor frustration tolerance Difficulty in social interaction/peer relationships Behavioral issues Poor eye contact and increased social anxiety Avoidance of activities that demand sustained attention through overt resistance, using repetitive phrases to divert attention, manipulative behaviors Low motivation/poor ADL adherence Poor understanding of social norms	Cognitive enhancement training	Improved cognitive functioning with a number of skills including computer usage
	Wechsler Intelligence Scale for Children (WISC)		Enrollment in an inclusive school	Academic progress is slated to complete secondary school
	Child Behavior Checklist (CBCL)		Systematic desensitization	Improved social functioning with better peer relationships
			Token economy systems	Improved communication (with confidence and affirmation)
			Skills of independent functioning	

(continued)

Table 18.2 (continued)

Department	Tests performed at intake	Key findings	Treatments offered	Response
Physical and neurodevelopmental therapists	Standard neurodevelopmental evaluation as per protocol; includes the Gesell Developmental Schedules	Clumsy child with mildly uncoordinated gait and balance Fine motor disability with poor prehensile grip and handwriting Diminished activity levels and low motivation for physical activity	Neurodevelopmental therapy including training for fine motor functions including handwriting	Improved coordination
				Improved handwriting with ability to complete academic tasks in time
				Improved activity levels
CAM Physicians	Standard Ayurveda assessment	Memory and attention deficits	Shiroabhyangam	Health and activity, sleep, appetite, and digestion have all improved
			Shirodhara	
	Standard naturopathy assessment	Chakra diagnosis highlighted unstable chakras related to sleep, GI tract, and mental activity	Yoga, acupressure, reflexology, mud therapy	Improved ADL and improved quality of life ratings

The clinical syndrome is typical of early neurodevelopmental disorder. The initial presentation was diagnosed as "infantile spasms" with head nodding and myoclonic jerks being core features. On occasion, these presented rather more vigorously as "salaam seizures," essentially a variant in the semiology of infantile spasms involving intense flexor spasms. As Mahesh progressed to early adolescence, staring spells or absence-like episodes were also observed. Thus, while all events could be representative of primary generalized epilepsy, the absence-like staring spells are variable and could in some way actually represent partial onset seizures [1]. The early EEG pattern identified was modified hypsarrhythmia with right frontal seizure onset. The generalized abnormalities in the EEG have continued to manifest; however, frontal localization of epileptiform dysfunction has not been reported since early childhood. Flattening of the hippocampi bilaterally has been reported in serial MRIs done later, but no other abnormalities have been noted. In addition, he has tested negative for a complete range of biochemical and metabolic markers over time.

The cognitive, behavioral, and psychosocial profile is also in keeping with early neurodevelopmental disability, with associated intellectual impairment, learning issues, mood and anxiety features, social cognition difficulties, social anxiety, and avoidance all being well documented in this population [2, 3].

As Mahesh developed tolerance toward most of the antiepileptic drugs, the clinical team opted for the pharmacogenetics testing. Pharmacogenomics findings suggest that Mahesh is a poor metabolizer of benzodiazepines and extensive metabolizer of the majority of drug classes evident by his variability in HLA-B, which can lead to the development of carbamazepine-induced Stevens-Johnson syndrome.

Clinical Pearl: Pharmacogenetics

Genetic variation contributes to the higher interindividual response to antiepileptic drugs. However, most genetic biomarkers identified so far have limited sensitivity, specificity, and clinical applications [4]. Metabolism of many antiepileptic drugs is mediated by the cytochrome P450 (CYP) family; some of the CYPs have allelic variants that may affect serum AED concentrations [5]. So far, the testing has gained significant success in predicating the response to carbamazepine. The presence of the HLA-B*1502 [6] and HLA-A*3101 [7] alleles has been associated with carbamazepine-induced hypersensitivity reactions, Stevens-Johnson syndrome, and toxic epidermal necrolysis (SJS-TEN). Currently, "precision medicine" focuses upon the identification of candidate genes to discover more target sites allowing personalized therapeutic choices.

Treatment Strategies

Given the lack of efficacy with prior modalities, a cross-disciplinary, integrated approach has been the focus of Mahesh's treatment since his initial neuropsychiatric evaluation at age 15. Since that time, he has been undergoing an integrative medical

therapy-based rehabilitation program at a cross-disciplinary, multimodal neuropsychiatric treatment center. The treatment is led by Mahesh's psychologist and integrates a variety of physical, speech, and occupational therapies along with a range of complementary and alternative medicine (CAM) treatment modalities: Ayurveda, naturopathy, yoga, and nutrition.

Psychological Interventions

Mahesh's psychotherapeutic treatment has included a range of interventions. His overall psychological interventions have been delivered in three phases as shown below in Fig. 18.1. Currently, repeated stimulus is being provided to Mahesh toward the goal directed activity and supportive psychotherapy for the parents toward future perspectives.

Mahesh has also been treated with cognitive enhancement therapy (CET). CET uses a combination of computer-based exercises and group therapy to function both as a cognitive habilitation program and development of social and other skills. Group exercises help to improve problem-solving skills and the ability to relate to other people, while computer-based cognitive training modules are designed to improve core cognitive functioning in areas of attention, memory, problem-solving, visuospatial tasks, and social cognition (e.g., being able to take others' perspectives, cognitive flexibility, getting the gist) [8]. Since CET is an integrated treatment approach, each component is intended to complement the other treatment modalities.

Mahesh underwent a comprehensive cognitive enhancement therapy plan that integrated 60 h of computer-based training targeted at improving attention, memory, and problem-solving with 45 structured social-cognitive group sessions designed to improve abilities, such as perspective taking, social context appraisal, and emotion regulation abilities.

Fig. 18.1 Psychological intervention chart of Mahesh. *In Progress

A range of CAMS interventions have been included in Mahesh's treatment protocol. These include involvement in yoga and Ayurveda-based therapies. Other treatments such as reflexology, massage, acupressure, and mud therapy have been included. These have provided substantial benefit to Mahesh in terms of stress management and relaxation and have been instrumental in improvement of his mood and overall functioning. They have also been augmentative of his physical and occupational therapy protocols, providing added benefit.

Mahesh has had an excellent response to the integrated care and rehabilitation approach. Even though the improvement in his seizure control has been marginal and fluctuant, he has improved across domains from a functional viewpoint. Cognition and learning have improved and with it his academic performance. He is now on the verge of completing his school final exam. From an emotional and behavioral perspective, he is no longer depressed or anxious; he has overcome his social anxiety and phobic avoidance, made friends in school, and even had a girlfriend for a period of time. From a motoric perspective, fine motor disability has improved significantly, and he is better coordinated, less clumsy, and able to engage in gym and sports activities. As Mahesh developed a liking toward baking, vocational training in home science was included in his rehabilitation regime with extracurricular activities such as plays and expression classes.

CAMS Interventions

Ayurveda

According to Ayurveda, an imbalance of the Vata dosha, one of the three bodily humors, accounts for several neurological and psychiatric disorders. Psychiatric disorders fall under the Ayurvedic classification of Unmada. The very definition of Unmada incorporates a cluster of inappropriate actions exhibited by the individual as a result of distortion of the normal mind, intellect, conscious knowledge, memory, desire, manner, and behavior. The Ayurvedic treatment chosen for Mahesh is *Shiro Abhyanga* (Ayurvedic head massage with medicated oil focused on the shoulders, neck, face, and head, the areas most vulnerable to stress and tension) and *Shirodhara* (medicated oil is poured in streams over the forehead of the patient). Figure 18.2 depicts *Shirodhara*.

Yoga

Yoga has the ability to enhance mental tranquility, as well as improve energy levels, body balance, and coordination. As a branch of the Ayurvedic system of medicine, it is believed to have therapeutic value in correcting imbalance of the bodily humors that may result in mental illness. The positive effect of yoga as therapy may stem from improved attention span and focus, body awareness, and self-regulation. Adopting specific postures (asanas) is at the core of yoga therapy. Major reflex areas chosen for Mahesh were those, thought to the following specific asanas: *savasana*

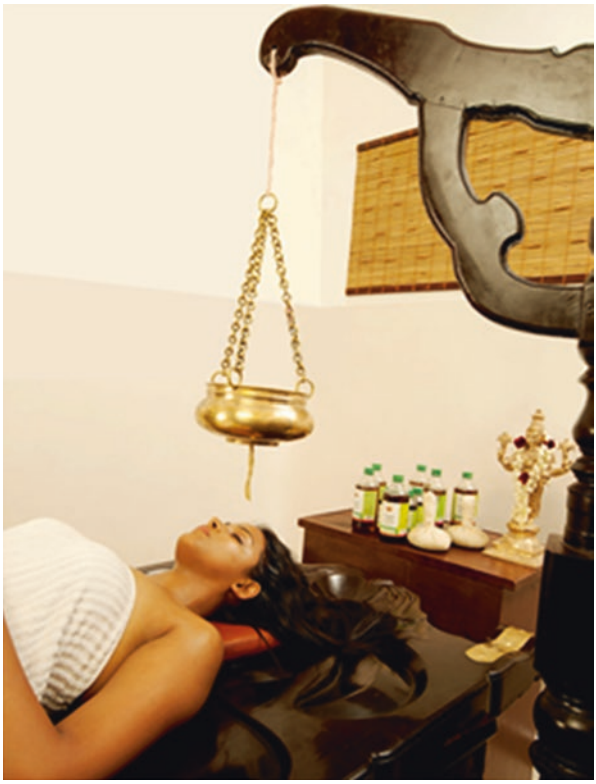

Fig. 18.2 Shirodhara

Fig. 18.3 Savasana

(the corpse pose, total body relaxation lying on the back) (Fig. 18.3), *adho mukha svanasana* (standing, with downward-facing dog stretch) (Fig. 18.4), *adho mukha swastikasana* (seated cross-legged with head bent forward and resting on folded arms on a low stool) (Fig. 18.5), and *suryanamaskar* (Fig. 18.6).

Reflexology

Reflexology is a noninvasive, complementary practice involving thumb and finger techniques to apply alternating pressure to reflexes shown on reflex maps of the

Fig. 18.4 Adho mukha svanasana

Fig. 18.5 Adho mukha swastikasana

body located on the feet, hands, and outer ears, corresponding to organs and systems of the body. The major benefits of reflexology are considered to be its ability to stimulate nerve function, increase energy levels, improve circulation, enhance joint mobility, boost immune responses, and induce a deep state of relaxation.

Fig. 18.6 Suryanamaskar

Major reflex areas chosen for Mahesh were those thought to correspond with the health of the spine, brain, thyroid, pituitary, solar plexus, liver, and kidney. The commonly used reflexology points are in Fig. 18.7.

Acupressure

The role of acupressure has been documented in traditional Chinese medicine for more than 2000 years for treatment of pain and other illnesses. Acupressure is performed by applying pressure to specific points of the body known as acupressure points which is thought to manipulate the flow of chi (qi) energy at the body locations where chi may have become congested or completely blocked. Acupressure to the scalp area especially over what is known as the governing meridian points is considered to help boost language skills in children with neurodevelopmental disorders. Figure 18.8 depicts the governing meridian points.

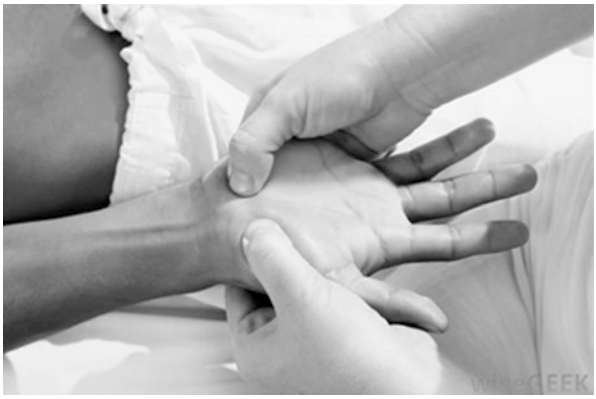

Fig. 18.7 Reflexology

Mud Therapy

A naturopathy treatment modality, mud therapy, may be employed as mud pack to the abdomen (Fig. 18.9). Mud is considered to have beneficial effect of cooling and relaxing the body.

Case Reflections

Mahesh's case reminds us about many core features of the management of epilepsy in the context of complex neurodevelopmental disorders. Seizure semiology is important in epilepsy care and more than one seizure type can predominate in an individual. Even more important is that the same seizure type may have variable manifestations. Beyond seizures, the cognitive, behavioral, and psychosocial sequelae can be independently disabling and can not only worsen the seizure disorder itself but can markedly worsen global function. Thus, identifying and tackling these comorbidities are critical to ensuring betterment and good clinical outcomes for the sufferer.

Lessons Learned About Neuropsychiatry

Neuropsychiatry in clinical practice is "multidisciplinary." The neuropsychiatrist works closely with a range of allied healthcare professionals – clinical psychologists, social workers, nurses, physical and occupational therapists, and other medical specialists, especially neurologists, neurosurgeons, neuroradiologists, neurophysiologists, and neuropharmacologists.

Multidisciplinary models need not be limited by conventional "predominantly Western" concepts. The case of Mahesh teaches us that there clearly is a role for

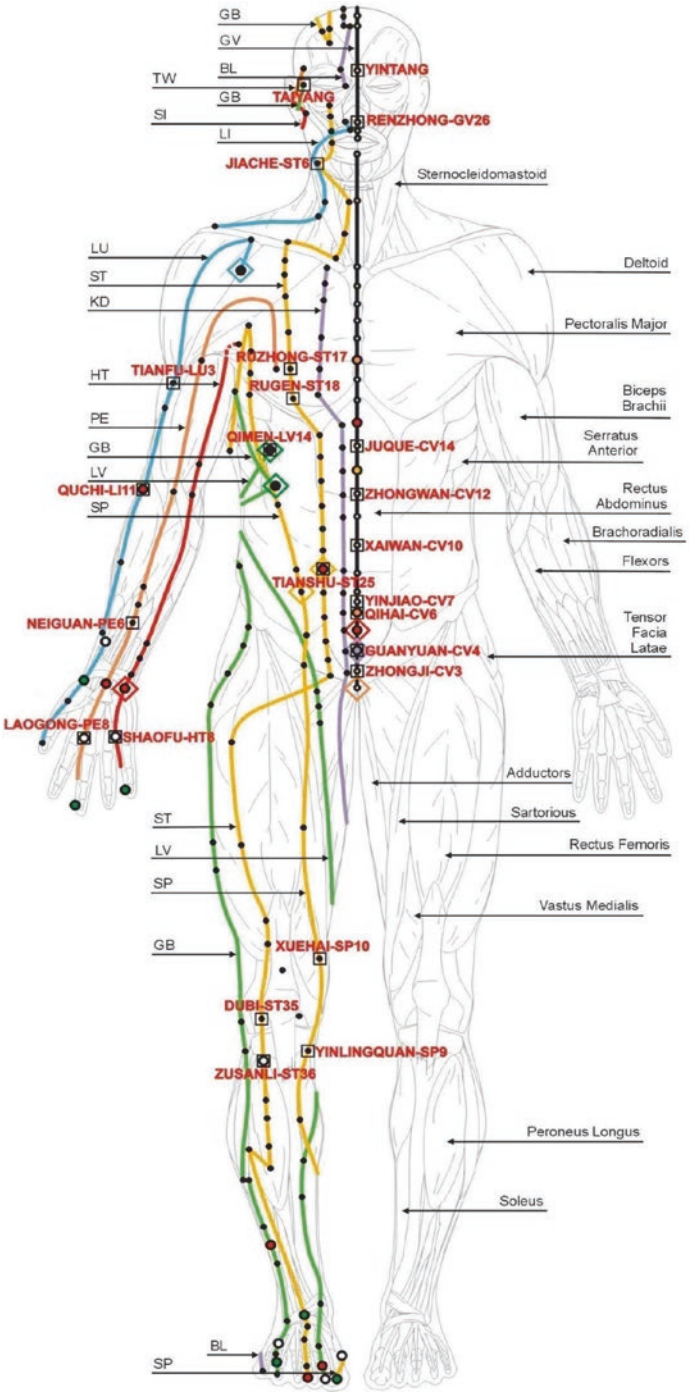

Fig. 18.8 Acupressure points

Fig. 18.9 Mud therapy

treatments drawn from non-Western cultures, even alternative healing methods that do have Western origins. These, however, need to complement, not replace conventional practice, and must have the rigor in the implementation expected as part of "good clinical practice" world over.

Neuropsychiatric patients with complex conditions and comorbidities like Mahesh may well require us to go "beyond medication" in seeking solutions. Patients with neuropsychiatric illness are chronic sufferers and, like many with chronic disease, are frustrated with the lack of progress they perceive when offered with conventional medicine alone. Many patients and patient groups today are open to, even encourage, holistic solutions.

The key to a good outcome may not exist in bettering the primary condition alone (in Mahesh's case seizures). One will also need to work toward management of the comorbidities, in this case cognitive, behavioral, and psychosocial. Also, lifestyle modifications may be necessary to optimize factors, such as sleep, appetite and digestion, and weight gain or loss, to name a few. Holistic solutions that predominate in CAM models of care may well be very useful to patients with neuropsychiatric and indeed other chronic illness and disability.

Observations from the Parents

We are happy to see our son Mahesh become a confident young man who will soon leave school with a diploma. When we first started this program, we did not anticipate that he would make such significant progress. While his seizures remain a problem in a mild way and have not been cured, we are happy his mood, anxiety, and behavior and also his communication, social skills, and independence have improved greatly. We feel that the holistic program with many specialists, offering him personalized care and attention, has made a big difference. Mahesh likes his school and this city where he came for treatment so much that he now is not keen to return home. In fact he wishes to continue to stay here, close to his school, friends, and treatment team, even if that means living on his own.

References

1. Piña-Garza JE. Chapter 1 – Paroxysmal disorders. In: Fenichel's clinical pediatric neurology [Internet]. 7th ed. London: W.B. Saunders; 2013. p. 1–46.
2. Marrus N, Hall L. Intellectual disability and language disorder. Child Adolesc Psychiatr Clin N Am. 2017;26(3):539–54.
3. Espie C, Watkins J, Curtice L, Espie A, Duncan R, Ryan J, et al. Psychopathology in people with epilepsy and intellectual disability; an investigation of potential explanatory variables. J Neurol Neurosurg Psychiatry. 2003;74(11):1485–92.
4. Glauser TA, Holland K, O'Brien VP, Keddache M, Martin LJ, Clark PO, Cnaan A, Dlugos D, Hirtz DG, Shinnar S, Grabowski G. Pharmacogenetics of antiepileptic drug efficacy in childhood absence epilepsy. Ann Neurol. 2017;81(3):444–53.
5. Balestrini S, Sisodiya SM. Pharmacogenomics in epilepsy. Neurosci Lett. 2017;667:27–39.
6. Franco V, Perucca E. The pharmacogenomics of epilepsy. Expert Rev Neurother. 2015;15(10):1161–70.
7. McCormack M, Alfirevic A, Bourgeois S, Farrell JJ, Kasperavičiūtė D, Carrington M, Sills GJ, Marson T, Jia X, de Bakker PI, Chinthapalli K. HLA-A* 3101 and carbamazepine-induced hypersensitivity reactions in Europeans. N Engl J Med. 2011;364(12):1134–43.
8. Hogarty G, Greenwald DP. Cognitive enhancement therapy: the training manual [Internet]. University of Pittsburgh Medical Center; 2006. Available from: www.CognitiveEnhancementTherapy.com.

When It's Not Just a Febrile Seizure: Epileptic Encephalopathy

19

Yoshimi Sogawa and Miya Asato

Case

Charlie was born at full term via normal delivery, but the pregnancy was complicated because of maternal epilepsy of childhood onset. Charlie's mother had a few febrile seizures when she was young and then had sporadic generalized convulsive seizures when she was growing up. Her last seizure was 5 years ago in college, when she did not take her medication regularly. She had stopped taking antiepilepsy medication when she discovered she was 8 weeks pregnant. She did not have any seizures during pregnancy, and she resumed taking her antiepilepsy medication after her baby's delivery. Charlie weighed 2500 g and had no problems during the newborn period.

Clinical Pearl #1
Some antiepilepsy medications (valproic acid in particular) are associated with increased risk of teratogenicity including neural tube defects. Seizures during pregnancy can pose health risks to both the mother and her unborn child as convulsive seizures could result in maternal death and pregnancy loss [1, 2]. Effects of antiepilepsy medication on other infant outcomes such as development are still being studied.

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Charlie did well until 6 months of age when he developed a seizure with a fever of 103°F. According to his mother, his vaccination status was up to date. He finished the 6-month-old set of immunizations 2 weeks earlier. His mother checked him while he was sleeping when she heard some noises coming from his bed. He was lying on his back, foaming at the mouth, with his eyelids open, and his eyes were rolled back. He was shaking all over. The seizure lasted 1–2 min. In the local emergency room, he was arousable with non-focal neurological examination and subsequently diagnosed with a febrile seizure and sent home.

Charlie had another febrile seizure at the age of 8 months, and this time he had a prolonged convulsive seizure, status epilepticus. This seizure lasted over an hour. He was eventually thought to have a viral syndrome, and he recovered after a 5-day hospitalization and after his infectious workup was unremarkable. He had a follow-up visit with a pediatric neurologist, and at that time his EEG testing was normal (Fig. 19.1).

Charlie's first seizure at 6 months was a simple febrile seizure, which may occur in 2–5% of all children [3]. In children who are immunized and who have a normally functioning immune system, clinical judgment can determine that the need for further neurological diagnostic workup is required for a simple febrile seizure.

The second seizure occurred in the context of a fever again, but this one was considered a "complex" febrile seizure since it was prolonged. A convulsive seizure of over 30 min may potentially cause long-term consequences (including neuronal injury, neuronal death, alteration of neuronal networks and functional deficits) [4, 5].

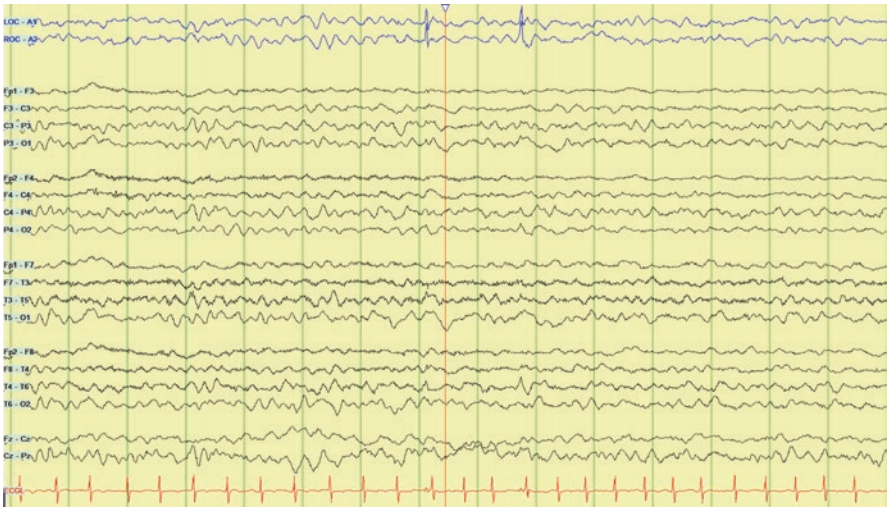

Fig. 19.1 Normal EEG at 8 months old, 5–6 Hz background activity. (Courtesy of Dr. Yoshimi Sogawa, Clinical EEG sample)

Over time, Charlie experienced a few more febrile seizures and another episode of status epilepticus with fever after a scheduled vaccination at age 12 months. He eventually developed seizures without fever. The new seizures were quick muscle jerks with head drops. Follow-up evaluation with his pediatric neurologist indicated that in addition to his mother having epilepsy, his grandfather had two seizures as a child but was never started on medication. His aunt had febrile seizures in infancy. Also, a 7-year-old cousin was also recently diagnosed with epilepsy. Given the extensive history, genetic testing was ordered. Charlie was found to have a mutation in a sodium channel gene, SCN1A, which is consistent with the mutation associated with Dravet syndrome. Charlie's mother was found to carry the same mutation although she did not have the same clinical phenotype.

Repeat EEG was abnormal showing a photoparoxysmal response, which is demonstrated by spike-and-wave discharges with photic stimulation at different frequencies (Fig. 19.2). Charlie and his family were sent for genetics consultation given his parents' wish to have more children.

Clinical Pearl #2

In very young children or in children with intractable epilepsy, genetic testing is often considered. Dravet syndrome is associated with difficult-to-control epilepsy and developmental, cognitive, and behavioral impairments [6, 7]. Genetic diagnosis can be informative as certain medications such as sodium channel-blocking agents (e.g., phenytoin, carbamazepine, lamotrigine) can aggravate seizures in Dravet syndrome.

SCN1A mutation is the most common gene mutation in Dravet syndrome (75%). Ninety-five percent of patients with Dravet syndrome associated with SCN1A mutations are de novo, and 5% are inherited. The mutation affects α1 subunit of the voltage-gated sodium channel, and seizures are triggered by impaired GABAergic or inhibitory firing. A family history of epilepsy and/or febrile seizures is present in 30–50% of families with genetic epilepsy with febrile seizures plus (GEFS+). GEFS+ is typically autosomal dominant with incomplete penetrance. Family members in affected families may have febrile seizures, febrile seizures with relatively benign epilepsy or more severe syndromes such as Dravet syndrome [8].

Children with Dravet syndrome often present with seizures triggered by fever postvaccination which may initially mimic febrile seizures [9, 10]. However, over time seizures occur without fever, and the diagnosis of epilepsy is typically made by their second birthday.

Families of children with Dravet syndrome often experience significant stress; frequent emergency room visits and hospitalization can be associated with missed days of work for parents and costs of medical care leading to financial concerns [11].

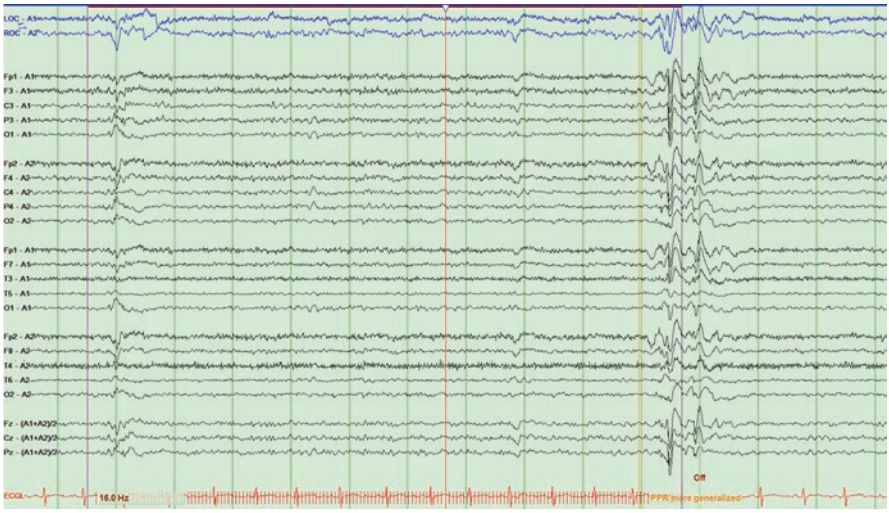

Fig. 19.2 Photoparoxysmal response

At 3 years of age, Charlie is being treated with three different antiepilepsy medications, but he continues to experience 10–30 seizures/day which vary in appearance. Some seizures are described as sudden body jerks, staring off with drooling, unilateral hand/mouth twitching, and/or occasional generalized convulsive seizures. Although Charlie was developing fairly well up to his first birthday, he only just learned to walk at age 3 and is ataxic. His only spoken word is "mama." He picks up table foods but does not use a spoon. He does not seem interested in other children at the playground. Charlie's mother tried to return to work but could not locate appropriate child care to support his complex needs.

Clinical Pearl #3

Children with Dravet syndrome typically have a mixed type of epilepsy with different seizure types over time and an associated epileptic encephalopathy. The ongoing epilepsy, associated abnormal cerebral activity, and underlying genetically mediated pathology are thought to underlie the poor epilepsy and developmental outcomes. The frequent need for epilepsy polytherapy can also contribute to the complex neuropsychiatric profile of Dravet syndrome.

The complex neuropsychiatric phenotype of Dravet syndrome emerges as the child becomes older and impacts all spheres of development. Management of interictal (between seizures) behavior problems and multiple daily seizures can be challenging. Families often report that development appears to plateau during the second year of life. Hyperactivity, impulsiveness, and features of autism are common. Serial cognitive, behavioral, and educational assessment from early age may help the family and the behavioral support team to understand the emerging difficulties [12].

The loss of two functioning copies of the NAv1.1 gene affects GABAergic neurons in multiple regions of the brain [13]. For example, NAv 1.1 dysfunction in the cerebellum and basal ganglia contributes to motor abnormalities (e.g., ataxia and crouching gait). Involvement in the hypothalamus can be associated with loss of thermoregulation, sensitivity to fever, and sleep difficulties. Emerging work suggests dysfunction in cortical regions can contribute to autism, severe behavior dysregulation, and learning disabilities [13, 14].

Lessons Learned About Neuropsychiatry

This case of genetically-mediated epilepsy is increasingly recognized as an important phenotype to recognize in children presenting with what may initially appear as typical febrile seizures in infancy. Sometimes an infant's first clinical presenting symptom is febrile seizures following routine vaccination. As the child ages, however, the seizure pattern evolves into refractory myoclonic epilepsy (afebrile seizures), and other diagnostic entities should be considered.

Dravet syndrome was first described in 1978, but the most common genetic cause (SCN1A mutation, a sodium channel gene, NAv1.1) was only identified in 2001. The neuropsychiatric profile of children with Dravet syndrome is increasingly appreciated as a complex model that considers the genetic background of the family, ongoing uncontrolled epilepsy, the need for epilepsy polytherapy, and an associated progressive encephalopathy.

The pathogenesis of the neurobehavioral profile is complex, particularly as it relates to autism and disability. The highest incidence of autism associated with epilepsy is in those with intellectual disability and those with uncontrolled seizures [15]. However, the rarity of this severe disorder makes large controlled studies linking seizure control with behavioral and developmental outcomes difficult, making determinations around the phenomenology of encephalopathy, psychopathology, and development unclear. However, a large body of research work has indicated the presence of widespread brain dysfunction and structural abnormalities early in the course of epilepsy which appears sensitive to the age of the first seizure [16, 17]. Mouse model work has indicated that cognitive impairment, autistic-like traits, and sleep disturbance can be associated with selective deletion of NAv1.1 channels in the forebrain and thalamic GABAergic interneurons, indicating a potential target for treatment [18].

Seizures occurring early in life can be associated with deleterious effects on developmental outcome, underscoring the importance of recognition of eliciting family history and clinician appreciation of the evolving role of genetic testing in neuropsychiatric disorders.

References

1. Harden CL, Meador KJ, Pennell PB, et al. Practice parameter update: management issues for women with epilepsy – focus on pregnancy (an evidence-based review): teratogenesis and perinatal outcomes: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. Neurology. 2009;73:133–41.
2. Harden CL, Hopp J, Ting TY, et al. Practice parameter update: management issues for women with epilepsy – focus on pregnancy (an evidence-based review): obstetrical complications and change in seizure frequency: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. Neurology. 2009;73:126–32.
3. Steering Committee on Quality I, Management SoFSAAoP. Febrile seizures: clinical practice guideline for the long-term management of the child with simple febrile seizures. Pediatrics. 2008;121:1281–6.
4. Riviello JJ Jr, Ashwal S, Hirtz D, et al. Practice parameter: diagnostic assessment of the child with status epilepticus (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology. 2006;67:1542–50.
5. Glauser T, Shinnar S, Gloss D, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the guideline Committee of the American Epilepsy Society. Epilepsy Curr. 2016;16:48–61.
6. Brunklaus A, Zuberi SM. Dravet syndrome – from epileptic encephalopathy to channelopathy. Epilepsia. 2014;55:979–84.
7. Dravet C. The core Dravet syndrome phenotype. Epilepsia. 2011;52(Suppl 2):3–9.
8. Zuberi SM, Brunklaus A, Birch R, Reavey E, Duncan J, Forbes GH. Genotype-phenotype associations in SCN1A-related epilepsies. Neurology. 2011;76:594–600.
9. Verbeek NE, van der Maas NA, Sonsma AC, et al. Effect of vaccinations on seizure risk and disease course in Dravet syndrome. Neurology. 2015;85:596–603.
10. McIntosh AM, McMahon J, Dibbens LM, et al. Effects of vaccination on onset and outcome of Dravet syndrome: a retrospective study. Lancet Neurol. 2010;9:592–8.
11. Camfield P, Camfield C, Nolan K. Helping families cope with the severe stress of Dravet syndrome. Can J Neurol Sci. 2016;43(Suppl 3):S9–S12.
12. Granata T. Comprehensive care of children with Dravet syndrome. Epilepsia. 2011;52(Suppl 2):90–4.
13. Gataullina S, Dulac O. From genotype to phenotype in Dravet disease. Seizure. 2017;44:58–64.
14. Barry JM, Holmes GL. Why are children with epileptic encephalopathies encephalopathic? J Child Neurol. 2016;31:1495–504.
15. Tuchman R, Hirtz D. Mamounas LA. NINDS epilepsy and autism spectrum disorders workshop report. Neurology. 2013;81:1630–6.
16. Lin JJ, Mula M, Hermann BP. Uncovering the neurobehavioural comorbidities of epilepsy over the lifespan. Lancet. 2012;380:1180–92.
17. Cetica V, Chiari S, Mei D, et al. Clinical and genetic factors predicting Dravet syndrome in infants with SCN1A mutations. Neurology. 2017;88:1037–44.
18. Catterall WA. Forty years of sodium channels: structure, function, pharmacology, and epilepsy. Neurochem Res. 2017;42:2495–504.

Part V

Neuroinflammatory Conditions

Introduction

> Everything we do, every thought we've ever had, is produced by the human brain. But exactly how it operates remains one of the biggest unsolved mysteries, and it seems the more we probe its secrets, the more surprises we find.
>
> Neil deGrasse Tyson, PhD

The role of autoimmunity and inflammation is quickly becoming an important topic in a broad range of neuropsychiatric syndromes. Since the discovery of anti N-methyl-D-aspartate receptor antibodies in 2007, interest in these subjects has soared. This also corresponds to a growing interest in the impact of inflammation in other conditions such as tic disorders and obsessive compulsive disorder. A discussion of neuroinflammatory conditions is, by its nature, multidisciplinary and traverses multiple brain regions, integrating aspects of immunology, movement disorders, and other sub-specialties. This subject builds upon knowledge about neural circuitry discussed earlier in the text.

The section begins with a case of the, now classic, anti-NMDA-receptor encephalitis. The presentation is in some ways typical but emphasizes some points that are often forgotten: the condition occurs commonly in children and can certainly present in boys. It also addresses the challenging conversation of what to do when antibodies are negative, a common clinical occurrence. This is further explored in the following chapter which addresses the fact that, with the burgeoning interest in exploration of autoimmune causes of psychiatric disorders, sometimes, the answer is still an idiopathic, primary psychiatric cause. From here, there is a case and extensive discussion of the increasingly well-characterized phenomena of pediatric-onset multiple sclerosis and its similarities and differences compared with other pediatric autoimmune disorders such as acute disseminated encephalomyelitis. Finally, having established a vocabulary for the discussion of frontal-subcortical circuits in the

first section and an appreciation of the interaction between the immune system and specific parts of the brain, the final case of this section addresses the controversial and difficult topic of pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections and pediatric acute-onset neuropsychiatric syndrome, with a nuanced discussion of the work-up, differential diagnosis, and management.

When the Body Attacks the Brain

20

Jordan L. Nordquist, Owais Tirmizi, Siddhartha S. Nadkarni, and Aaron J. Hauptman

Case

Steve is a 15-year-old, right-handed male with no prior personal or family psychiatric history and a past medical history significant for congenital left-eye blindness due to optic nerve hypoplasia. He is a bright, social young man with many interests and friends and was a top student at his high school who had been progressing developmentally appropriately through his childhood and adolescence.

In June 2015, Steve developed viral-like symptoms including cough and fatigue. His parents noticed he was less attentive and engaged, which was unusual for him. He also began to experience uncharacteristic difficulties with his short-term memory. Over the course of a few weeks, his fatigue worsened, and he began to exhibit unusual emotional lability and mild agitation along with sleeping difficulties.

About 8 weeks after the start of his viral-like symptoms, Steve experienced a prolonged staring episode during which time he was unable to respond. Two days later, he was found unconscious on the floor of the bathroom. He was briefly

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unresponsive and had about 30 min of confusion after the incident along with amnesia for the period of time surrounding the event. He was evaluated in the emergency room where head CT, 1-h EEG, routine blood chemistry, CBC, serum drug screen, and urine drug screen were all normal. He was discharged home with outpatient neurology follow-up.

About 1 week later, he had his first witnessed generalized tonic-clonic seizure. He was admitted to the local children's hospital and given 2 mg lorazepam and a loading dose of levetiracetam at 750 mg twice daily. A brain MRI showed no abnormalities. After 24 h, he was discharged home to be seen by outpatient neurology the following day.

Over the next few weeks, he experienced persistent agitation along with intermittent nausea and vomiting. During this time, levetiracetam was increased to 750 mg in the morning and 1125 mg at bedtime. Much later, on recollecting this period of time, Steve describes remembering vivid hallucinations of "seeing snakes" and "feeling tied down," though was not able to articulate these experiences then. His insomnia worsened. Due to concerns that levetiracetam might be exacerbating his agitation and behavioral changes, he was transitioned to oxcarbazepine and was rapidly titrated to a dose of 600 mg in the morning and 900 mg at bedtime.

Steve had another witnessed generalized seizure at home and was transported to the emergency room where he experienced another seizure in the presence of clinicians. His worrisome, rapidly evolving clinical picture prompted medical hospitalization for further work-up and symptom management. MRI of the cervical, thoracic, and lumbar spine were all unremarkable.

Given his course of viral symptoms followed by new-onset seizures, agitation, memory decline, and intermittent hallucinations, a lumbar puncture was done, and a CSF fluid encephalitis panel was sent for specialized testing given a high index of suspicion for autoimmune encephalitis. Lumbar puncture demonstrated 11 WBC (2% segmented neutrophils, 97% lymphocytes, and 1% monocytes/histiocytes), with 2 RBC, protein 22, and glucose 62. CSF gram stain and culture were negative. HSV and enterovirus PCR on the CSF were negative. West Nile Ab was negative. The encephalitis panel results took over a week to return.

Steve underwent a 72 h continuous video EEG. No clinical seizure was captured during this time, and the EEG in awake, drowsy, and asleep states demonstrated no electrographic abnormalities despite waxing and waning levels of consciousness. Of note, during the period of video monitoring, intermittent dysarthria was observed, and he had complaints of sensory changes in the right upper extremity, but there was no abnormal electrographic activity observed with these complaints.

Over the next few days, Steve's confusion worsened. His parents described an episode where he was trying to listen to music on his headphones but couldn't figure out how to use them. At this point, florid psychotic symptoms appeared, including auditory hallucinations and bizarre behaviors such as episodes where he would lay on the floor and scream. At one point, Steve attempted to run out of his hospital room. He could not follow verbal redirection, prompting 24-h supervision and

intermittent mechanical restraint. He would have long periods of staring into space, unresponsive.

At this time, encephalitis work-up returned positive for preliminary anti-N-methyl-D-aspartate receptor (ANMDAR) antibodies with a 1:10 anti-NMDA antibody titer (reference <1:1). Other components of the paraneoplastic panel were negative including anti-neuronal nuclear antibodies (types 1, 2, and 3), anti-glial nuclear antibody type 1, Purkinje cell cytoplasmic antibodies (types 1 and 2), amphiphysin antibody, CRMP-5-IgG, and others. CSF NMDAR antibody cell-based assay was positive, and assay was 1:32 (reference range <1:2), confirming diagnoses of ANMDAR encephalitis. Malignancy evaluation, including abdominal, chest, and pelvis MRI and scrotal ultrasound, was negative.

When ANMDAR encephalitis was confirmed, a course of methylprednisolone sodium succinate IV infusion daily was rapidly initiated. After 48 h of steroid treatment, a 5-day course of IVIG administration began. He continued to decline clinically with significant agitation, sleep disturbance, and speech difficulties.

Overnight EEG at this time was markedly abnormal with asymmetric generalized slowing. Four seizures were captured. These lasted up to 2 min and included right frontal or bifrontal onset with semirhythmic right frontal delta initially up to 60 μV which evolved into a spike-wave pattern at approximately 2 Hz in the bifrontal regions with spread to left lateral hemisphere with increasing rhythmicity at 2.5–3 Hz, generalizing in about 30 s. He showed eye deviation to the right, rhythmic shaking of the right hand, and non-responsiveness. Steve's left arm was postured flexed at the elbow, and he developed clonic shaking along with his legs.

Given declining clinical status despite corticosteroids and IVIG, he was treated with a single dose of cyclophosphamide (750 mg/m^2 body surface area) along with two doses of rituximab (375 mg/m^2 body surface area) given over 2 weeks. Steve continued to be severely encephalopathic and nonverbal. He would not eat or drink and required parenteral nutrition. He had persistent ongoing vital sign abnormalities, including elevated heart rate, blood pressure, and temperature variability. Over this period, Steve would alternate between mute stupor and agitation. He could only sleep for about 20 min at a time. Delirium was suspected, and low-dose quetiapine 50 mg was given at bedtime without symptom improvement or exacerbation.

During an episode of agitation, lorazepam 2 mg IV was administered, and Steve's clinical picture improved suddenly and drastically. He interacted and even briefly spoke. Thirty minutes after the treatment, stupor, mutism, and purposeless movements returned. This prompted a strong suspicion for catatonia. Lorazepam challenge was started at 2 mg IV. He had a robust response, confirming clinical diagnosis of catatonia. Bush-Francis Catatonia Rating Scale (BFCRS) score was 25 due to excitement, stupor, mutism, staring, catalepsy, grimacing, echo phenomena, verbigeration, rigidity, negativism, waxy flexibility, withdrawal, impulsivity, automatic obedience, passive obedience, ambitendency, grasp reflex, perseveration, combativeness, and autonomic abnormalities.

Quetiapine was discontinued, and IV lorazepam was quickly titrated. After 3 days, Steve's lorazepam dose was 8 mg, correlating with decrease in BFCRS score to 15. After 10 days, Steve's BFCRS score was 6 with 12 mg lorazepam. After 18 days of lorazepam titration to a maximum dose of 14 mg divided four times daily, BFCRS had declined to 3 with only residual echolalia and automatic obedience which soon resolved completely. During the period of lorazepam titration, two additional doses of rituximab were also administered.

With time, other symptoms improved as well. Steve's sleep schedule normalized; food intake improved, permitting feeding tube removal; and communication began to improve. After almost 2 months in the hospital, he was transferred to an inpatient rehabilitation unit where he remained for 2 weeks for treatment of his ongoing speech deficits, gross and fine motor dysfunction, and ongoing challenges with activities of daily living.

Steve was discharged home. He had improvements in all functional domains but still continued to struggle in many respects. Over the next 5 months, lorazepam was slowly tapered. He transitioned to outpatient physical, occupational, and speech therapy. He was able to feed and dress himself but needed help with choosing what to eat. He ambulated independently and was able to transfer on his own but needed prompting for multistep tasks requiring motor control, coordination, attention, and planning. For example, Steve needed prompting on how to operate a washing machine and reminders to put the soap in first before starting the laundry. He was able to fold clothes, dress, and put on his shoes but still had difficulty with shoelaces. Fine motor control particularly with his right hand showed vast improvements with time and therapeutic intervention but still was not at baseline.

Steve was continued on oxcarbazepine 300 mg twice daily following his hospital discharge for seizure prophylaxis. He experienced only one breakthrough seizure 2 months after discharge. By 6 months after discharge, he was able to taper fully off of the medication.

Prior to encephalitis, Steve had been a consistently straight-A student performing at or above grade level up through the tenth grade. Three months post-hospitalization, Steve underwent educational psychological testing at the recommendation of his teachers and family given ongoing learning difficulties. Testing included the Differential Ability Scales (DAS-II) which demonstrated low-average intellectual functioning (DAS-II = 80) with borderline verbal ability, low-average reading, average mathematical skills, and borderline written expression. Given Steve's high premorbid level of functioning, there was no baseline psychoeducational or neuropsychological testing data from before his illness for comparison.

Formal neuropsychological evaluation was performed at 8 months following hospital discharge. Intellectual function appeared to be in the normal range with FSIQ of 105 assessed by the Wechsler Abbreviated Scale of Intelligence (WASI-II), with particular areas of strength in block design and vocabulary. Working memory was impaired, and Steve's performance in digit span was in the 16th percentile.

Motor and sensory functioning showed some persistent deficits in fine motor dexterity and speed. Language skills assessed by Boston Naming Test (45th percentile) and Delis-Kaplan Executive Functioning System (D-KEFS) illustrated impairments in letter and category fluency (25th and 9th percentiles, respectively). Expressive Vocabulary Test (EVT-2) showed weakness as Steve scored in the 30th percentile.

Tests of Memory and Learning (TOMAL-2) showed fair memory for stories in immediate (75th percentile) and delayed (63rd percentile) trials with continued impairment in facial memory (37th percentile). Executive functioning as measured by D-KEFS was most notable for difficulty in a task of number-letter switching (1st percentile), with visual scanning (63rd percentile), number sequencing (50th percentile), letter sequencing (37th percentile), and motor speed (84th percentile) with Steve self-reporting difficulties in inhibition and working memory on his Brief Rating Inventory of Executive Function (BRIEF-SR). Rey-Osterrieth Complex Figure Test demonstrated immediate and delayed recalls at the 50th and 37th percentiles.

Neuropsychological testing was repeated 18 months following hospital discharge. Steve showed significant improvement in language over the 18-month course of recovery with repeat D-KEFS letter and category fluency (91st and 75th percentiles, respectively) as well as Boston Naming scores (86th percentile). The EVT-2 also showed marked improvement with Steve scoring in the 70th percentile. Furthermore, he had made gains in executive functioning as demonstrated by marked improvement in D-KEFS number switching (50th percentile) in comparison with his markedly impaired testing from 10 months before.

In order to help with adjustment back to life outside the hospital, management of new challenges, and processing of his traumatic and confusing experiences of illness, Steve started to work in weekly individual psychotherapy with a psychiatrist. Treatment continued for 20 months after discharge and utilized several psychotherapeutic modalities.

First, in-depth psychoeducation was provided to Steve and his family regarding his illness, current literature on expected outcomes, relapse rates, and other details. Supportive psychotherapy, utilizing a person-centered approach, provided the bulk of the intervention afterward, focusing on empathy and unconditional positive regard toward Steve and his family in the process of contextualizing and understanding their experiences. In this environment, Steve was able to process this significant life adjustment and move toward acceptance and positive change. Aspects of psychodynamic psychotherapy, family therapy, and motivational interviewing were also engaged toward these goals.

Before the start of his illness, Steve had been progressing well along normal developmental lines with increased independence appropriate for the transition from childhood to early teenage years. He self-identified as intelligent and motivated which had allowed academic successes that had been evolving into college ambition. His illness in some ways halted this progression, and he felt frustration

with this setback in his developmental progress. In treatment, Steve described having few memories of the 3 months when his illness was at its highest acuity. He talked about feeling like he went to sleep before his long hospitalization and then woke up, unable to speak, and physically disabled. Despite the trauma of these experiences, Steve showed great resilience. He worked hard in all of his treatments which contributed to a steady recovery. Toward the end of his treatment, Steve was almost completely back to his premorbid baseline. He had moved from anger toward acceptance regarding his situation and his battle with the illness which had nearly taken his life.

Despite some degree of low-grade neurocognitive difficulty, Steve returned to school in his normal academic setting with only minor academic accommodations necessary. To date, he has not experienced significant encephalitis or catatonia relapse. His psychotic symptoms resolved without relapse, and he required no ongoing treatment with neuroleptics. He is still progressing through school and plans to graduate with his high school class and intends to start college in the fall.

Discussion

Encephalitis is any condition of brain inflammation and can result secondarily from a wide range of etiologies, including infectious, chemical, traumatic, autoimmune, or other causes. Autoimmune encephalitis is causally related to an inflammatory condition or response such as a systemic autoimmune disorder, an instantiation of molecular mimicry against a tumor or infection, or paraneoplastic disease processes [1]. Anti-N-methyl-D-aspartate receptor encephalitis (ANMDARE) is related to the general category of limbic encephalitis, a term coined over 50 years ago for the symptom cluster of seizures, dysautonomia, and delirium, that now include many categorized (and as-yet uncategorized) autoimmune antibodies against specific components of the nervous system including intracellular and cell-surface proteins [2, 3].

Autoimmune Encephalitis

NMDA receptor encephalitis was first discovered in 2007 by Joseph Dalmau and his research team. This discovery of a specific autoimmune antibody that can produce such a drastic neuropsychiatric syndrome has sparked an explosion of research and clinical attention to this category of disorders [4]. Other important forms of pediatric autoimmune encephalitis include Hashimoto's encephalitis, glutamic acid decarboxylase 65 (GAD65), and voltage-gated potassium channel (VGKC) encephalitis. In addition, there is a growing appreciation of seronegative autoimmune encephalitis, and specific antibodies and the response to immunomodulatory therapies are not required for an AE diagnosis more broadly [5].

ANMDARE is the most common form of autoimmune encephalitis [6]. The California Encephalitis Project found ANMDARE to be more common than any single viral encephalitis, including enterovirus and herpes simplex, two of the more common viral etiologies. It also is the leading cause of pediatric encephalitis of a single, known origin [7]. Around 40% of cases of ANMDARE occur in individuals under the age of 18, and it is associated with a 4% mortality and significant associated morbidity [8]. To date, the youngest reported case has been in a 21-month-old. The condition has a 4:1 ratio of females to males over the age of 12 and a slight preponderance of males in younger ages [7, 9–11]. Unlike in adults with ANMDARE where tumor is often found, most commonly ovarian teratoma, an association with tumor is much less common in children, and there have been no reported cases with testicular seminoma in young males [8]. Other forms of limbic encephalitis are much rarer in children, but pediatric cases of GAD 65 antibody encephalitis and VGKC encephalitis have been reported [1].

NMDARE presents with a cluster of neuropsychiatric symptoms including catatonia, psychosis, mood and anxiety symptoms, language changes, movement disorder, and seizures. In children younger than 12, neurological symptoms such as seizures and new-onset movement abnormalities often present earlier and coincide with behavioral changes such as aggression, tantrums, sleep changes, and disordered language [10]. Teenagers present similarly to adults, with a stepwise progression of symptoms starting with a flu-like prodrome followed by personality changes and psychiatric symptoms over the next days to weeks and subsequently evolving into frank neurological symptoms [12].

NMDARE cases frequently present first to psychiatric care, which exemplifies the extent to which, particularly in adults and older adolescents, psychiatric manifestations are often striking and seen early in the illness. The condition is generally acute or subacute in presentation. Ninety percent of cases develop neuropsychiatric symptoms. New onset of psychosis, mood disorder, behavioral dysregulation, sleep disorder, agitation, and anxiety symptoms can commonly be seen. The condition can mirror primary psychiatric conditions such as schizophrenia and bipolar disorder, particularly when clear neurological symptoms like seizures or dyskinesias are delayed, subtle, or not present. Neurological symptoms often include seizures, dyskinesias (especially orofacial), language changes including frank mutism, and delirium. About 70% of cases of ANMDARE include symptoms of frank catatonia during some point in their disease course [12, 13].

Definitive diagnosis of ANMDARE is made by antibody presence in CSF and/or serum, although false-negative and false-positive findings can occur. CSF evaluation is particularly important as 14% of cases will show CSF findings without autoantibodies present in serum [14]. Other CSF abnormalities may include oligoclonal bands, lymphocytic pleocytosis, and protein elevation. EEG may demonstrate abnormalities such as diffuse background slowing with electrographic seizures present in about 60% of cases. In some cases, though more commonly in adults than in children, a combined delta and beta wave pattern known as “extreme delta brush” is present [8] (see Fig. 20.1). Evaluation should also include abdomen and pelvis

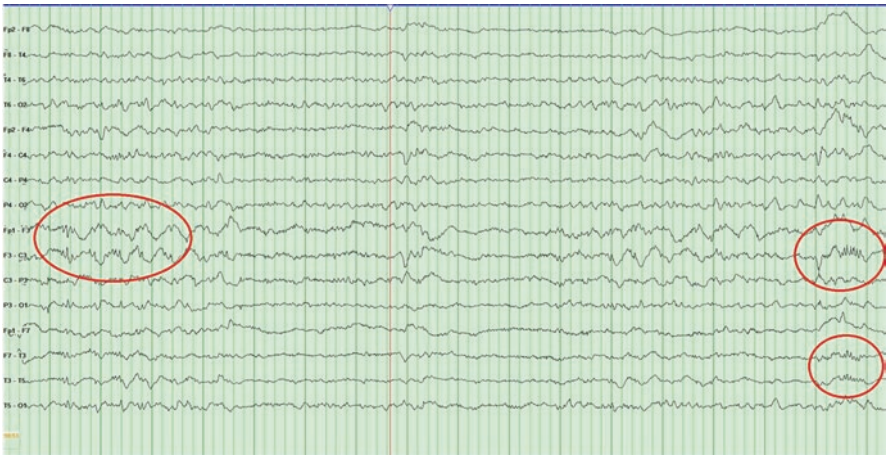

Fig. 20.1 EEG example of "extreme delta brush," an epileptiform pattern characteristic of anti-NMDA receptor encephalitis

MRI and/or ovarian ultrasound in females and testicular ultrasound in males to evaluate for associated tumors.

Treatment in autoimmune encephalopathy is often complex. In addition, about 50% of the time, an autoimmune encephalitis is highly suspected, but specific antibodies cannot be characterized, or treatment is considered to be necessary, but the diagnostic panel has not yet returned. Thus, care often requires a multipronged approach including (1) supportive management for autonomic instability, seizures, dyskinesia, catatonia, etc.; (2) immune-modifying agents; and (3) management of psychiatric and other medical comorbidities.

First-line treatment for ANMDARE is high-dose steroids and intravenous immunoglobulin or plasma exchange. The majority of patients may require a second-line treatment such as rituximab or cyclophosphamide [15]. Mycophenolate mofetil and azathioprine are sometimes used as oral maintenance agents [1]. Intensive medical care, often for extended periods and including ICU-level care, may be necessary in order to manage sequelae of autonomic instability, seizure, agitation, psychiatric phenomena, and other symptoms. Good outcome is predicted by early treatment and lack of need for ICU-level care. Prominence of catatonia symptoms may also predict poor outcome [16]. Long-term psychiatric follow-up is recommended as psychiatric symptoms can continue to wax and wane for months to years, often requiring close monitoring and judicious symptomatic management.

Lessons Learned About Neuropsychiatry

Steve's case outlines many aspects of the classic adolescent presentation of NMDAR encephalitis. His symptoms progressed along lines that are characteristic of the illness with early non-specific flu-like symptoms followed by behavioral and sleep

symptoms with subsequent onset of frank neurological symptoms (initially seizures and then frank aphasia, apraxia, and mutism) along with agitated psychosis and dysautonomia. Notably, Steve developed a full-blown catatonia syndrome, which is present in about 70% of individuals with anti-NMDAR encephalitis. This was initially misidentified, thus delaying treatment, but improved markedly once identified and managed.

One of the important messages from Steve's case is how well he ultimately did, given good management and long-term, close care with attention to multi-domain neurocognitive and motor rehabilitation. Importantly, clinicians must be aware that even positive outcomes in this illness are marked by long-term, neurocognitive challenges. Prognosis depends on early diagnosis and treatment. Many individuals experience ongoing neurocognitive symptoms, re-emergence of psychosis, catatonia, and other psychiatric phenomena and require close monitoring. While his story can paint a clinical picture that demonstrates classical symptoms and progression well, it illustrates even better the many challenges that even those who have good health outcomes experience. In short, sequelae do not stop just with survival through the acute phase of the condition.

Neuroanatomy

Anti-NMDA receptor antibodies are neuronal surface antibodies that target the NR1 subunit of the glutamatergic NMDA receptor. Clinicians may be familiar with this spectrum of symptoms from substance abuse cases where low-dose ketamine or phencyclidine, both noncompetitive NMDAR antagonists, can yield symptoms similar to prodromal psychosis (paranoia, ideas of reference, and mild cognitive dysfunction, particularly on executive function tasks). High-dose intoxication with these substances yields agitated delirium (memory disturbance, motor stereotypies and dyskinesias, dysautonomia, and frank psychosis). At very high doses, these medications can yield catatonia and coma. Dalmau points out that the low-dose NMDA receptor antagonism mirrors symptoms at the early and recovery stages of ANMDAR encephalitis, while the high- and very high-dose intoxication syndromes correspond with the period of peak encephalitis symptomatology [17]. Studies suggest that NMDAR antibodies may result in a structural remodeling of the hippocampus in a similar way that ketamine-induced functional decrease in the region occurs that results in hippocampal network dysfunction. Models explore overlap between ANMDARE and suspected schizophrenia pathophysiology, where excessive dopaminergic tone in schizophrenia may be secondary to an underlying NMDAR function decrease [17].

A wide range of both surface and internal anti-neuronal antibodies have been characterized and more are being isolated and characterized. For example, other neurotransmitters for which antibodies have been characterized (and which are routinely tested for in encephalitis panels such as those by Athena and Mayo Clinic) include AMPA (α-amino-hydroxymethyl-isoxazole propionic acid receptor), D2 (dopamine D2 receptor), GABA-A and GABA-B (γ-aminobutyric

acid receptor), glycine, glutamate, LGI1 (leucine-rich, glioma-inactivated 1), CASPR2 (contactin-associated protein-like 2) proteins of the VGKC (voltage-gated potassium channel complex), etc. Furthermore, each of these forms of antibody-mediated encephalopathy has a different set of characteristics and associated conditions. It is also important to note that a significant proportion of suspected autoimmune encephalitis cases currently come back negative for known antibodies, leading to substantial diagnostic confusion and controversy.

Clinical Pearls

- Limbic encephalitis should be suspected in adolescents and young adults who have atypical, rapid-onset presentations of psychiatric conditions. If symptoms also include movement abnormalities, cognitive changes, speech dysfunction, and autonomic abnormalities, work-up should progress rapidly, and the threshold for encephalitis treatment should be low.
- The typical presentation includes a flu-like prodrome followed by subacute or acute, new-onset psychiatric symptoms followed by frank neurological symptoms such as movement disorder, seizures, and aphasia. Severe cases require ICU-level management for life-threatening sequelae.
- Presentation of autoimmune encephalitides in young children under the age of 12 follows a less typical course and often includes a vaguer cluster of presenting symptoms such as tantrum and behavioral changes prior to frank neurological decompensation.
- Treatment should include high-dose steroids, IVIG, and/or plasmapheresis and often requires a second or third immunomodulating therapy such as rituximab or cyclophosphamide. Long-term immunomodulating therapies are sometimes required. Psychiatric and other neurological symptoms can reemerge following general resolution of the acute phase of the illness necessitating longer-term or periodic use of antiepileptic and antipsychotic medications.
- Recovery is generally good over the long term but requires multidisciplinary management including neurology, psychiatry, a range of rehabilitation specialties, rheumatology, primary care, immunology, and others. Outcomes can include long-term neurocognitive deficits, for which younger individuals with ANMDARE seem to be at higher risk. Neurocognitive testing at multiple intervals can help to monitor improvements, and neurocognitive rehabilitation can be helpful in developing skills for managing any ongoing deficits.
- These are extremely difficult conditions for families to come to terms with and require intensive cross-disciplinary support in the acute diagnostic, hospitalization and follow-up phases (Tables 20.1 and 20.2).

Table 20.1 Suggested criteria for autoimmune encephalitis [5, 1]

Possible limbic encephalitis	Definite limbic encephalitis	Probable AE despite negative antibodies	Suspected ANMDAR encephalitis	Definite ANMDAR encephalitis
Psychiatric symptoms, mental status alteration, and/or working memory onset which is rapid and subacute	Psychiatric symptoms, mental status alteration, and/or working memory onset which is rapid and subacute and suggests limbic involvement	Psychiatric symptoms, mental status alteration, and/or working memory onset which is rapid and subacute and unrelated to pre-existing symptoms or conditions	Rapid onset of 3 of 6:	Criteria for "suspected ANMDARE" are met, and positive CSF antibody titers are present
			Psychiatric or cognitive dysfunction	
			Speech dysfunction	
			Seizure	
			Movement abnormalities	
			Decreased level of consciousness	
			Dysautonomia	
One of the following is present:	Both of the following are present:	Absence of well-characterized autoantibodies but presence of one or more:	One or more of:	
Focal CNS abnormalities	CSF pleocytosis and/or EEG demonstrating epilepsy or temporal lobe slow waves	MRI findings consistent with encephalitis	EEG abnormalities	
New-onset seizures without other explanation	Bilateral T2 abnormalities highly restricted to the medial temporal lobes	CSF pleocytosis, oligoclonal bands, and/or, elevated CSF IgG index	CSF pleocytosis or oligoclonal bands	
CSF pleocytosis				
MRI findings consistent with encephalitis such as T2 hyperintensities in medial temporal lobes, regions of demyelination or inflammation, etc.				
Other possible causes are ruled out	Other possible causes are ruled out	Exclusion of well-defined autoimmune syndromes and other possible causes are ruled out	Other possible causes are ruled out	

Table 20.2 Work-up. A partial list of tests to consider in the work-up in suspected autoimmune encephalitis. Modified from [1]

Laboratory tests	Imaging	Others
CSF:	MRI brain, MRA, PET, ovarian/testicular ultrasound, MRI abdomen, and pelvis	Neuropsychological testing
Standard CSF analysis (cell count, culture, glucose, gram stain, oligoclonal bands/IgG index, opening pressure)		Genetic testing such as chromosomal microarray, fragile X, etc. may be considered if a neurodevelopmental disorder is suspected
Viral, fungal, and bacterial infection work-up		
Specialized testing: Autoimmune antibody panel, ACE level		Electroencephalography
Serum:		
CBC, CMP, thyroid panel (TSH, T3, T4) including anti-TPO and antithyroid antibodies		
Autoimmune antibody panel and other autoantibodies not included in encephalitis panel		
Rheumatological labs (ANA, ESR, CRP, lupus anticoagulant, ACE level, anticardiolipin, anti-DNAse B, anti-Sm, Ro, and La antibodies)		
Infectious diseases: ASO titer		
von Willebrand factor antigen		
IgG/IgM		
C3,C4		
Serum immunoglobulins		
Serum ceruloplasmin		
Serum copper		
Creatine kinase		
Other labs:		
Infectious work-up (strep, mycoplasma, throat culture, etc.)		
Urine copper, heavy metals, porphyrins		

Reflections from Steve's Family

Steve's reflection

I remember very little from the 4 months I was sick. The most I can remember is just before I got acute. Some memories are almost surreal, like they didn't even happen; and yet, they are so intertwined with the truth that I still even now have trouble figuring out what really happened. My recovery period is when I what I have the most memory of the constant help from my doctors and therapists who never gave up and pushed me to become stronger and better...to become myself again. I'll never forget those days where my speech therapist helped me learn to talk

again, the day I was able to walk upstairs again thanks to my physical therapist, the day when my occupational therapists and I baked cookies for everyone in the rehab department. One of the most important things I'll remember is the smile from a boy and little girl who had rooms across from me. How could I forget the doctor who asked me the same question every time I saw her "what's in my stethoscope" it was 3 goldfish in a blue background. My therapists and doctor impacted my life so much; through their hard work and their attitude, it felt as if they truly cared about me. That has impacted my life so much that I want to be able to do the same thing when I'm older and become someone's hero also, whether it be a doctor or even become a physiatrist myself. This experience has had some rough patches and some terrible things happened, but I'm alive and well. I've grown stronger from it as a person on both physical and emotional levels. I've learned that no matter how hard or scary something is, as long as you have a positive attitude and keep on going, you can't be stopped.

Steve's father's reflection:

Describing this experience is very difficult. The clinical description does not vividly explain the firsthand experience. I would liken it to watching a loved one have a psychotic break then, consecutively, a traumatic brain injury. Watching the rapid and varying symptoms play out can be devastating and frightening, especially with most clinicians' lack of firsthand experience treating this illness. The psychological effect and burden initially require close and deep connections with a support network. The lack of information for the patient and family cause a great deal of anxiety when trying to plan for treatment and eventual recovery. Also a multidisciplinary and aggressive rehabilitation I believe are key to a robust recovery as with Steve. In our experience the close psychiatric support and follow-up were essential in our recovery relieving the burden set upon us with an illness that is very difficult to predict lingering deficits or relapse.

In short I firmly believe the quick diagnosis and a very aggressive initial clinical treatment followed by extensive rehabilitation were the key factors in the "best case scenario" Steve experienced. Steve had strong family support that was conducive to a long-term recovery. Make no mistake: this illness nearly took his life, and his family feels the effects of nearly losing a child. The uncertainty of relapse and knowing the devastating affects is an anxiety caregivers have to live with indefinitely.

References

1. Mooneyham GC, Gallentine W, Van Mater H. Evaluation and management of autoimmune encephalitis: a clinical overview for the practicing child psychiatrist. Child Adolesc Psychiatr Clin N Am. 2018;27(1):37–52. ISSN 1558-0490. Disponível em: https://www.ncbi.nlm.nih.gov/pubmed/29157501.
2. Corsellis JA, Goldberg GJ, Norton AR. "Limbic encephalitis" and its association with carcinoma. Brain. 1968;91(3):481–96. ISSN 0006-8950. Disponível em: http://www.ncbi.nlm.nih.gov/pubmed/5723018.
3. Dalmau J, Graus F. Antibody-Mediated Encephalitis. N Engl J Med. 2018;378(9): 840–51. https://doi.org/10.1056/NEJMra1708712.
4. Dalmau J, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol. 2007;61(1):25–36. ISSN 0364-5134. Disponível em: http://www.ncbi.nlm.nih.gov/pubmed/17262855.

5. Graus F, et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol. 2016;15(4):391–404. ISSN 1474-4465. Disponível em: https://www.ncbi.nlm.nih.gov/pubmed/26906964.
6. Granerod J, et al. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. Lancet Infect Dis. 2010;10(12):835–44. ISSN 1474-4457. Disponível em: http://www.ncbi.nlm.nih.gov/pubmed/20952256.
7. Gable MS, et al. The frequency of autoimmune N-methyl-D-aspartate receptor encephalitis surpasses that of individual viral etiologies in young individuals enrolled in the California Encephalitis Project. Clin Infect Dis. 2012;54(7):899–904. ISSN 1537-6591. Disponível em: http://www.ncbi.nlm.nih.gov/pubmed/22281844.
8. Dalmau J, et al. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol. 2011;10(1):63–74. ISSN 1474-4465. Disponível em: http://www.ncbi.nlm.nih.gov/pubmed/21163445.
9. Armangue T, Petit-Pedrol M, Dalmau J. Autoimmune encephalitis in children. J Child Neurol. 2012;27(11):1460–9. ISSN 1708-8283. Disponível em: http://www.ncbi.nlm.nih.gov/pubmed/22935553.
10. Florance NR, et al. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. Ann Neurol. 2009;66(1):11–8. ISSN 1531-8249. Disponível em: http://www.ncbi.nlm.nih.gov/pubmed/19670433.
11. Goldberg EM, et al. Anti-N-methyl-D-aspartate receptor-mediated encephalitis in infants and toddlers: case report and review of the literature. Pediatr Neurol. 2014;50(2):181–4. ISSN 1873-5150. Disponível em: http://www.ncbi.nlm.nih.gov/pubmed/24315538.
12. Titulaer MJ, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol. 2013;12(2):157–65. ISSN 1474-4465. Disponível em: http://www.ncbi.nlm.nih.gov/pubmed/23290630.
13. Dalmau J, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol. 2008;7(12):1091–8. ISSN 1474-4422. Disponível em: http://www.ncbi.nlm.nih.gov/pubmed/18851928.
14. Gresa-Arribas N, Titulaer MJ, Torrents A, et al. Antibody titres at diagnosis and during follow-up of anti-NMDA receptor encephalitis: a retrospective study. Lancet Neurol. 2014;13:167–77.
15. Zekeridou A, et al. Treatment and outcome of children and adolescents with N-methyl-D-aspartate receptor encephalitis. J Neurol. 2015;262(8):1859–66. ISSN 1432-1459. Disponível em: http://www.ncbi.nlm.nih.gov/pubmed/25987208.
16. Desena AD, Greenberg BM, Graves D. Three phenotypes of anti-N-methyl-D-aspartate receptor antibody encephalitis in children: prevalence of symptoms and prognosis. Pediatr Neurol. 2014;51(4):542–9. ISSN 1873-5150. Disponível em: http://www.ncbi.nlm.nih.gov/pubmed/25070939.
17. Dalmau J. NMDA receptor encephalitis and other antibody-mediated disorders of the synapse: the 2016 Cotzias lecture. Neurology. 2016;87(23):2471–82. ISSN 1526-632X. Disponível em: https://www.ncbi.nlm.nih.gov/pubmed/27920282.

Pitfalls in the Diagnosis of Autoimmune Limbic Encephalitis

21

Sheldon Benjamin

Case

Darryl, a 17-year-old right-handed male on a psychiatric inpatient unit, was referred for neuropsychiatric evaluation of probable autoimmune encephalitis of unknown type.

History of Present Illness

Darryl was described by his mother as an athletic "A student" with particularly strong math skills until age 13 in sixth grade, when he gradually became withdrawn and apathetic, eventually developing paranoid delusions. His older brother had recently left for college, and he was being bullied by classmates. Darryl was hospitalized for 3 months after having mimed stabbing someone at school with a pencil. The presumptive diagnosis was depression with psychotic features. During his admission, he was tried on risperidone, then aripiprazole, and was finally discharged somewhat improved on risperidone and perphenazine with cabergoline for treatment of risperidone-induced hyperprolactinemia. After several months, depression and psychotic symptoms increased, and escitalopram was added without improvement. Seven months after discharge, he was readmitted for 1 week and transitioned from escitalopram to lithium. By 19 months after his initial hospitalization, Darryl's psychomotor slowing and apathy had worsened, trials of increased neuroleptic dosage had appeared to cause further deterioration, he had lost 33 lbs, compulsive symptoms had developed, and he was admitted to pediatrics for evaluation of weight loss. A comprehensive medical evaluation was unrevealing.

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At 21 months after the index hospitalization, Darryl was transferred to psychiatry for electroconvulsive therapy (ECT). After 6 weeks of right unilateral alternating with bilateral ECT three times per week, his apparent catatonic symptoms had improved, his appetite had returned, and he was managing his own ADL's and talking, now 25 months after his first hospitalization. He was tapered to one treatment every other week. Compulsive and psychotic symptoms increased. He appeared to further deteriorate with addition of an SSRI. ECT was increased to twice weekly without improvement. ECT was temporarily halted in month 31 to allow for a baseline electroencephalogram (EEG) and inpatient neurological assessment to investigate other reasons for deterioration. Routine laboratory testing was unrevealing. In addition, thyroid studies were all normal including thyroid-stimulating hormone 1.33, free T4 1.7, T3 108, thyroid peroxidase <1, anti-thyroglobulin antibody <1, and thyroglobulin 3.6. Antinuclear antibody (ANA) was homogeneous and positive at 1:80 only, 1:40 on repeat. Multiple urine toxicology screens were negative throughout the course of his illness. EEG revealed epileptiform activity, and an MRI was normal.

ECT continued to be held pending more detailed evaluation of the epileptiform activity. Darryl was admitted for long-term EEG monitoring (LTM) and was found to have right temporal slowing and frequent right more than left temporal spike-wave discharges. Nine 30-s right temporal seizures with secondary generalization were recorded. One appeared to cause a behavioral arrest, and a few others were associated with staring or brief arousal from sleep. A single left temporal seizure with secondary generalization lasting 1 min was recorded. The event detection button was depressed once when his mother observed him staring and appearing "stuck," but the EEG background during the event was no different from his baseline. A presumptive diagnosis of temporal lobe epilepsy was made, and he was started on divalproex, to which lacosamide was later added.

Given the emergence of seizures in the midst of a catatonic presentation, a diagnosis of paraneoplastic autoimmune limbic encephalitis was entertained. However, an extensive laboratory evaluation was unrevealing (Table 21.1). Depression continued to increase on anticonvulsants. Repeat EEG at 32 months post initial hospitalization revealed right temporal intermittent rhythmic delta activity (TIRDA). An MRI was consistent with enlargement of the right amygdala and heterogeneously increased T2 signals in the right greater than left amygdala. Magnetic resonance spectroscopy (MRS) revealed increased choline-to-creatinine signal ratio in the right amygdala compared to the left as well. Serum ammonia was elevated at 344 so he was converted from divalproex to oxcarbazepine. In the 33rd month, Darryl's mother noted that, although not back to baseline, his symptoms were at their most improved level since they began 3 years earlier. His appetite had improved. He was playing basketball with family members, talking, and going to the swimming pool. However, he again became paranoid, called an ambulance, and was hospitalized at his own request. LTM was repeated and showed occasional 2–5 s right temporal epileptiform discharges, rare left temporal discharges, and right temporal slowing, which improved since the original LTM study earlier. By month 34 the MRI and MRS findings had normalized. Sleep EEG's were within normal limits in months 33

Table 21.1 Laboratory evaluation

Months since index hospitalization	Test	Result
General labs		
31	Cerebrospinal fluid	Glucose 63, total protein 28, normal opening pressure
31	Cerebrospinal fluid antibodies	All negative
	Neuronal nuclear	All negative or within normal limits
	Acetylcholine receptor binding	
	Purkinje cell cytoplasmic	
	Purkinje cell	
	Amphiphysin	
	GAD-65	
	CRMP	
	Glial neuronal nuclear	
	Glial	
	NMDA-NR1	
	Voltage-gated potassium channel	
	Yo	
	AMPA-R	
	GABA-B	
	Hu	
	CASPR	
	LGI-1	
	Ma 1 and 2	
	CV2	
	Common antigen antibodies (CaAb)	
31	Homocysteine	10.3 (normal)
31	ANA	Positive only at 1:80 and then 1:40 (speckled) on repeat
31	Urine organic acids	Negative
32	C-reactive protein	0.1 (normal)
35	Urine copper	None detected
36	Serum protein IgG	844 (normal)
37	Cerebrospinal fluid	Glucose 64, total protein 28
		Neopterin 13 (normal)
		Beta-2-microglobulin 0.49 (normal)
		Oligoclonal bands negative
		Albumin 22.7 (normal)
		IgG 3.5 (normal <3.4)
37	Serum protein electrophoresis	IgG 1256 (normal)
		IgA 99 (normal)
		IgM 123 (normal)
37	C-reactive protein	0.1 (normal)

(continued)

Table 21.1 (continued)

Months since index hospitalization	Test	Result
37	Serum amino acids	Normal
37	Serum pyruvate	0.12 (normal)
43	Serum ceruloplasmin	30 (normal)
43	PET CT (whole body)	Incidental finding of left ventricular hypertrophy
43	Cardiac echo	Multiple mild abnormalities, including collapsed left atrium, small pericardial effusion, and some plural effusion; abnormalities no longer present at follow-up
43	Testicular ultrasound	Negative
Neurodiagnostic labs		
31	EEG	Frequent right temporal spike-wave discharges and focal right temporal slowing
31	EEG	
32	LTM EEG	
33	EEG awake and drowsy	Normal
35	EEG awake and drowsy	Normal
43	3-day EEG with foramen ovale electrodes	
31	MRI	Normal
31	MRI	Increased right amygdala size
31	MR spectroscopy	Increased choline signal right amygdala
33	MRI and MR spectroscopy	Normal (including normal amygdalae)
43	MRI	Normal amygdalae and hippocampi, possible subtle right temporal white matter signal increase, small meningoencephalocele left posterior inferior temporal gyrus present in previous MRI's in retrospect

and 35. Darryl's psychosis had worsened some though was still improved compared to his pre-ECT condition. The transient enlargement of the right amygdala was interpreted as presumptive evidence of autoimmune encephalitis, however, and a decision was made to treat empirically.

Darryl was treated with methylprednisolone 1 g IV daily for 3 days and then weekly for 6 weeks with intention to taper further. His psychotic symptoms worsened, and he began having brief staring spells. EEG was negative. A full course of IVIG was then given still with no improvement. Three doses of lorazepam 2 mg IV did not improve his increasingly catatonic symptoms. Following an epilepsy case conference that concluded there was a reasonable likelihood that the underlying problem could be epileptic encephalopathy with psychosis, a decision was taken in

month 43 to repeat the LTM, this time with foramen ovale electrodes placed surgically to detect deeper subthreshold epileptiform activity. The study was completely negative, and the pediatric neurology consultant recommended tapering anticonvulsants. Repeat MRI was normal except for a small (less than 1 cm) congenital left superior temporal meningoencephalocele. Laboratory studies were also repeated. Testicular ultrasound was negative, and a full-body PET/CT study was unrevealing save for some transient cardiac findings. He appeared to become more aggressive with tapering of oxcarbazepine, and this was reinstated. Lacosamide was tapered without apparent behavioral impact. He was transferred back to the child psychiatry unit. There clozapine was started (month 45), and some minor improvement was noted in that he became more cooperative. However, he continued to communicate very little, avoided interactions with others, and restricted his food intake.

At 5.5 years following the index hospitalization, Darryl remained hospitalized in a public sector unit. In the context of clozapine, oxcarbazepine, and milieu therapy, he had gradually become somewhat more interactive with improvement in vegetative features and aggressive behavior, but persistent psychotic features.

Examination

Darryl was seen for neuropsychiatric evaluation 4 years and 2 months after his initial hospitalization. At that time, he was unable to cooperate for examination and refused vital signs. He was tall and thin without apparent dysmorphic, dermatologic, or marfanoid features. His eyes appeared to wander, and he actively avoided eye contact. He did not respond to verbal commands or to having various objects placed in front of him, simply averting his gaze. He was resistant to any attempt at physical contact, pushing to leave the room and responding with "no" when cajoled by a favorite staff member. Examination was therefore limited to observation. There was no facial asymmetry, and he appeared to alert to noise and visual threat bilaterally. He was able to sit, stand, and walk without assistance and moved all four extremities well. He walked with a normal gait and stride length. There were no abnormal involuntary movements.

Medical History

Darryl has no known history of febrile seizures in childhood. He tested positive for *Borrelia burgdorferi* exposure and was treated with a full course of doxycycline in the 1st year after the onset of his symptoms.

Developmental History Darryl was the product of a full-term pregnancy and normal vaginal delivery. By age 18 months he was receiving speech and language services. He was diagnosed with pervasive developmental disorder not otherwise specified due to his impaired social skills and interpersonal behavior. In kindergarten, he had a comprehensive educational evaluation, and he received special education services for the remainder

of his schooling. An educational evaluation 4–5 months before symptom onset estimated his IQ as within the average range. However, he had not been able to cooperate for psychological or neuropsychological evaluation since the onset of symptoms.

Family History Darryl is the third of five siblings born to a technical worker and a mother who worked at home. His oldest brother is said to have a severe anxiety disorder, one that caused him to repeat a grade in high school twice due to fear of leaving his room. There is no other known family history of mental illness or neurological disorders including epilepsy.

Medications

Oxcarbazepine 600 mg BID
Clozapine 50 mg once daily
Lorazepam 1 mg BID

Discussion

This unfortunate 17-year-old boy with autism spectrum disorder suffers from an unremitting psychotic disorder that presented as catatonia, though the symptom severity has varied some. There have been some improvements in the past 5 years, once in the context of frequent ECT (during which, for a short time he began to approach his baseline) and more recently in the context of clozapine and oxcarbazepine treatment. Empiric steroid treatment clearly resulted in a psychotic exacerbation. IVIG therapy produced no change. He has received an exceedingly thorough evaluation, fueled in part by a therapeutic conviction that he suffered from a form of autoimmune encephalitis.

Differential Diagnosis

Given the presentation of catatonia combined with clear-cut temporolimbic seizures during LTM, consideration of the possibility of autoimmune limbic encephalitis was appropriate. The extensive autoantibody panels eliminated all relevant paraneoplastic and autoimmune conditions known at that time. In addition, he had thyroid studies including anti-TPO and anti-thyroglobulin antibodies sufficient to rule out the somewhat controversial and possibly non-specific syndrome of autoimmune thyrotoxicosis. Anti-GAD65 studies were also unrevealing.

Darryl's MRI findings were vague and not consistent with MRI criteria for autoimmune encephalitis. Amygdala hypertrophy has been cited in a number of psychiatric disorders (schizophrenia and PTSD to name a few) but also as a sequel of ECT treatment. One MRI had a suggestion of subtle temporal white matter changes on

T2 images, but these were not seen on repeat study. At no time was there evidence of hyperintensity in the hippocampi on FLAIR images.

The temporolimbic seizures found on LTM appear to be the major "hard" finding in this case. Darryl did not have known febrile seizures in childhood, nor did he have known TBI, and there was no suspicion that the historical database provided by family and other providers was incomplete. MRI did not show mesial temporal sclerosis. No immediate family members have been diagnosed with epilepsy. The active epileptiform EEG following ECT and the absence of epileptiform pattern later, even with foramen ovale electrodes, could be consistent with ECT activation of a latent limbic focus that subsequently became inactive following ECT. His psychotic symptoms are also inconsistent with what is known about the interictal psychosis and alternating psychosis seen in temporolimbic epilepsies, both in terms of phenomenology and time course. Although it would be difficult to definitively rule out a genetic epileptic diathesis, the temporolimbic electrographic seizures seen during LTM were most likely related to his ECT treatment. Although a few seizure discharges appear to have been associated with behavioral arrest and staring, most were electrographic only without behavioral correlation. There were also staring episodes without electrographic seizures during LTM. Despite the appearance of roving gaze and unresponsiveness to commands which certainly could be seen in rare cases of partial complex status epilepticus, he was also observed to have this appearance during a completely normal 3-day long EEG with subcortical foramen ovale electrodes. This effectively rules out partial seizures as an explanation of the observed behaviors.

Darryl most likely does have some level of congenital brain dysfunction, not only related to Autism Spectrum Disorder (ASD) but based on the suggestion of a small posterior temporal meningoencephalocele (implying possibly abnormal brain development) and his propensity for developing electrographic seizures after a course of ECT.

The positive test for borreliosis (Lyme disease) is also not helpful. Darryl was treated appropriately with antibiotics and does not have evidence of focal neurologic dysfunction. No psychotic disorder of this severity has ever been conclusively linked to Lyme disease.

The minimally positive ANA findings are of doubtful diagnostic significance. About 30% of individuals tested in the normal population have ANA positive at the first dilution (1:40) and about 10% have positive ANA at the second dilution (1:80). Positive ANA when less dilute than 1:320 is unlikely to be due to rheumatologic disease. In any case there were no signs of rheumatologic disease on history or examination and no signs of white matter disease on MRI.

A severe psychotic disorder with onset in adolescence and evidence of functional deterioration raises the possibility of congenital neurodegenerative diseases [1]. Wilson's disease was ruled out by laboratory investigation. The absence of significant cerebral white matter signal abnormalities and the absence of focal signs on exam make white matter dementias improbable. There were also no abnormal involuntary movements, nor were there basal ganglia abnormalities on several MRI studies.

The presence of a severe anxiety disorder in the brother may increase the chances that Darryl also suffers from a mood or anxiety disorder.

The most likely diagnosis in this case is ASD combined with a severe psychotic disorder, either major depressive disorder (MDD) with psychotic features or a schizophrenia spectrum disorder, presenting with catatonia. The epileptic discharges seen during LTM are consistent with the phenomenon of tardive seizure disorder following ECT [2, 3]. The transient left amygdala enlargement could also be attributed to ECT [4].

Treatment

Given the aggressive behavior following oxcarbazepine taper and clozapine's effect on the seizure threshold, Darryl was continued on an anticonvulsant mood stabilizer while on clozapine. Since the underlying problem may well include MDD and there is no contraindication to lamotrigine with clozapine, lamotrigine might be considered as an alternative to oxcarbazepine if needed. However, this might not help reduce his aggressive behaviors.

Since Darryl's behaviors are at times consistent with catatonia, a trial of lorazepam 1 mg TID is appropriate. If not improved, zolpidem 5 mg BID (at 8 a.m. and 2 p.m.) could be added. If no improvement is noted at that point, augmentation with amantadine 50 mg (at 8 a.m. and 2 p.m.) could be added while continuing clozapine. Memantine could be used as an alternative to amantadine if the stimulant effect is not needed.

Despite the likely history of ECT-induced tardive seizures, he could still be cautiously treated with ECT in the future. His ability to cooperate for hour-long rTMS treatments as an alternative would be quite limited. If he is treated with ECT in the future, he should be placed on an anti-seizure regimen following treatment and have post treatment EEG evaluation.

Clinical Pearls

The proposed diagnostic criteria for antibody-negative but probable autoimmune limbic encephalitis require all of:

1. Rapid progression (<3 months) of working memory deficit, altered mental status, or psychiatric symptoms
2. Exclusion of well-defined autoimmune encephalitides (e.g., typical limbic encephalitis, Bickerstaff's brainstem encephalitis, acute disseminated encephalomyelitis)
3. Absence of well-characterized autoantibodies in serum and CSF and two of:
   a) MRI abnormalities suggestive of autoimmune encephalitis;
   b) CSF pleocytosis, oligoclonal bands, or elevated IgG index or both; brain biopsy showing inflammatory infiltrates [5]

The most common causes of the catatonic syndrome are mood disorders.
Do not discount chronic idiopathic psychiatric disorders in the differential diagnosis of catatonia in adolescents.

Lessons Learned About Neuropsychiatry

In the absence of positive CSF or MRI findings classically seen in autoimmune encephalitis, treatment with steroids and related compounds could be detrimental to Darryl's mental status.

ECT-induced tardive seizures should be considered for new-onset seizures in the context of ECT treatment.

Unilateral amygdaloid swelling on MRI is a non-specific finding that does not increase the chances of autoimmune limbic encephalitis.

References

1. Benjamin S, Lauterbach MD, Stanislawski AL. Congenital and acquired disorders presenting as psychosis in children and young adults. Child Adolesc Psychiatr Clin N Am. 2013;22(4):581–608.
2. Devinsky O, Duchowny MS. Seizures after convulsive therapy: a retrospective case survey. Neurology. 1983;33(7):921–5.
3. Williams A, Adetunji B, Odulate A. Tardive seizure: a case report. J ECT. 2006;22(4):271.
4. Tendolkar I, van Beek M, van Oostrom I, Mulder M, Janzing J, Voshaar RO, et al. Electroconvulsive therapy increases hippocampal and amygdala volume in therapy refractory depression: a longitudinal pilot study. Psychiatry Res. 2013;214(3):197–203.
5. Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol. 2016;15(4):391–404.

The Hidden Symptoms of Pediatric-Onset Multiple Sclerosis

22

Ashley Marie Clayton and Leigh E. Charvet

Case

Melissa was first seen in clinic when she was 16 years old. She was accompanied by her parents and grandmother and presented with sensory disturbance, urinary retention, and headache. MRI brain imaging showed 24 lesions on T2-weighted images, the largest of which was 2–3 cm. Lesions were bilateral and involved white matter only in the juxtacortical, callosal, and infratentorial regions. Eight of the lesions were gadolinium-enhancing on T1-weighted images.

Later that same year, a second event occurred where she experienced left optic neuritis. Melissa was diagnosed with relapsing remitting multiple sclerosis (MS). She initiated treatment with interferon beta-1a (Rebif). Interferon beta-1a is one of the now several disease-modifying therapies that target the immune system and is common in the treatment of patients with MS. Briefly after starting interferon beta-1a, Melissa began experiencing headaches, hair loss, and flu-like symptoms and was switched to treatment with rituximab. She began receiving rituximab infusions every 6 months, always accompanied at her visits with both parents.

Around the time of her MS diagnosis, Melissa's treating neurologist suggested a neuropsychological evaluation to serve as a baseline assessment of her cognitive functioning. Areas tested included general intellectual functioning, academic achievement, attention/executive functioning, learning and memory, visuospatial abilities, speech and language, and fine motor and psychosocial functioning.

General intellectual functioning was within the high average range, with a significant 15-point discrepancy between verbal and perceptual reasoning. Academic achievement showed Melissa's word identification, decoding, and spelling were within normal limits, though slightly below expectations given her intellect. Learning and memory results for both verbal and visual learning and retrieval were within

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normal limits. Melissa's visual spatial and visual constructive skills were normal across several measures. In terms of speech and language, solid receptive and expressive language skills were demonstrated throughout testing. However, subtle deficits were noted in the areas of working memory (calculations) and complex attention. Executive functioning performances were marked by errors of impulsivity and omission, and she was also mildly impulsive across a continuous performance test of attention. On a timed fine motor task, Melissa was markedly slower than average.

During the clinical interview with Melissa's parents as well as Melissa, she appeared to be managing her MS diagnosis well. She maintained a close relationship with her family and peers and was eager to discuss both her academic and her social life with the neuropsychologist evaluating her during this time.

At age 19, Melissa was noted to be very moody, sleeping a lot, and had experienced noticeable weight loss. Neurological examination was unremarkable, and she appeared to be free of any sensory, motor, or vision symptoms. Bloodwork was ordered to rule out any other possible cause of her symptoms. Results were found to be normal.

Melissa entered into her first year of college, attending a university in another state. Due to the distance, she was only able to have return visits home during the major holiday breaks, and her parents worried about her being far away. She initially did well, with strong grades and good adjustment in her first semester. However, after returning from a winter break at home, she became withdrawn and isolated. She made few social connections and moved to a single dorm room that contributed to her social isolation. Her grades slowly deteriorated across the second semester.

Her mother called multiple times throughout these months to report Melissa's ongoing tearfulness and continued increased sleep. Melissa was referred to a psychiatrist on staff when she returned home for summer break. During her evaluation, she described a history of depressive symptoms including increased sleep and appetite, weight gain, significant fatigue, anhedonia, isolation, guilty ruminations, and tearfulness. She reported that symptoms fluctuated but overall were worsening. She also verbalized that her high standards for achievement and recent grades during this time did not meet her expectations. She felt extreme anxiety regarding her grades, but that the anxiety generalized to other aspects of her life including thoughts regarding disease progression and worrying about her family. Melissa mentioned that she felt increasing sadness, hopelessness, and an internal sense of agitation. After a fight with a longtime friend one evening, she made superficial cuts along her wrist with a kitchen knife. She denied any actual suicidal thoughts or intent, past cutting behavior, or previous suicidal thoughts or behaviors. At evaluation, Melissa was diagnosed with major depressive disorder and anxiety and started on the selective serotonin reuptake inhibitor escitalopram.

She returned to the university to start her second year. However, she described having problems with concentration and reading comprehension and difficulty completing her assignments on time. She continued to struggle emotionally as well, noting homesickness and experiencing further social isolation. Ultimately, she earned poor grades and took an incomplete for two of her more challenging courses. Melissa and her family began considering a transfer to a college nearer to their home.

A referral for another neuropsychological evaluation was placed and consequently conducted over a school break. During the clinical interview, Melissa stated

that she was apprehensive with her upcoming return to school. She was taking a light course load but had concerns about earning enough credits to graduate on time with her class. She reported short-term memory issues that interfered with her learning, with difficulty recalling events from day to day.

A similar battery of testing administered during her first evaluation was readministered to determine any decline or pattern of decline. No change in Melissa's general intellectual functioning was noted, remaining in the high average range. However, she had further declined on measures of attention and executive functioning, with problems with planning, inhibition, and impulsivity. Further, her most significant area of change was found to be in the area of memory and learning. Auditory learning for a list of unrelated words as well as a recall of narrative stories was mildly impaired for immediate recall as well as following a delay and with distraction. She had severely slowed fine motor functioning for pegboard completion when using her left (non-dominant) hand. Her escitalopram dose was increased from 10 to 20 mg, and she was referred for individual psychotherapy. It was also recommended that she practice mindfulness meditation to manage her mood symptoms and improve her ability to focus her attention.

In addition, she was enrolled in a clinical trial at the center that provided computer-based cognitive remediation paired with transcranial direct current stimulation (tDCS), with 1.5 mA applied to the left dorsolateral prefrontal cortex (left anodal). Through the study, she completed 40 cognitive training and tDCS treatments. While in the trial, Melissa was administered mood questionnaires before and after daily treatment sessions as well as depression scales before and after study completion. With these treatments, her depressive episode resolved, and she reported experiencing benefit from the cognitive training. She transferred to a college closer to her home and moved into an apartment with three childhood friends. So far, she is doing well with her school work and has not had a return of depressive symptoms.

Multiple Sclerosis

Clinical Pearl #1
Pediatric MS vs. ADEM [1]

- ADEM is typically monophasic.
- ADEM is more likely in those ages 11 and younger.
- Neuroimaging can highlight distinctions:
  - Corpus callosum lesions are less frequent in ADEM.
  - Nonenhancing lesions indicating prior episodes consistent with MS.
- ADEM presentation is more likely to include fever, vomiting, confusion, and seizures.

MS is a demyelinating disease of the central nervous system and can have a wide range of presentations and disability levels. MS is a common neurological disease affecting those of working age and has long been considered an adult disease.

However, over the past 15 years, pediatric onset, defined as occurring in those ages 17 and younger, has become increasingly recognized and characterized [1]. Pediatric-onset multiple sclerosis (POMS) represents only 3–5% of the MS population, making it a rare disorder of childhood. While typically POMS occurs in the middle to late teenage years, there have been cases described to occur as young as infancy [1, 2].

POMS is diagnosed according to clinical and radiological features separated by space and time [1]. Differential diagnoses in childhood include acute disseminating myelitis (ADEM) [1]. ADEM is an autoimmune disease that is characterized by a sudden attack on the brain and spinal cord often following a viral infection. At initial onset, it can be difficult to distinguish pediatric MS from monophasic ADEM. Another overlap is found in the initial symptom presentation. For both diagnoses, symptoms can start around the same age. Initial MR imaging, CSF white blood cell count, and protein values often are very similar as well. However, MS can be indicated by both enhancing and nonenhancing lesions at initial presentation along with progression of lesions on repeat imaging.

One feature of pediatric- vs adult-onset MS is more frequent relapses but less overall accumulation of neurologic disability, at least early in the course of the disease [2]. Instead, the main areas of impairment are the "invisible" or hidden symptoms of the disorder such as cognitive involvement and mood disorders, along with fatigue [3].

It is estimated that approximately one-third of patients with POMS have at least some degree of cognitive impairment [3, 4]. While the mechanism remains unclear, the most common deficits are in the areas of cognitive processing speed and working memory along with fine motor coordination and may also include problems with verbal and visual learning [4]. Mild deficits in social cognition have also been reported [5]. Cognitive impairments cannot be directly linked to lesion location or overall lesion burden, and it is difficult to identify those patients most at risk for decline.

While adults with MS are at greater risk for mood disorders [3, 6], patients with POMS have frequent psychiatric comorbidities as well, though include a wider range of disorders [7]. Broad pediatric behavioral rating inventories (e.g., the Behavior Assessment Scale for Children) indicate an overall increased frequency in clinically significant problems, but again without a consistent problem area across patients [8]. Further, those with cognitive involvement tend to be at greater risk for psychiatric and behavioral problems [7, 8].

Clinical Pearl #2

- Neuromodulation therapies are rapidly evolving and may ultimately have a first-line role in the nonpharmacological treatment of depression, especially in those patients living with a neurologic illness. tDCS is an investigative therapy that delivers low-amplitude, direct current through electrodes placed on the scalp.
- Potentially milder than the FDA indicated neuromodulation therapies of electroconvulsive treatment and repetitive transcranial magnetic stimulation, tDCS has the added benefits of being portable and less expensive.

- Many small trials have been completed, with positive signals suggesting strongest benefit for improving mood and enhancing cognitive function [9].
- Although controlled clinical trials have been disappointing [9], the Canadian Network for Mood and Anxiety Treatments and experts in Europe note that tDCS is an effective method for treating depression [9].

While cognitive and psychiatric problems are of concern across the lifespan in MS, it is especially critical to detect and address these issues in POMS. During development and transition to adulthood, even subtle cognitive and/or emotional problems can influence educational, occupational, and social achievement trajectories through adulthood. Further, psychosocial stressors have been linked to chronic childhood illness and may be associated with earlier age of presentation in MS [10].

Case Reflections

Mood disorders are thought to occur in MS both due to the neurologic disease process and from the psychological reaction to living with a chronic illness [3]. Major depressive disorder (MDD) and anxiety are two of the most common psychiatric disorders associated with MS [6]. While the exact percentage is unknown, clinically significant depressive symptoms can occur in up to 40% of people with MS [6]. The cause of these symptoms is likely to be multifactorial, both associated with ongoing disease activity and neurodegeneration, as well as the psychosocial stressors associated with the chronic course of illness. It is more difficult to diagnose MS patients with MDD because symptoms such as fatigue and concentration and memory problems can occur independently in the disease and may not indicate depression.

Risk factors for mood and anxiety disorders include being newly diagnosed or when experiencing a relapse or pseudo-relapse of symptoms. As with the general population, women with MS are considered to be at greater risk for depression. Factors such as social isolation from peers and family dynamics, as with Melissa's case, can contribute to the onset of depression, especially in POMS. In Melissa's case, tDCS and mindfulness-based meditation in addition to escitalopram helped resolve her depression and increase positive affect.

Melissa's family reacted to her diagnosis with a variety of emotions. Initially, Melissa's parents felt a tremendous amount of guilt and blamed themselves for her diagnosis. They tended to overprotect Melissa by not allowing her to come to her appointments on her own and by frequently calling to update the clinical team on her physical and emotional status regardless if this was requested by Melissa or not. There seemed to be a pattern of Melissa's depression worsening in the context of her perceived lack of support from her parents. Establishing a solid support system from the beginning of a POMS diagnosis can be one of the most helpful steps for both the patient and family. Education regarding the disease state treatment, and prognosis, may have eased the parents' concerns [11].

Lessons Learned About Neuropsychiatry

Melissa's case illustrates that, although rare, MS can have an onset in children. Outside of symptoms of acute relapses of the disease, patients with POMS most frequently experience "invisible" or "hidden" symptoms that are neuropsychiatric. These include cognitive impairment, marked by slowed processing and working memory/executive problems, as well as emotional and behavioral problems including mood disorders. These symptoms mirror those seen in adult MS, although the behavioral problems can be more broad and include specific issues resulting from reaction to a chronic illness experienced during childhood.

As illustrated by Melissa's care, it is important to have a comprehensive treatment team approach, starting at the time of diagnosis. Access to a neuropsychologist and psychiatrist familiar with the disease is an asset to timely and effective management of symptoms.

In addition to the pathological features of MS that may contribute to emotional and behavioral problems, reaction to illness is another major feature to be addressed by the treatment team. A family systems approach may be useful for a patient working toward independence and transitioning to adult care. Improved locus of control and increased healthcare self-efficacy can allow teens and young adults to optimally manage their disease.

Melissa's case illustrates the potential benefit of tDCS as a nonpharmacologic option for the management of mood disorders. While it is investigational and there are many unanswered questions, tDCS may have a role in the treatment of depression. Her case also highlights the need for treatment options and particularly for effective interventions to prevent and ameliorate cognitive impairment. Further research is needed to identify those at risk and ultimately prevent cognitive involvement of the disease.

References

1. Tardieu M, Banwell B, Wolinsky JS, Pohl D, Krupp LB. Consensus definitions for pediatric MS and other demyelinating disorders in childhood. Neurology. 2016;87(9 Suppl 2):S8–S11.
2. Waldman A, Ness J, Pohl D, Simone IL, Anlar B, Amato MP, et al. Pediatric multiple sclerosis: clinical features and outcome. Neurology. 2016;87(9 Suppl 2):S74–81.
3. Amato MP, Krupp LB, Charvet LE, Penner I, Till C. Pediatric multiple sclerosis: cognition and mood. Neurology. 2016;87(9 Suppl 2):S82–7.
4. Julian L, Serafin D, Charvet L, Ackerson J, Benedict R, Braaten E, et al. Cognitive impairment occurs in children and adolescents with multiple sclerosis: results from a United States network. J Child Neurol. 2013;28(1):102–7.
5. Charvet LE, Cleary RE, Vazquez K, Belman AL, Krupp LB, MS USNfP. Social cognition in pediatric-onset multiple sclerosis (MS). Mult Scler. 2014;20(11):1478–84.
6. Murphy R, O'Donoghue S, Counihan T, McDonald C, Calabresi PA, Ahmed MA, et al. Neuropsychiatric syndromes of multiple sclerosis. J Neurol Neurosurg Psychiatry. 2017;88(8):697–708.
7. Weisbrot D, Charvet L, Serafin D, Milazzo M, Preston T, Cleary R, et al. Psychiatric diagnoses and cognitive impairment in pediatric multiple sclerosis. Mult Scler. 2014;20(5):588–93.

8. Charvet L, Cersosimo B, Schwarz C, Belman A, Krupp LB. Behavioral symptoms in pediatric multiple sclerosis: relation to fatigue and cognitive impairment. J Child Neurol. 2016;31(8):1062–7.
9. Bikson M, Unal G, Brunoni A, Loo C. What Psychiatrists need to know about transcranial direct current stimulation. Psychiatric Times. 2017.
10. Shaw MT, Pawlak NO, Frontario A, Sherman K, Krupp LB, Charvet LE. Adverse childhood experiences are linked to age of onset and reading recognition in multiple sclerosis. Front Neurol. 2017;8:242.
11. Krupp LB, Rintell D, Charvet LE, Milazzo M, Wassmer E. Pediatric multiple sclerosis: perspectives from adolescents and their families. Neurology. 2016;87(9 Suppl 2):S4–7.

PANDAS and PANS: An Inflammatory Hypothesis for a Childhood Neuropsychiatric Disorder

23

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Case

Nancy is a 9-year-old female referred to pediatric neuroimmunology clinic with a sudden onset of obsessive-compulsive disorder (OCD). Approximately 4 weeks prior to her presentation there, Nancy had been diagnosed with streptococcal pharyngitis by her pediatrician via a throat culture. The pediatrician prescribed a 10-day course of amoxicillin, with resultant resolution of her pharyngitis symptoms. On the day after the 10-day course was completed, Nancy's mother noticed that she began acting a little more anxious than usual. Nancy was not historically an anxious child, but her mother noted she seemed more "on edge." The following day, Nancy began washing her hands repeatedly, avoiding touching things, and showering multiple times per day. She began experiencing emotional meltdowns and separation anxiety from her mother and began to pull her hair out when frustrated, which she had never previously done.

Within the next week, Nancy began to wet the bed at night, though she had been accident-free since she was toilet-trained at age 2.5 years, and she would complain frequently of needing to urinate despite having just voided. Nightly, she would become emotionally dysregulated at the smallest provocation; these episodes would involve screaming, crying, and tearing out her hair and would often last up to 3 h. As Nancy's symptoms worsened, she would have difficulty keeping her symptoms "in check" while she was at school. Her teacher began to notice that she had trouble completing assignments and tolerating when her schoolwork was not perfect. Her teacher also reported to Nancy's parents that Nancy was refusing to write in class,

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and when she did, it appeared to be closer to scribbles than her usual, neat penmanship.

Her pediatrician prescribed an additional 10-day course of amoxicillin for concerns over reinfection with Group A *Streptococcus* (GAS), recommended she begin seeing a therapist for cognitive behavioral therapy, and referred her to a urologist due to the frequent enuresis. A urology work-up was unable to identify a reason for her urinary urgency, and the urologist referred her for a psychological consultation, suggesting that Nancy's symptoms may be attributed to pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). Nancy was subsequently referred to a Pediatric Neuropsychiatry and Immunology Clinic which specialized in the evaluation and management of this condition.

Presentation and Relevant History

Upon evaluation, Nancy's symptoms were consistent with pediatric-onset obsessive-compulsive disorder (OCD) and were notable for a rapid progression in severity over the course of a few days. Nancy had no history of previous psychiatric or behavioral difficulties and no prior psychiatric treatment or hospitalizations. Her medical history was significant only for five GAS infections over the past 5 years, including the one that is relevant to her current presentation. Her first documented GAS infection, around 5 years of age, resulted in scarlet fever, but her parents denied any behavioral changes concurrent with that infection. Based on parent reports, pregnancy, delivery, and early childhood were unremarkable. Developmental milestones were met within normal limits. Family medical history was unremarkable for psychiatric conditions, including OCD, tic disorders, and attention deficit hyperactivity disorder.

Nancy's OCD severity was evaluated using the Children's Yale-Brown Obsessive-Compulsive Disorder Scale (CYBOCS); Nancy scored a 24 (out of a possible 40 points), which indicated moderate OCD severity. She described recurrent obsessions related to a fear that she would get sick due to a contaminant in the environment and that objects touched by other people were subsequently "contaminated" and may make her ill. Nancy also exhibited several compulsions that became functionally limiting for her and her family. She would lick her hands as a means to "clean" them. She frequently checked the bottom of her shoes to be sure she had not stepped in any "contaminants," such as dog poop.

Nancy had lab work conducted which showed elevated reactivity against Group A streptococcal proteins (antistreptolysin O titer = 946 (normal range 0–640) and anti-DNAseB titer = 2110 (normal range 0–375)). Her ESR and C-reactive protein results were within normal limits, and her antinuclear antibody was nonreactive. A test of her immunoglobulin levels for IgA, IgG, and IgM was within normal limits and showed no evidence for immune deficiency. Nancy had no focal neurological findings on exam, and did not exhibit any tics or adventitious movements; an MRI was deemed unwarranted at the time. To further evaluate Nancy's fine motor difficulties, she was administered with Grooved Pegboard and Beery-Buktenica

Developmental Test of Visual-Motor Integration (VMI). Although her basic fine motor skills were average on the pegboard, her visual motor skills fell in the 18th percentile, which when compared to her history of intact fine motor skills suggested a disruption of her visual-motor processing.

Nancy was determined to meet criteria for PANDAS. A referral was made for cognitive behavioral therapy in their local area. Nancy was also initiated on a 2-week course of a nonsteroidal anti-inflammatory drug (NSAID) using naproxen sodium, dosed at 10 mg/kg BID. A follow-up appointment to discuss additional management of her symptoms, including psychotropic medications, was scheduled for 6 weeks following this initial appointment.

Disease Course

At her 6-week follow-up appointment, Nancy stated her OCD symptoms had improved considerably. She had completed her course of naproxen without significant side effects and did not experience a worsening of her symptoms following discontinuation. She had also begun seeing a cognitive behavioral therapist for weekly sessions, and she reported that she felt more in control of her symptoms now that she was learning strategies to "fight" them. Her parents also endorsed feeling more confident knowing how to coach Nancy through times that she expressed OCD, separation anxiety, or increased irritability, thanks to strategies they learned as well. Her CYBOCS score was reduced to an 18, which indicated borderline/mild OCD severity. At her next follow-up appointment, 12 weeks following her initial evaluation, she and her family reported continued symptom improvement. The OCD obsessions were mostly transient, and she was no longer experiencing compulsions except on rare occasions when she felt stressed. Her CYBOCS had at that point decreased to 12, indicating subclinical OCD severity. It was determined that Nancy would continue in behavioral therapy for the additional 8 weeks. No further medical therapy was deemed necessary.

Discussion

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) and pediatric acute-onset neuropsychiatric syndrome (PANS) refer to the acute and dramatic onset of a constellation of neuropsychiatric symptoms in children, defined primarily by obsessive-compulsive and tic symptoms, and may further include symptoms of inattention, hyperactivity, food restriction, and separation anxiety [1, 2]. The diagnostic criteria for PANDAS detail a sudden onset of these symptoms following an antecedent Group A streptococcal (GAS) infection and require that these be the first time a child has displayed significant obsessive-compulsive or tic symptoms in their life. Further requirements for the diagnosis are a prepubertal age of onset, episodic exacerbation or remittance of symptoms in conjunction with further GAS infections, and neurological abnormalities, which

include motoric hyperactivity and adventitious movements, particularly of the hands and fingers. This diagnostic category was later broadened to include infectious triggers other than GAS and to include acute avoidance of food intake as an additional diagnostic criterion. This diagnosis has been termed pediatric acute-onset neuropsychiatric syndrome (PANS), and it should be noted that PANDAS and PANS are mutually exclusive diagnoses, with PANDAS being the appropriate diagnosis if the infection preceding symptom onset was a Group A streptococcal infection.

The PANDAS diagnosis was introduced by Dr. Susan Swedo at the National Institute of Mental Health in the 1990s and was the product of investigations into OCD symptoms in children with Sydenham chorea (SC). SC is a neuropsychiatric disorder characterized by involuntary, hyperkinetic movements and is recognized as the major neurological manifestation of acute rheumatic fever (ARF), a constellation of inflammatory conditions which occur following GAS infection.

While the pathogenesis of SC remains unknown, multiple neuroimaging studies suggest inflammatory involvement of the basal ganglia may underlie the varied neuropsychiatric symptoms of the disorder. The involvement of the basal ganglia in SC may explain why patients with SC also frequently display new-onset obsessive-compulsive symptoms, as the basal ganglia have been frequently implicated in the pathogenesis of OCD [2]. In studying the association between SC and OCD, Dr. Swedo and colleagues described a group of children who failed to meet criteria for SC, though displayed new-onset OCD symptoms following a GAS infection. The PANDAS diagnosis was subsequently proposed as a variant of SC, with the hypothesis that both disorders share a similar post-infectious, inflammatory etiology.

A cohort of PANDAS patients was described for the first time in 1998 [3]. Based upon age of onset, comorbid diagnoses, and phenomenology of obsessive-compulsive symptoms (i.e., contamination obsessions, ordering/arranging obsessions), the cohort of PANDAS patients described does not appear to differ considerably from the typical symptoms of pediatric-onset obsessive-compulsive disorder (OCD). However, the dramatic onset of these symptoms, periods of significant symptom exacerbation and remission, and association with recent streptococcal infections have been shown in cohort studies to differentiate between these two populations.

The introduction of PANDAS and PANS as unique diagnostic entities apart from pediatric OCD and tic disorders has been, and continues to be, controversial. The primary objection to this classification has been the assumption that, in PANDAS/PANS patients, the symptoms arise from an inflammatory or autoimmune etiology as opposed to the genetic or environmental factors which are hypothesized to typically underlie OCD or tic symptoms. This controversy has been compounded by a lack of available biomarkers for identifying PANDAS/PANS patients, a relatively low prevalence of OCD in the pediatric population (1–2%), and the association of OCD and tic symptoms with a nearly ubiquitous infection in school-age children (i.e., "strep throat").

Relevant Neuroanatomy and Pathophysiology

Multiple lines of evidence suggest dysfunction in cortical-striatal circuitry contributes to both OCD and tic disorder symptoms. Accordingly, the hypothesized mechanism in both PANDAS and SC involves an inflammatory response directed at these neural networks. Evidence for this hypothesis has been provided from an MRI study which displayed volumetric increases in the basal ganglia nuclei of PANDAS subjects compared to controls, as well as a positron emission tomography (PET) study which found increased activation of microglia, the resident immune cell in the brain, in PANDAS subjects compared to those with Tourette's syndrome [2].

Additional support for autoimmunity in PANDAS comes from the identification of reactivity of serum and CSF to postmortem human caudate and putamen samples [2]. Recently, this finding has been extended through experiments which infused serum from PANDAS subjects into the striatum of mice; serum from PANDAS subjects, compared to healthy controls, was found to bind selectively to the cholinergic acetyltransferase (ChAT)-expressing neurons of the striatum [4]. This binding was found to decrease in correlation with symptomatic reductions in OCD severity following intravenous immunoglobulin (IVIG) treatment in the PANDAS subjects [4].

Additional research is necessary to investigate these potential autoimmune antibodies in PANDAS subjects; furthermore, it should be noted that these antibodies have only been investigated in patients with PANDAS, while no autoimmune antibodies have been identified in patients with PANS. However, if future investigations demonstrate that these antibodies are reliably identifiable in patients with PANDAS/PANS and are pathogenically relevant to PANDAS/PANS symptomatology, it would provide evidence that PANDAS/PANS may more accurately be classified as an acute, post-infectious basal ganglia encephalitis.

Treatment Strategies

Few randomized, controlled treatment trials have been conducted in children with PANDAS, which limits a clinician's ability to make empirically informed treatment decisions for this population. As such, a number of consensus guidelines for treatment of PANDAS/PANS have been published by a consortium of academic investigators and clinicians, and these guidelines cover the use of psychotropic or behavioral interventions, antimicrobial therapies, and immunomodulatory therapies. These three approaches are complementary and can be pursued concurrently [5].

Symptomatic treatments for OCD and behavioral symptoms include psychoeducation, psychotropic medications, and cognitive behavioral therapies. The consensus recommendations are to begin as soon as possible following diagnosis given the delay between treatment initiation and expected benefit (e.g., 8–12 weeks for psychotropic medications including upward taper; 12–16 weeks for cognitive behavioral therapy). Psychotropic medications are often indicated based on the presenting

symptoms. For example, selective serotonin reuptake inhibitors (SSRIs) remain the first-line pharmacological intervention for OCD symptoms, while alpha-2 adrenergic agonists (clonidine and guanfacine) are the initial pharmacological intervention for tic symptoms. If comorbid attention deficit hyperactivity disorder (ADHD) symptoms are present, stimulants, atomoxetine, and alpha-2 adrenergic agonists, guanfacine and clonidine, may be indicated. Inpatient psychiatric hospitalization may be required for children with symptoms of self-injury, suicidality, or severe aggression. Hospitalization may also be required for children presenting with symptoms of severely restricted food or fluid intake that result in inadequate nutrition and hydration.

Behavioral interventions are also frequently indicated in the treatment of PANDAS-/PANS-related symptoms. Cognitive behavioral therapy (CBT) with exposure and response prevention (CBT/ERP) is the first-line choice for OCD and anxiety symptoms and has been found to be effective in treating OCD symptoms in PANDAS patients. Behavioral interventions may also include implementation of an Individualized Education Plan (IEP) or 504 Plan to provide school accommodations and services to support the child's specific needs and address the impacts of symptoms in the academic setting. For example, students with handwriting deterioration may benefit from the use of a computer for note taking, those with urinary frequency may be allowed to leave the class when needed, and a student with frequent absences related to the disorder may be excused from missed work, to name a few [6].

An additional consideration in the treatment of PANDAS/PANS involves antimicrobial therapy. The consensus guidelines suggest that all patients being evaluated for PANDAS/PANS receive a throat swab for evaluation of Group A streptococcal pharyngitis. The use of streptococcal serologies (i.e., antistreptolysin O and anti-DNAseB) for the diagnosis of PANDAS/PANS at a single time point (i.e., initial evaluation) is discouraged, though serial evaluations of streptococcal serologies displaying increasing titers may be indicative of a streptococcal infection in lieu of a throat swab and may aid in the diagnosis of PANDAS. Treatment of streptococcal pharyngitis typically involves oral, or alternatively intramuscular, penicillin, though may include cephalosporin or macrolide antibiotics for those with penicillin allergies. Azithromycin should be used cautiously given the emergence of macrolide-resistant streptococcal strains, and the potential for QT prolongation when used in combination with psychotropic medications which also prolong the QT interval, such as SSRIs and antipsychotics [7].

As stated in the consensus guidelines, there is currently insufficient evidence to support long-term use of antibiotics for prophylaxis against streptococcal infections in children with PANDAS/PANS. However, this practice is frequently employed clinically in children with PANDAS/PANS who display recurrent streptococcal infections or individuals with immunoglobulin deficiencies. Further research is warranted to determine the risks and benefits of prophylactic antibiotic children with PANDAS/PANS.

Bacterial infections other than Group A *Streptococcus* are an additional factor for consideration in the use of antimicrobial therapy. Case reports of childhood infections with *Mycoplasma pneumoniae* suggest that infections with this agent are

associated with the development of obsessive-compulsive symptoms, restless leg syndrome, and, rarely, necrotic lesions of the basal ganglia. Similar to serologies for Group A *Streptococcus*, serologies for *M. pneumoniae* may frequently return false-positive results, particularly when using single time point serologies of IgG and IgM titers against *M. pneumoniae.* Confirmatory testing using indirect immunofluorescence assays or PCR testing is recommended for evaluation of acute *M. pneumoniae* infection, and treatment with azithromycin or a tetracycline is warranted following confirmation, or a high degree of suspicion, of infection. Additional bacterial triggers of PANS in children, including Lyme disease or *Borrelia burgdorferi* infections, have not been reported in the scientific literature [7].

Finally, based upon the hypothesis that PANDAS and PANS are due to an inflammatory or autoimmune reaction, immune-modulating therapies have been employed in both research trials and clinical management in children with PANDAS. The first of these trials employed therapeutic plasma exchange (PEX), intravenous immunoglobulin (IVIG), and a "sham-IVIG" control group [8]. Results from this trial displayed a 58% and 70% decrease in OCD symptom severity from baseline to a 1-month follow-up in the IVIG and PEX groups, respectively, with no significant change in the "sham-IVIG" group [8]. A second clinical trial in PANDAS patients, employing IVIG versus a placebo infusion with a blinded, randomized design, failed to show a significant difference in the reduction of OCD symptom severity between baseline ratings and a 6-week follow-up evaluation [9]. The discrepant results from these two trials have cast doubt on the efficacy of IVIG in the treatment of PANDAS symptoms, though further research is needed to explain the discordant findings between these two trials.

A number of additional immunomodulatory therapies for the treatment of PANDAS/PANS symptoms have been reported in open-label case reports and included in the consensus treatment guidelines for the treatment of PANDAS/PANS [10]. The use of nonsteroidal anti-inflammatory (NSAID) therapies (commonly naproxen sodium, dosed at 10 mg/kg BID, maximum 500 mg per dose) in PANDAS/PANS patients has been shown to both decrease neuropsychiatric symptoms acutely in PANDAS/PANS patients and shorten the duration of symptom exacerbations following infections, though this intervention has yet to be investigated in a randomized clinical trial. Duration of these therapies is recommended to be approximately 6 weeks, with careful monitoring of symptoms of GI distress and NSAID-associated bruising or bleeding symptoms; longer-term therapy has been used in selected cases along with monitoring of liver function tests, CBC, BUN/creatinine, and urinalysis.

Both oral and IV steroids have also been employed in the treatment of the neuropsychiatric symptoms of PANDAS/PANS. A publication detailing the use of steroids in a community-based clinic of PANDAS/PANS patients reported the duration of symptom exacerbations was significantly shorter when either short courses (5 days) or extended courses (up to 8 weeks) were used, compared to exacerbations which were not treated with steroid therapy [10]. The authors note that side effects were common in those treated with steroids (44%), the most notable being a transient increase in the severity of neuropsychiatric symptoms in the days following steroid initiation.

Additional research is warranted into treatment responses in children who meet criteria for PANDAS/PANS. The heterogeneous response to IVIG, preliminary findings of autoimmune antibodies in PANDAS patients, and reports of response to NSAIDs and steroids suggest neuropsychiatric symptoms in some patients with PANDAS/PANS may be related to autoimmune antibodies, while others with PANDAS/PANS may display symptoms due to inflammatory cytokines. Should future research lead to a diagnostic test for autoimmune antibodies in PANDAS/PANS similar to current tests for NMDA receptor autoimmune encephalitis, it may allow for empirically validated therapies for PANDAS/PANS in the near future.

Clinical Pearls

1. Patients with a sudden, severe onset of OCD or tic disorders warrant a medical work-up to rule out causes of acute infections, such as Group A streptococcal pharyngitis. Those with marked movement disorder symptoms warrant a work-up for Sydenham chorea, including an echocardiogram to rule out rheumatic carditis. Other causes for sudden neuropsychiatric changes, such as viral and autoimmune encephalitis, should be ruled out when appropriate prior to provision of a diagnosis of PANDAS/PANS. This may require brain imaging, lumbar puncture, serology, etc. in order to thoroughly evaluate other symptom etiologies.
2. Patients who meet criteria for PANDAS/PANS may show benefit from short courses of anti-inflammatory medications, though treatment with additional first-line therapies for OCD or tic disorders may be warranted and necessary.
3. Children with mild OCD can experience exacerbation of their underlying symptomatology in the setting of stressors, which include infections. As a result, careful screening for the existence of signs and symptoms of OCD, anxiety, and other compulsive disorders should be done.

Lessons Learned About Neuropsychiatry

The contribution of the immune system to the development of neuropsychiatric disorders continues to be of significant interest to the fields of psychiatry and neurology. For disorders in which autoimmune antibodies have been identified, such as anti-NMDA receptor encephalitis, little controversy exists regarding the link between pathological immune processes and neuropsychiatric symptoms. For putative disorders such as PANDAS/PANS, the evidence for immune involvement is suggestive, though remains incomplete. However, with continuing advances in neuroimaging modalities, antigen discovery techniques and careful analysis of clinical data, the continued controversy over the diagnosis of PANDAS/PANS may soon be put to rest (Tables 23.1 and 23.2).

Table 23.1 Diagnostic criteria for pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)

1. Sudden onset of OCD/tic symptoms and an episodic course of symptom severity
2. Presence of OCD or tic disorder
3. Prepubertal age of onset
4. Temporal association between onset of symptoms and a GAS infection
5. Associated neurological abnormalities (adventitious movements, marked motoric hyperactivity, handwriting deterioration)

Swedo SE, Leckman JF, Rose NR. From research subgroup to clinical syndrome: modifying the PANDAS criteria to describe PANS (Pediatric Acute-onset Neuropsychiatric Syndrome). Pediatr Therapeut. 2012;2:113

Table 23.2 Diagnostic criteria for pediatric acute-onset neuropsychiatric syndrome (PANS). In addition to onset correlated with an infection agent other than GAS and symptoms that cannot be better explained by a known medical or neurological disorder, patients must experience an abrupt and dramatic onset of OCD behaviors or severe eating restrictions, along with at least two accompanying symptoms

(a) Markedly increased level of anxiety, particularly new onset of separation anxiety
(b) Emotional lability and/or depression
(c) Irritability, aggression and/or severely oppositional behaviors
(d) Deterioration in school performance, including sudden difficulties with concentration or learning
(e) Developmental regression (“baby talk,” temper tantrums)
(f) Sensory or motor abnormalities, including handwriting deterioration, new onset of motor hyperactivity, adventitious movements, pronator drift, or truncal instability
(g) Somatic signs, including increased urinary frequency or increased urge to urinate, enuresis, or sleep disorder (e.g., insomnia, night terrors, refusal to sleep alone)

Swedo SE, Leckman JF, Rose NR. From research subgroup to clinical syndrome: modifying the PANDAS criteria to describe PANS (Pediatric Acute-onset Neuropsychiatric Syndrome). Pediatr Therapeut. 2012;2:113

References

1. Chang K, Frankovich J, Cooperstock M, Cunningham MW, Latimer ME, Murphy TK, Pasternak M, Thienemann M, Williams K, Walter J, Swedo SE, PANS Collaborative Consortium. Clinical evaluation of youth with pediatric acute-onset neuropsychiatric syndrome (PANS): recommendations from the 2013 PANS consensus conference. J Child Adolesc Psychopharmacol. 2015;25(1):3–13.
2. Williams KA, Swedo SE. Post-infectious autoimmune disorders: Sydenham’s chorea, PANDAS and beyond. Brain Res. 2015;1617:144–54.
3. Swedo SE, Leonard HL, Garvey M, Mittleman B, Allen AJ, Perlmutter S, Lougee L, Dow S, Zamkoff J, Dubbert BK. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. Am J Psychiatry. 1998;155(2):264–71.
4. Frick LR, Rapanelli M, Jindachomthong K, Grant P, Leckman JF, Swedo S, Williams K, Pittenger C. Differential binding of antibodies in PANDAS patients to cholinergic interneurons in the striatum. Brain Behav Immun. 2018;69:304–11. https://doi.org/10.1016/j.bbi.2017.12.004.

5. Swedo SE, Frankovich J, Murphy TK. Overview of treatment of pediatric acute-onset neuropsychiatric syndrome. J Child Adolesc Psychopharmacol. 2017;27(7):562–5.
6. Thienemann M, Murphy T, Leckman J, Shaw R, Williams K, Kapphahn C, Frankovich J, Geller D, Bernstein G, Chang K, Elia J, Swedo S. Clinical Management of pediatric acute-onset neuropsychiatric syndrome: part I—psychiatric and behavioral interventions. J Child Adolesc Psychopharmacol. 2017;27(7):566–73.
7. Cooperstock MS, Swedo SE, Pasternack MS, Murphy TK. Clinical management of pediatric acute-onset neuropsychiatric syndrome: part III—treatment and prevention of infections. J Child Adolesc Psychopharmacol. 2017;27(7):594–606.
8. Perlmutter SJ, Leitman SF, Garvey MA, Hamburger S, Feldman E, Leonard HL, Swedo SE. Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood. Lancet. 1999;354(9185):1153–8.
9. Williams KA, Swedo SE, Farmer CA, Grantz H, Grant PJ, D'Souza P, Hommer R, Katsovich L, King RA, Leckman JF. Randomized, controlled trial of intravenous immunoglobulin for pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. J Am Acad Child Adolesc Psychiatry. 2016;55(10):866–7.
10. Frankovich J, Swedo S, Murphy T, Dale RC, Agalliu D, Williams K, Daines, Hornig M, Chugani H, Sanger T, Muscal E, Pasternack M, Cooperstock M, Gans H, Zhang Y, Cunningham M, Bernstein G, Bromberg R, Willett T, Brown K, Farhadian B, Chang K, Geller D, Hernandez J, Sherr J, Shaw R, Latimer E, Leckman J, Thienemann M. Clinical management of pediatric acute-onset neuropsychiatric syndrome: part II—use of immunomodulatory therapies. J Child Adolesc Psychopharmacol. 2017;27(7):574–93.

Part VI

Hormonal Regulation, Arousal, and Sleep

Introduction

> The brain is a world consisting of a number of unexplored continents and great stretches of unknown territory.
>
> Santiago Ramón y Cajal, MD, PhD

This section represents a variety of conditions involving complex mental states and regulation of homeostasis. The subjects of hypothalamic dysfunction, circadian rhythmicity, and alteration of consciousness are complexly interwoven topics involving large-scale physiological systems. Disorders that impact these systems overlap a broad range of diagnostic categories and require an appreciation of multi-system organization. Seeking neuropsychiatric explanations for these presentations requires the clinician to appreciate atypicality of psychiatric presentations and complex medical comorbidity while considering how large-scale functions of alertness, sleep, and mood regulation are managed in the brain. They also require an appreciation of neurological localization, psychiatric diagnostics, neurodevelopment, epilepsy, and other neuropsychiatric comorbidities explored in previous chapters. Because of their large-scale system involvement, none of these cases has an obvious and clear-cut presentation.

The first case encompasses an in-depth exploration of pediatric catatonia and delirium. This is a significantly underappreciated subject which integrates both historical underpinnings of psychiatry with contemporary neuropsychiatric and diagnostic approaches. It is an under-recognized disorder, particularly in pediatric patients, and integrates aspects of medical management, neurodevelopmental disability, and complex neuropsychiatric diagnosis. The second case explores the complex neuropsychiatric presentation, management, and outcome of hypothalamic hamartoma. Although uncommon, this condition reveals an important neuropsychiatric role of the

hypothalamus: emotional regulation. Finally, the third case explores sleep disorders including periodic limb movement syndrome, restless legs syndrome, and obstructive sleep apnea and their impact on attention and executive function in children.

These three cases together provide a conclusory lesson, illustrative of what is often the job of the pediatric neuropsychiatrist: differentiation between neuropsychiatric conditions utilizing clinical acumen and modern diagnostic tools. Often, the question is whether an atypical presentation is a psychiatric variant or whether it hides an underlying cause which might necessitate specific management. Here are explored the differential diagnostic conundrums of catatonia versus delirium, primary sleep disorder versus ADHD, and spontaneous rage versus mood reactivity. These represent very specific diagnostic dilemmas in ways which can be broadly applied to pediatric neuropsychiatric diagnosis and treatment.

24

Catatonia in an Adolescent Girl with Inflammatory Bowel Disease: Complexity of Diagnosis, Treatment, and 3-Year Outcome

Allan Michael Andersen and Lee Elizabeth Wachtel

Case

Mary, a 15-year-old female with a 2-year history of ulcerative colitis, was transferred to an academic hospital following severe behavioral disturbance in the setting of corticosteroid administration and colectomy. Her premorbid functioning had been good, with involvement in multiple extracurricular activities, social relationships, and high academic achievement. Family history was significant for a mother with ulcerative colitis and steroid-associated depression in the past, a maternal aunt with possible bipolar disorder, and a father with obsessive-compulsive disorder and autism spectrum disorder traits.

Prior to transfer, Mary had presented to the outside hospital in a demoralized mood over failure to respond to multiple outpatient drug trials for ulcerative colitis, including methotrexate, 6-mercaptopurine, and prednisone. Intravenous hydrocortisone doses totaling 200 mg daily and steroid enemas were administered without improvement. A consulting psychiatrist was asked to evaluate the patient for anxiety and paranoia. She endorsed delusions that nursing staff had been replaced with imposters, appeared to be responding to visual and auditory hallucinations, had impaired alertness and attention, and had difficulty following simple instructions.

Treatment was started with risperidone for presumed steroid-induced psychosis with possible delirium, increasing to 2 mg daily over 3 days. At the same time, lorazepam was started as needed for agitation, increasing up to 2 mg every 6 h over

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the same 3-day period. Colectomy was performed 3 days later due to refractory rectal bleeding. Lorazepam and risperidone were discontinued abruptly in the post-operative setting.

On her third postoperative day, Mary presented with a sudden change in clinical status, exhibiting stupor, mutism, waxy flexibility, negativism, verbigeration, echolalia, low-grade fever, and tachycardia. Lorazepam was resumed and increased to 3 mg intravenously every 4 h, but doses led to only temporary, limited improvement of psychomotor symptoms. She endorsed nihilistic delusions of self and family members dying, losing jobs, and becoming divorced. Head CT, lumbar puncture, MRI, and EEG were all normal, and serum creatine phosphokinase values were within normal limits, ruling out neuroleptic malignant syndrome (NMS).

Due to concern for catatonia and the potential need for electroconvulsive therapy (ECT), the patient was transferred to an academic medical center where consultants from child psychiatry were called. On arrival, her presentation was more suggestive of delirium than catatonia, with waxing and waning consciousness, delusions, inattention, and disorganized speech. Motor signs of catatonia were absent. A gradual taper of lorazepam and the addition of low-dose haloperidol were therefore recommended to treat suspected delirium. She tolerated these interventions but continued to have intermittent periods of agitation and endorsed hallucinations of a nurse flying outside her window and paranoid delusions that she was being monitored and videotaped. Haloperidol was discontinued due to mild extrapyramidal symptoms and risperidone restarted. Over several days she gradually improved, with less disorientation, fewer hallucinations, improved mood stability, and resolution of her mild vital sign instability. Mini-Mental Status Exam (MMSE) improved from 18/30 to 27/30 during this time period.

Transfer to inpatient child psychiatry for further evaluation was recommended, but given Mary's improvement her family opted for discharge while continuing her lorazepam taper. On her first day home, the family noticed occasional odd behaviors including leaning lower and lower over the toilet as if about to fall in, requiring her mother to pull her back up, interspersed with periods of normal behavior. The following day, she was extremely energized, impulsively grabbed her mother's keys and attempted to get into her car and drive away. Her third day home, she saw her surgeon for a follow-up visit and was noted to have reduced speech, an odd affect, and made a bizarre statement that she had a penis. On her fourth day home, she refused her morning dose of lorazepam and over the following hours became enuretic, refused food and water, and stated that she was pregnant.

Re-hospitalization

Noticing this deterioration, Mary's mother brought her back to the Emergency Department of the same academic hospital where she was evaluated and found to be agitated and disoriented, with a vacant affect, staring spells, and mild tachycardia. She was directly admitted to the child psychiatry unit with ongoing pediatrics and GI consultation.

Over the following 2 weeks, her slow lorazepam taper continued, and Mary was continued on antipsychotic medication, but symptoms of delirium were slow to improve. She demonstrated ongoing delusions that she was dead and had three children, periods of elevated affect, and impulsive behavior alternating with periods of psychomotor slowing and echolalia. Further medical workup included urine toxicology, serum ceruloplasmin, ophthalmological evaluation for Kayser-Fleischer rings, ANA, anti-dsDNA, anti-Smith, anti-thyroglobulin, anti-TPO, anti-VGKC, and anti-NMDA serum antibodies, serum B12, folate, vitamin D 25-OH, vitamin E, vitamin B1, serum TSH, T4, and free T3, HIV, STS, ammonia, and thiamine, all of which were negative or within normal limits. ESR and CRP trended down during her course. Urine heavy metals and porphyrins were not obtained due to difficulty with urine collection and clinical improvement during her course. Her hematocrit remained stable with only mild, intermittent rectal bleeding.

Given her negative medical workup and lack of explanation for persistent delirium despite supportive treatment, empiric treatment for catatonia with lorazepam was resumed, with limited effect. Given the lack of improvement, treatment with ECT was recommended by the inpatient team following review of the case by two independent child psychiatrists. With consent from her parents, bilateral ECT was initiated, with EEG seizure durations ranging from 30 to 60 s. She exhibited a dramatic improvement in symptoms over the following days.

After 18 bilateral treatments, the patient had a full remission of catatonic symptoms, with a Bush-Francis Catatonia Rating Scale of 0 and a Mini-Mental Status Exam score of 30/30. Throughout Mary's course of ECT, evidence of underlying bipolar affective disorder symptomatology was noted (brief periods of elevated mood, rapid speech, and disinhibited behavior), prompting initiation of lithium and olanzapine at 2.5 mg daily. Lithium was titrated up to a serum level of 0.4 meq/l and was held the night before and morning of ECT in order to minimize risk of post-ECT confusional state.

Follow-Up Treatment

Mary was discharged to home on bilateral maintenance ECT (m-ECT), beginning weekly for 4 weeks, and gradually tapered down over 4 weeks to monthly for the next 9 months. She resumed school with accommodations under an Individualized Education Plan (IEP) due to impaired working memory, which was thought to be related to both her catatonia and m-ECT. She graduated high school 1 year behind her class but had significant challenges over 3 years following her hospitalization. Six months after m-ECT was discontinued, she experienced a severe manic episode with psychotic symptoms but no signs of catatonia. She once again responded well to ECT, which was then maintained on a weekly to biweekly basis as an outpatient, with the goal to eventually taper her back to monthly treatments.

In the past 3 years, Mary also suffered from persistent post-traumatic stress disorder symptoms including flashbacks and becoming easily startled. She has also had persistent tachycardia and recurrent episodes of feeling "frozen" and

unable to move, which respond to lorazepam 0.5 mg PRN administration. Lithium was discontinued after approximately 2 years due to worsened renal function, and she currently continues on a regimen of bilateral m-ECT monthly to biweekly, lamotrigine, aripiprazole, lorazepam, and guanfacine, with close monitoring by her outpatient psychiatrist. Yoga and meditation have helped with anxiety. Mary continues to be followed by her gastroenterologist, but her inflammatory bowel disease (IBD) has been difficult to manage, with the development of a fistula requiring an ileostomy. Conclusive diagnosis of her IBD has been elusive, with mixed signs of Crohn's and ulcerative colitis on both anatomic and serologic testing.

Patient Perspective

Mom:

"The tricky part is keeping catatonia back in the box. I always feel like it's lurking. I have to stay on top of it or we could have a major setback." Mom notices when the patient gets a "certain look in her eye…I can sense that something's off." She also notes repetitive hand movements, difficulty speaking (appears to have word-finding difficulties, has to "pause and think") and a "deer in the headlights look."

Mary:

"I don't feel very hopeful." Mary reports that it is difficult to think about a long-term plan for her life when she has so much difficulty with short-term tasks. She continues to have episodes of intense fear and "freezing" that are debilitating.

Diagnostic Impression

Catatonia is a neurobiological syndrome of distinct motor, vocal, and behavioral symptoms that were initially classified as a single entity in 1874 by Karl Kahlbaum. Erroneously subsumed for decades within the diagnosis of schizophrenia, catatonia is actually found in a wide range of psychiatric, neurological, somatic, and drug-related etiologies that may occur in both youth and adults. The most common comorbidity of catatonia is an affective disorder. The syndrome is characterized by profound psychomotor changes, classically including immobility, mutism, and bizarre postures and behaviors, as well as vocal symptoms including mutism or reduced communication, echolalia, or verbigeration. However, "the clinician who looks only for the classic description of catatonia will miss many cases" [1–3]. A list of catatonia signs is provided in Table 24.1.

In fact, over 40 signs of catatonia have been described [1, 3]. The DSM-5 specifies a clinical picture dominated any combination of 3 or more from a possible 12 signs of catatonia, of which some appear as frank opposites (e.g., stupor and agitation), with notation that individuals often alternate between different forms of catatonia. The DSM-5 also cautions against the extreme aggression and self-injurious behavior

Table 24.1 Catatonia signs

Excitement	Extreme hyperactivity, constant motor unrest which is apparently non-purposeful
Immobility/stupor	Extreme hypoactivity, immobility. Minimally responsive to stimuli
Mutism	Verbally unresponsive or minimally responsive
Staring	Fixed gaze, little or no visual scanning of environment, decreased blinking
Posturing/catalepsy	Maintains posture(s), including mundane (e.g., sitting or standing for hours without reacting)
Grimacing	Maintenance of odd facial expressions
Echopraxia/echolalia	Mimicking of examiner's movements/speech
Stereotypy	Repetitive, non-goal-directed motor activity (e.g., finger-play, repeatedly touching, patting or rubbing self)
Mannerisms	Odd, purposeful movements (hopping or walking tiptoe, saluting passersby, exaggerated caricatures of mundane movements)
Verbigeration	Repetition of phrases or sentences
Rigidity	Maintenance of a rigid position despite efforts to be moved
Negativism	Apparently motiveless resistance to instructions or to attempts to move/examine the patient. The patient does the opposite of the instruction
Waxy flexibility	During reposturing, patient offers initial resistance before allowing himself to be repositioned (similar to that of bending a warm candle)
Withdrawal	Refusal to eat, drink, and/or make eye contact
Impulsivity	Patient suddenly engages in inappropriate behavior (e.g., runs down the hallway, starts screaming, or takes off clothes) without provocation. Afterward, cannot explain
Automatic obedience	Exaggerated cooperation with examiner's request, or repeated movements that are requested once
Passive obedience (mitgehen)	Raising arm in response to light pressure of finger, despite instructions to the contrary
Gegenhalten/ counterpull	Resistance to passive movement that is proportional to strength of the stimulus; response seems automatic rather than willful
Ambitendency	The patient appears stuck in indecisive, hesitant motor movements
Grasp reflex	Strike open palm of patient with two extended fingers of examiner's hand. Automatic closure of patient's hand
Perseveration	Repeatedly returns to the same topic or persists with same movements
Combativeness	Usually in an undirected manner, without explanation

that may occur during episodes of catatonia, and which may require special clinical care and supervision to mitigate against injury [4].

A classification scheme containing three main forms of catatonia has been proposed [5]: hypoactive (retarded/withdrawn/delirious), hyperactive (excited/manic/nonmalignant/hyperkinetic), and malignant or lethal catatonia, the latter characterized by hyperthermia, rigidity, and autonomic instability. Malignant catatonia was initially recognized by Stauder in 1934 and represents a true medical emergency requiring acute treatment as untreated malignant catatonia is fatal in 10–20% of cases, often within days [2, 3, 6].

The DSM-5 classifies catatonia as attributed to a specific mental disorder or medical condition, or "not elsewhere classified" (NEC), with exclusionary criteria that it does not occur solely during the course of a delirium [7]. The diagnosis of catatonia associated with another mental disorder (293.89) requires the presence of 3 of 12 signs of catatonia including stupor, cataplexy, waxy flexibility, mutism, negativism, posturing, mannerism, stereotypy, agitation, grimacing, echolalia and echopraxia. Signs and symptoms should not be secondary to another medical or psychiatric disorder and should cause significant distress and impairment to the individual [7].

Historical Perspective of Catatonia

Historically, catatonia was quickly purloined by Kraepelin into the diagnosis of dementia praecox at the end of the nineteenth century and tightly linked to the diagnosis of schizophrenia due to theoretical dogma until very recently. Multiple catatonia scholars called for the classification of catatonia within a "home of its own," separate from schizophrenia, and further literature has called for the recognition of catatonia as an independent medical syndrome [2, 8, 9]. Over the last three decades, the field of neuropsychiatry has begun to find catatonia again, "hidden in plain sight" [10] among a wide variety of neuropsychiatric and medical settings, in both children and adults. Mood disorders are now recognized as the most common underlying neuropsychiatric illness in catatonia, with psychotic illness the second most frequent comorbidity [5, 11]. In children, four large studies have documented catatonia in 12–20% of individuals with autism spectrum disorder (ASD), and multiple case reports and case series describe the clinical courses and response to ECT among such children, where psychomotor agitation in the form of extreme self-injury may be a prominent symptom [10, 12–15]. Catatonia has also been recognized to occur in many other neurodevelopmental and genetic conditions, including Down's, fragile X, and velocardiofacial syndromes [16–18].

Despite this progress, catatonia is still underdiagnosed in both adult and pediatric populations [10]. In one retrospective study of over 100 inpatients, catatonia was diagnosed in 17.8% of cases, yet only two of these patients had been correctly diagnosed during their initial hospital course [14]. This is likely due to a combination of factors: the lingering effects of former classification schemes, diagnostic overshadowing when catatonia occurs in settings other than schizophrenia (particularly developmental disabilities), substandard care environments with little clinical attention paid to signs of catatonia, and a lack of awareness of the broad criteria for catatonia, its multiple forms, its variable time course, and the breadth of clinical conditions in which it may manifest [2, 3]. ECT-related stigma also

contributes to the lack of ready recognition of the catatonic syndrome, given that the anti-catatonic paradigms include benzodiazepines in escalating dosages and ECT when the latter is insufficient, or the severity of the clinical situation necessitates more rapid symptom resolution. This may be particularly relevant in child psychiatry, where practitioners may be even more reticent to readily consider ECT as a therapeutic option [19].

Neuropsychiatric Reflections of This Case

The case presented here is the second report in the literature of catatonia associated with IBD. Doherty and colleagues reported a 17-year-old male with colitis who received high-dose hydrocortisone by IV. He subsequently developed "catatonic stupor" but had an "excellent" response to a course of five ECT treatments. The authors noted aptly, "with any patient on high-dose steroid medication the clinician should take good note of any behavioral or psychological change" [20].

In many respects, this young woman's case was typical of catatonia and provides a comprehensive overview of the process of diagnosis and treatment of the syndrome, including consideration of differential diagnoses, attempt to treat any underlying contributing conditions, and the application of catatonia-specific treatments.

The case further illustrates how the current diagnostic criteria and treatment algorithms both aid and hinder clinicians presented with catatonic patients. The current DSM-5 criteria allow for diagnostic heterogeneity, but potentially at the cost of diagnostic specificity. Specifically, criterion D in the DSM-5 prohibits the diagnosis of catatonia exclusively during the course of a delirium, which may not actually be in accord with clinical reality, and likely complicated the process of diagnosis and treatment in our case [7].

This patient had multiple known risk factors for catatonia. First, there was a strong family history of both affective illness and suspected autism spectrum disorder. Such genetic vulnerability may have predisposed the patient to the development of catatonia during her worsening medical illness and the significant emotional distress she experienced regarding her deteriorating state of health and pain.

Next, she was exposed to high-dose corticosteroids, which are well-known triggers for psychopathology, including affective, psychotic, and catatonic symptoms. She was subsequently exposed to and abruptly withdrawn from high-dose benzodiazepines and additionally exposed to a high-potency neuroleptic, both known risk factors for catatonia [3].

Finally, her longitudinal course during and after hospitalization suggested the presence of an underlying major affective syndrome; as previously discussed, affective illness is the single most common catatonia-associated neuropsychiatric illness

in adults [5]. Her long-term course has been significant for persistent anxiety, autonomic dysfunction, and impairment in cognition, also often present in catatonia patients [21, 22].

Although catatonia was suspected early in this young lady's course, her catatonic symptoms were not consistent over time, often did not resemble "classic" catatonia, and at many times appeared more consistent with delirium. In fact, she most likely had superimposed catatonia and delirium for much of her course, despite the theoretical contradiction to giving both diagnoses per the DSM-5 [4]. Emerging evidence from adults in intensive care unit settings suggests that a substantial proportion of those in intensive care experience both delirium and catatonia, often in combination [23, 24].

In general, clinical guidelines have suggested that the treatment of delirium takes precedence over catatonia when both are suspected [1, 5]. This patient's medical workup was extensive and appropriate in a case when both delirium and catatonia are suspected but was time-consuming and delayed treatment initiation. During this time, specific treatment for catatonia, including lorazepam and ECT, was not offered because both can worsen delirium [25–27]. At the same time, the treatment of delirium includes low-dose antipsychotics, which may worsen catatonia, making treatment selection challenging from both angles. Interestingly, case reports do document the efficacy of ECT in relieving delirium [28, 29]. In the end, even though her clinical picture was mixed, her excellent response to ECT served as a key factor in confirming her diagnosis of catatonia.

Relevant Neuroanatomy and Pathophysiology

It is now known that catatonia occurs in a wide variety of medical and psychiatric settings, including mood disorders, schizophrenia, pervasive developmental disorders, drug exposures, endocrinopathies, and infectious diseases [2, 6, 30, 31]. Autoimmune conditions affecting the brain, such as systemic lupus erythematosus, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), and anti-NMDA encephalitis, are commonly found in the catatonia literature [32–34]. Corticosteroid exposures have also been linked to catatonia, both iatrogenic, as in one case where steroids were given for the treatment of dermatomyositis [35], and endogenous [36], as in one case of ACTH-secreting tumor. In many cases, an underlying neuropsychiatric illness is known or suspected, and there may be additional medical or neurologic symptoms that worsen with the progression of catatonic symptoms, as in our case above. The sheer diversity of clinical situations associated with the syndrome in case reports and case series has

led some to hypothesize that catatonia is a final common pathway for severe neuropsychiatric illness [1].

Despite increased awareness of the variety of clinical scenarios in which catatonia may manifest itself, its precise underlying pathophysiology is unknown. Multiple theories [6] have been proposed, taking into account the specific clinical features of catatonia, the breadth of its known etiologies, and its response to specific treatments, namely, GABAergic medications and ECT [2, 3].

The motor circuitry dysfunction model implicates frontal-subcortical circuits and other circuits and proposes disrupted GABAergic and dopaminergic transmission between orbitofrontal structures and the lateral hypothalamus, accounting for the hyperthermia seen in some cases, and the prominent motor features of catatonia. Dopamine blockade by neuroleptics supports this model [37].

The neurotransmitter model focuses on the roles of GABA, glutamate, and dopamine and is supported by the dramatic clinical responses produced by GABAergic medications in catatonic patients, their high tolerance for such medications, and imaging findings showing decreased GABAa receptors in the left sensorimotor cortex found in at least one study. The theory is further supported by the clinical observation that dopamine receptor antagonists (neuroleptics) can provoke or worsen catatonia [3, 37].

The epilepsy model proposes that clinical similarities exist between psychomotor seizures and catatonic symptoms. Their responses to the same treatments (GABAergic anticonvulsants and ECT) also link the two disorders. Although EEG recordings in catatonic patients typically do not show epileptic activity, a pattern of diffuse slowing may be seen, consistent with nonconvulsive status epilepticus. Alternately, and of note, such EEG findings could also be accounted for by delirium.

The genetic model accounts for the fact that some genetically transmitted syndromes such as Prader-Willi syndrome have an increased incidence of catatonia, possibly related to the fact that some GABA substrates are encoded for on the 15q11-13 region [38, 39].

The endocrine model proposes that ECT restores neuroendocrine function in the hypothalamic-pituitary-adrenal axis. Gjessing originally linked periodic catatonia to thyroid abnormalities and hypothalamic dysfunction, and multiple case reports associate endocrinopathies and catatonia [2, 3].

Finally, the immune model proposes that immune response to infectious diseases and other processes play a role in the pathogenesis of catatonia. This is supported by a number of case reports and series in both children and adults [32, 33]. Further supporting this avenue of research are findings that benzodiazepines modulate the HPA axis and can directly alter immune function via benzodiazepine receptors on immune cells [6].

Treatment Strategies

Like delirium, catatonia should be considered in any case when a patient's responsiveness and psychomotor function deteriorate, particularly if there are known risk factors for catatonia. The diagnosis of catatonia requires a thorough history, clinical examination, laboratory evaluation, and process of differential diagnosis to seek the cause of the disturbance. We suggest the following diagnostic and treatment algorithm, as shown in Fig. 24.1, which is applicable in both pediatric and adult patients.

Some signs such as mutism and immobility will be apparent during a routine mental status examination. Others, particularly motor abnormalities such as automatic obedience or gegenhalten, must be specifically elicited as part of a structured neuropsychiatric examination, as detailed by Pincus [40]. The most striking symptoms such as posturing and waxy flexibility are present only in a minority of cases but are strongly indicative of catatonia when present. In patients with autism, it should be noted that repetitive or stereotypic behaviors including echolalia, mutism, grimacing, stereotyped behaviors or mannerisms, and self-injury may also occur at baseline; indeed, the crossover between many symptoms of autism and catatonia has led to the hypothesis that autism may itself be a forme fruste of catatonia [41]. Symptoms may increase insidiously over a prolonged period, culminating in a

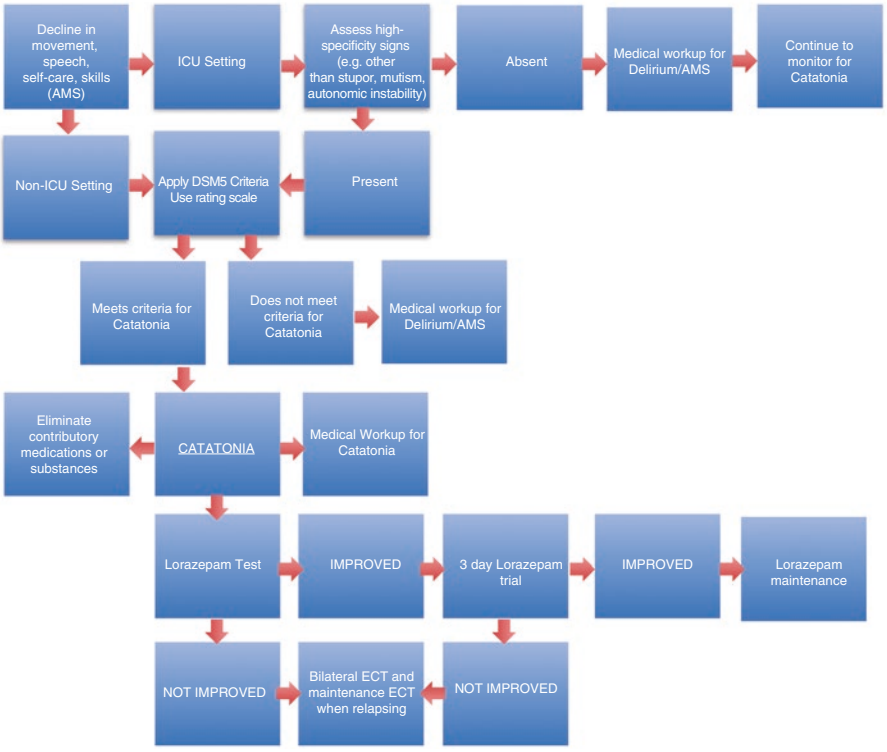

Fig. 24.1 Treatment algorithm

severe state of catatonia, which necessitates vigilance on the part of the clinician caring for the autistic patient. Only a significant departure from baseline autistic symptoms suspicious for catatonia, which often occurs in adolescence, should be taken as evidence of catatonia.

When catatonia is suspected, use of a rating scale to aid in making the diagnosis and assessing severity is recommended. The Bush-Francis Catatonia Rating Scale is the most commonly used and is our recommendation due to its ease of integration during psychiatric evaluation. It offers a threshold score for making a diagnosis of catatonia and has excellent sensitivity and specificity and good inter-rater reliability [30].

Following identification of the catatonic syndrome, differential diagnosis is important. An outline of differential diagnosis is provided in Table 24.2. Patients that fit the hypoactive of hyperactive pattern have distinct differential diagnostic

Table 24.2 Differential diagnosis of catatonia

The differential diagnosis of catatonia among hyperkinetic disorders includes:
1. Acute dystonia
2. Tardive dyskinesia
3. Akathisia
4. Withdrawal dyskinesias
5. Tics/Tourette disorder
6. Selective mutism
7. Conversion disorder
8. Compulsions in obsessive-compulsive disorder
9. Epilepsy
10. Delirium
11. Delirious mania
12. Abnormal illness behavior
The differential diagnosis among hypokinetic disorders includes:
1. Parkinsonism and Parkinson's disease
2. Stiff person syndrome
5. Epilepsy
6. Status epilepticus
7. Delirium
8. Coma
9. Cerebrovascular events
10. Vegetative states
11. Critical illness myopathy or polyneuropathy
12. Autoimmune encephalopathy
13. Selective mutism
14. Conversion disorder
15. Abnormal illness behavior
The differential diagnosis when catatonic signs are present with autonomic changes and muscle stiffness[a]:
1. Malignant hyperthermia
2. Neuroleptic malignant syndrome
3. Serotonin syndrome

[a]Special attention is indicated when autonomic changes are present with muscle stiffness as these may represent malignant catatonia, a medical emergency

patterns. For patients who present with malignant or lethal catatonia, there is additional urgency due to the high mortality rate associated with such. It is also important to note that catatonic symptoms often wax and wane, and patients may transition between various catatonic presentations during their illness course, and thus each catatonic state represents a state of high risk [5].

As illustrated by our case, delirium is a particularly important consideration within the differential diagnosis as it may mimic the hyperactive and hypoactive forms of catatonia. This is particularly true in intensive care settings where the prevalence of delirium is high. A recent prospective cohort study of 136 patients in an intensive care setting demonstrated that while 43% had only delirium and 3% had only catatonia, fully 31% had both illnesses, suggesting a possible pitfall of the DSM-5 catatonia criteria [23]. Because the signs most common to both delirium and catatonia in ICU settings are non-specific, including autonomic abnormality, stupor, staring, and mutism, an alternate diagnostic algorithm may be indicated in this setting that places more emphasis on high-specificity signs [24].

Numerous medical and neurologic conditions have been identified as etiologically linked to catatonia in various case reports and case series, as detailed in Table 24.3, and should be considered as potential underlying conditions in need of identification and treatment. Basic laboratory investigations in catatonia should include a CBC, CMP, ESR, brain MRI, EEG, CSF analysis, ANA, urine and organic metabolic testing, and serum CPK. A drug screen including common illicit drugs is also recommended. Additional laboratory testing may be indicated, as shown in Table 24.4, depending on the index of clinical suspicion of other diseases. Review of previously administered medications, particularly benzodiazepines, dopaminergic drugs, and other GABAergic medications is essential as discontinuation of these can prompt catatonia. Regardless of etiology, however, the anticatatonic treatment paradigms remain the same and should be rapidly implemented in any case of catatonia.

Although there are currently no validated biomarkers for the diagnosis of catatonia, response to lorazepam may be diagnostic. A "lorazepam challenge test," or test dose of 1 or 2 mg of lorazepam administered per os, intramuscularly, or intravenously, may result in a clinically observable, and sometimes dramatic, change in catatonic symptoms within 5 min. If no change is observed, an additional dose should be given within 5 min if intravenous, 15 min if intramuscular, or 30 min if per os. If an improvement is observed, regular dosing of lorazepam can begin. Dosing may be as high as 24 mg daily in adults to maintain symptom resolution, in many cases without appreciable sedation. In one naturalistic study of 66 children, doses of up to 15 mg daily were given with few side effects and 65% of patients improved [42].

Of note, other GABAergic medications including barbiturates have been used for the same purpose, as has zolpidem more commonly in Europe. In France, the "zolpidem challenge test" often replaces that of lorazepam. However, barbiturates have a less favorable safety profile, and zolpidem can only be administered orally. Antiepileptics including valproate, carbamazepine, phenytoin, topiramate, and

Table 24.3 Etiologies found in catatonia

Psychiatric
Bipolar disorder
Major depressive disorder
Schizophrenia/schizoaffective disorder
Obsessive-compulsive disorder
Post-traumatic stress disorder
Tic disorders/Tourette syndrome
Conversion disorder/psychogenic catalepsy
Developmental/genetic
Intellectual disability including Down's syndrome
Autism spectrum disorder
Childhood disintegrative disorder
Prader-Willi syndrome
Metabolic
Hypercalcemia
Diabetes mellitus
Hepatic encephalopathy
Homocystinuria
Tay-Sachs disease
Wilson's disease
Diabetic ketoacidosis
Porphyria
Neurologic
Epilepsy
Fatal familial insomnia
Dystonia
Neuroleptic malignant syndrome
Bilateral globus pallidus disease
Thalamic and parietal lobe lesions
Frontal lobe disease
Cerebrovascular disease
Head trauma
Kleine-Levin syndrome
Autoimmune/paraneoplastic
Anti-NMDA receptor encephalitis
Lupus erythematosus
PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections)
Infectious
Encephalitis or other CNS infection
HIV/PML
Tertiary syphilis
Substance-induced
Alcohol, benzodiazepine, gabapentin, or dopaminergic agent withdrawal
Neuroleptics

(continued)

Table 24.3 (continued)

Corticosteroid
Illicit drugs including synthetic cannabinoids, MDMA, cocaine, hallucinogens
Ciprofloxacin
Bupropion
Baclofen

Table 24.4 Laboratory testing to consider in catatonia

Serum creatine kinase (CK)
Complete blood count (CBC)
Comprehensive metabolic panel (CMP)
Urinalysis (UA)
Erythrocyte sedimentation rate (ESR)
Serum vitamin B12
Serum folate
Serum vitamin D 25-OH
Serum vitamin E
Serum vitamin B1
Serum thyroid-stimulating hormone (TSH)
Serum free triiodothyronine (free T3)
Serum free thyroxine (free T3)
Human immunodeficiency virus (HIV)
Serology test for syphilis (STS)
Serum ammonia
Serum iron
Antinuclear antibodies
Anti-double-stranded DNA (anti-dsDNA)
Anti-Smith antibody
Anti-thyroglobulin antibody
Anti-thyroperoxidase (anti-TPO)
Magnetic resonance imaging (MRI) of the brain with and without contrast
Lumbar puncture (LP) for cerebrospinal fluid (CSF) analysis
Anti-NMDA antibody (serum and CSF)
Anti-voltage-gated potassium channel (anti-VGKC) antibody
Urine drug screen
Urine organic acids
Urine heavy metals
Urine porphyrins
Serum ceruloplasmin
Electroencephalogram (EEG)
Ophthalmological examination for Kayser-Fleischer rings

levetiracetam have also been used with good effect in a few case reports but are not routinely recommended. Amantadine has further been described in cases when catatonia was provoked by high-potency neuroleptics but requires further study before it can be routinely recommended.

ECT should be started for patients with suspected catatonia who do not robustly respond to aggressive benzodiazepine treatment, with required dosages often reaching or even exceeding 24 mg daily, and do not maintain a response to benzodiazepines despite escalating dosing or whose catatonic symptoms require immediate resolution to minimize patient morbidity, such as negativism requiring nasogastric or gastrostomy tube feedings, or catheterization, immobility leading to contractures or skin ulceration, or incessant dangerous self-injury with high risk for severe tissue damage. ECT is also indicated when patients present with malignant catatonia, or any signs of hemodynamic and thermoregulatory instability. ECT is highly effective in catatonia, with complete response rates up to 80–90% reported in the literature [11]. In a review of 12 children with severe ASD and catatonia, almost all experienced a significant response to ECT. In another large case series of children and adolescents, response was favorable in 76%, and only one patient had no response. The number of ECT treatments is variable, with some patients requiring prolonged acute ECT courses. In some cases, maintenance ECT will be needed, as often occurs in autism spectrum disorders. In severe cases or malignant catatonia, daily "en bloc" or even double-stimulus daily treatment for several days may be required. Although the modern electrode studies support equal efficacy between right unilateral, bifrontal, and bitemporal electrode placement in major depression, the ECT paradigms for catatonia support bilateral treatment given the need for swift and robust response [43].

General medical care during the treatment course of catatonia is important. Patients who are immobile may develop dehydration, pressure ulcers, and deep venous thrombosis. Thus, like any patient with neurological impairment, these should be routinely monitored for and preventative care implemented, including IV hydration or artificial feeding, regular body repositioning, compression sleeves, and adaptive mattresses for patients with reduced mobility [3].

The prognosis for acute response to catatonia-specific treatments when properly applied is generally good [44], but patients may require sustained courses of maintenance ECT. In the long-term, the overall prognosis often depends on the underlying condition associated with catatonia, if identifiable. Schizophrenia typically has a poorer prognosis than affective illness. Catatonia may be chronic and recurrent in some cases, particularly when the affective or psychotic illness is not under good control [3]. The persistence of catatonia in ASDs may be related to the fact that autism is a static, rather than episodic, condition; indeed, many patients with ASDs and catatonia have been reported to require m-ECT for ongoing stability [45]. The presence of excitement during a catatonic episode may indicate underlying bipolar disorder and may represent a more favorable prognosis as compared to schizophrenia [5]. Lithium has been used for the prevention of recurrent catatonia in cases where the underlying illness was thought to be bipolar disorder, as in our case, but requires appropriate monitoring. Lithium has also been reported as beneficial during the m-ECT course of some patients with catatonia in the context of ASD [45].

Clinical Pearls

The diagnosis of catatonia should be considered in all patients with characteristic signs, particularly if known risk factors are present. Catatonia should be considered even in complex medical cases when signs of delirium are also present. The symptoms of catatonia are readily recognizable and easily evaluated, and prompt identification and treatment of the syndrome confers vast patient benefit. Diagnostic overshadowing in children with autism and developmental disabilities, particularly in those more severely affected or with impaired communication, is a real risk. This may lead to a lack of timely diagnosis and treatment when the clinical deterioration is simply chalked up to autism. Administration of lorazepam can be diagnostic and should be considered early in the course of treatment. Delays in catatonia-specific treatment are associated with increased morbidity and mortality. ECT is the definitive treatment of catatonia when benzodiazepines are ineffective or insufficient.

Lessons Learned About Neuropsychiatry

Catatonia exemplifies the complexity of neuropsychiatric disease. On the one hand, patients may present with classic and obvious signs and respond dramatically to specific treatment. Yet in many cases, such as the one profiled in this chapter, the clinical picture is more complex, and the process of differential diagnosis becomes more important. Etiologic theories of catatonia seem to point to GABAergic functioning as the key element, but little progress has been made in understanding the pathophysiology of catatonia or discovering clinically useful biomarkers, like so many complex neuropsychiatric illnesses.

References

1. Penland HR, Weder N, Tampi RR. The catatonic dilemma expanded. Ann General Psychiatry. 2006;5(1):14.
2. Fink M. Rediscovering catatonia: the biography of a treatable syndrome. Acta Psychiatr Scand. 2013;127(Supplement 441):1–50.
3. Fink M, Taylor M. Catatonia. A clinician's guide to diagnosis and treatment. Cambridge, UK: Cambridge University Press; 2003.
4. Diagnostic and statistical manual of mental disorders (5th ed.): American Psychiatric Association; 2013.
5. Taylor MA, Fink M. Catatonia in psychiatric classification: a home of its own. Am J Psychiatr. 2003;160(7):1233–41.
6. Dhossche DM, Stoppelbein L, Rout UK. Etiopathogenesis of catatonia: generalizations and working hypotheses. J ECT. 2010;26(4):253–8.
7. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, DSM 5. 5th ed. Washington, DC: American Psychiatric Association; 2013.
8. Fink M, Shorter E, Taylor MA. Catatonia is not schizophrenia: Kraepelin's error and the need to recognize catatonia as an independent syndrome in medical nomenclature.

Schizophr Bull. 2009. Epub 2009/07/10. doi: sbp059 [pii] 9.1093/schbul/sbp059. PubMed PMID: 19586994.
9. Taylor M, Fink M. Catatonia in psychiatric classification: a home of its own. Am J Psychiatr. 2003;160:1–9.
10. Dhossche DM, Wachtel LE. Catatonia is hidden in plain sight among different pediatric disorders: a review article. Pediatr Neurol. 2010;43(5):307–15.
11. Sienaert P, Dhossche DM, Vancampfort D, De Hert M, Gazdag G. A clinical review of the treatment of catatonia. Front Psych. 2014;5.
12. Wing L, Shah A. Catatonia in autistic spectrum disorders. Br J Psychiatry. 2000;176:357–62.
13. Billstedt E, Gilberg C, Gilberg C. Autism after adolescence: population-based 13- to 22-year follow-up study of 120 individuals with autism diagnosed in childhood. J Autism Dev Disord. 2005;35:351–60.
14. Ghaziuddin N, Marcotte K, Dhossche D. Retrospective chart review of catatonia in child and adolescent psychiatric patients. Acta Psychiatr Scand. 2012;125(1):33–8.
15. Breen J, Hare D. The nature and prevalence of catatonic symptoms in young people with autism. J Intellect Disabil Res. 2017;61(6):580–93.
16. Winarni T, Schneider A, Ghaziuddin N, Seritan A, Hagerman R. Psychosis and catatonia in fragile X: case report and literature review. Intractable Rare Dis Res. 2015;4(5):139–46.
17. Faedda G, Wachtel L, AM H, Shprintzen R. Catatonia in an adolescent with velo-cardio-facial syndrome. Am J Med Genet A. 2015;167A(9):2150–3.
18. Ghaziuddin N, Nassiri A, Miles JH. Catatonia in down syndrome; a treatable cause of regression. Neuropsychiatr Dis Treat. 2015;11:941–9. https://doi.org/10.2147/NDT.S77307. PubMed PMID: 25897230; PMCID: PMC4396650.
19. Wachtel L, Dhossche D. Challenges of electroconvulsive therapy for catatonia in youth with intellectual disabilities: another tomato effect? J ECT. 2012;28(3):151–3. Epub 2012/08/24. 10.1097/YCT.0b013e31825692e2. PubMed PMID: 22914627.
20. Doherty M, Garstin I, McClelland R, Rowlands B, Collins B. A steroid stupor in a surgical ward. Br J Psychiatry. 1991;158(1):125–7.
21. Fink M, Shorter E. Does persisting fear sustain catatonia? Acta Psychiatr Scand. 2017;136(5):441–4. https://doi.org/10.1111/acps.12796.
22. Dhossche DM. Vagal intimations for catatonia and electroconvulsive therapy. J ECT. 2014;30(2):111–5. https://doi.org/10.1097/YCT.0000000000000134.
23. Wilson JE, Carlson R, Duggan MC, Pandharipande P, Girard TD, Wang L, Thompson JL, Chandrasekhar R, Francis A, Nicolson SE. Delirium and catatonia in critically Ill patients: the delirium and catatonia prospective cohort investigation. Crit Care Med. 2017;45:1837.
24. Saddawi-Konefka D, Berg SM, Nejad SH, Bittner EA. Catatonia in the ICU: an important and underdiagnosed cause of altered mental status. A case series and review of the literature. Crit Care Med. 2014;42(3):e234–e41.
25. Pandharipande P, Shintani A, Peterson J, Pun BT, Wilkinson GR, Dittus RS, Bernard GR, Ely EW. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. Anesthesiol J Am Soc Anesthesiologists. 2006;104(1):21–6.
26. Reti IM, Krishnan A, Podlisky A, Sharp A, Melinda W, Neufeld KJ, Hayat MJ. Predictors of electroconvulsive therapy postictal delirium. Psychosomatics. 2014;55(3):272–9.
27. Barr J, Fraser GL, Puntillo K, Ely EW, Gélinas C, Dasta JF, Davidson JE, Devlin JW, Kress JP, Joffe AM. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med. 2013;41(1):263–306.
28. van den Berg KS, Marijnissen RM, van Waarde JA. Electroconvulsive therapy as a powerful treatment for delirium: a case report. J ECT. 2016;32(1):65–6. https://doi.org/10.1097/YCT.0000000000000247.
29. Ozdemir B, Celik C, Cinar A, Ozsahin A. Relief by electroconvulsive therapy for postsurgical delirium in malignant catatonia. J ECT. 2010;26(4):272–3.
30. Dhossche DM, Wachtel LE, Goetz M, Sienaert P. Catatonia in psychiatric illnesses. In: The Medical Basis of Psychiatry: Springer; 2016. p. 517–35.
31. Llesuy JR, Coffey MJ, Jacobson KC, Cooper JJ. Suspected delirium predicts the thoroughness of catatonia evaluation. J Neuropsychiatry Clin Neurosci. 2016:appi. neuropsych. 15090230.

32. Consoli A, Raffin M, Laurent C, Bodeau N, Campion D, Amoura Z, Sedel F, An-Gourfinkel I, Bonnot O, Cohen D. Medical and developmental risk factors of catatonia in children and adolescents: a prospective case–control study. Schizophr Res. 2012;137(1):151–8.
33. Carroll B, Anfinson T, Kennedy J, Yendrek R, Boutros M, Bilon A. Catatonic disorder due to general medical conditions. J Neuropsychiatry Clin Neurosci. 1993;6(2):122–33.
34. Leon T, Aguirre A, Pesce C, Sanhueza P, Toro P. Electroconvulsive therapy for catatonia in juvenile neuropsychiatric lupus. Lupus. 2014;23:1066. 0961203314533603.
35. Sullivan BJ, Dickerman JD. Steroid-associated catatonia: report of a case. Pediatrics. 1979;63(4):677–9.
36. Dong TS, Henry JT, Stanley K, Pannain S. Catatonia induced by an ACTH-secreting neuroendocrine tumor: a case report. AACE Clin Case Rep. 2015;1(4):e245–e9.
37. Northoff G. What catatonia can tell us about "top-down" modulation: a neuropsychiatric hypothesis. Behav Brain Sci. 2002;25:555–604.
38. Dhossche D, Bouman N. Catatonia in an adolescent with Prader-Willi syndrome. Ann Clin Psychiatry. 1997;4:247–53.
39. Dhossche D, Song Y, Liu Y-M. Is there a connection between autism, Prader-Willi syndrome, catatonia, and GABA? Int Rev Neurobiol. 2005;71:189–216.
40. Pincus JH, Tucker GJ. Behavioral neurology. Oxford, United Kingdom: Oxford University Press; 2002.
41. Dhossche D, Carroll B, Carroll T. Is there a common neuronal basis for autism and catatonia? Int Rev Neurobiol. 2006;72:151–64.
42. Raffin M, Zugaj-Bensaou L, Bodeau N, Milhiet V, Laurent C, Cohen D, Consoli A. Treatment use in a prospective naturalistic cohort of children and adolescents with catatonia. Eur Child Adolesc Psychiatry. 2015;24(4):441–9.
43. Fink M, Kellner CH, McCall WV. Optimizing ECT technique in treating catatonia. J ECT. 2016;32(3):149–50. https://doi.org/10.1097/YCT.0000000000000345. PubMed PMID: 27428478.
44. Bush G, Fink M, Petrides G, Dowling F, Francis A, Catatonia II. Treatment with lorazepam and electroconvulsive therapy. Acta Psychiatr Scand. 1996;93:137–43.
45. Wachtel L, Hermida A, Dhossche D. Maintenance electroconvulsive therapy in autistic catatonia: a case series review. Prog Neuro-Psychopharmacol Biol Psychiatry. 2010;34(4):581–7. Epub 2010/03/20. doi: S0278-5846(10)00105-3 [pii] 10.1016/j.pnpbp.2010.03.012. PubMed PMID: 20298732.

Hypothalamic Hamartoma

25

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Case

James initially presented as a 5.5-year-old right-handed boy in the Emergency Department for violent outbursts. At the time he was under the legal custody of child protective services and was residing in a group home due to parental neglect, physical abuse, and suspected sexual abuse. He was having daily episodes of aggressive behavior with screaming, self-injurious actions, and threatening behavior to others. These behaviors were characteristically provoked by relatively minor frustration such as being told that he had to wait momentarily for a drink of water. He had verbally threatened to kill staff members by acquiring a firearm or a knife and

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was also expressing his intention to harm himself. In addition to these episodes of anger and aggression, he was also inappropriate with impulsive behavior including vulgar sexually related gestures and touching of others.

He was admitted to the child psychiatry inpatient unit, where he was described as alert and appropriately interactive with good social eye contact, but restless with increased psychomotor activity. His speech and mood were normal, and orientation, memory, and intelligence were thought to be age-appropriate. He was goal-directed and there were no abnormal thoughts at the time of admission. He was diagnosed with post-traumatic stress disorder and unsocialized aggression and was treated with guanfacine. During 1 week of observation, he had difficulty with self-regulation and attention. He was sexually preoccupied, acting out with sexual gestures, and having difficulty with boundaries related to his peers. He claimed that another patient on the unit was his girlfriend, and he was intrusive with touching. He did not have rage behaviors. He was discharged home under the care of a new foster family on guanfacine with plans for outpatient therapy.

However, he required readmission within several days for aggression and rage. His new foster family had attempted to redirect some of his impulsive behaviors, leading to an episode of extreme dysregulation with screaming, biting, and hitting, including physically attacking a younger child in the household. At the time of admission, he was banging on furniture while using racially charged language. Once calm, he had a normal mental status examination aside from some motor restlessness. However, his behavior was labile and explosive, with outbursts when asked to participate in activities of daily living such as bathing. Guanfacine was increased, and he had slow improvement in symptoms during his second stay on the child psychiatry unit. He was discharged for outpatient management where he was subsequently also diagnosed with attention deficit/hyperactivity disorder, combined type. Dextroamphetamine was added to his ongoing treatment with guanfacine.

At 7.2 years of age, he was referred to endocrinology (for concerns about precocious puberty) and dermatology (for acne). At this time his foster family provided a 1-year history for accelerated growth (increased height with muscular body mass) and early secondary sexual characteristics, including body hair (axillary and pubic), adult body odor, and acne. Physical examination included height 142 cm (50th percentile for a boy of 10.5 years) with increased testicular volume and Tanner stages 3–4 for male genital development and pubic hair pattern. His bone age was markedly advanced to 13.5 years equivalent. Laboratory testing included elevated serum levels for testosterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) consistent with central precocious puberty (CPP). Magnetic resonance (MR) imaging of brain with and without intravenous contrast demonstrated a non-enhancing suprasellar mass (12 × 10×9 mm) with overall appearance and signal characteristics consistent with hypothalamic hamartoma (HH) (see Fig. 25.1). CPP was treated with the introduction of gonadotropin-releasing hormone (GnRH) agonist therapy (intramuscular leuprolide injections), and he was referred to a multidisciplinary Hypothalamic Hamartoma Program for evaluation and possible surgical treatment.

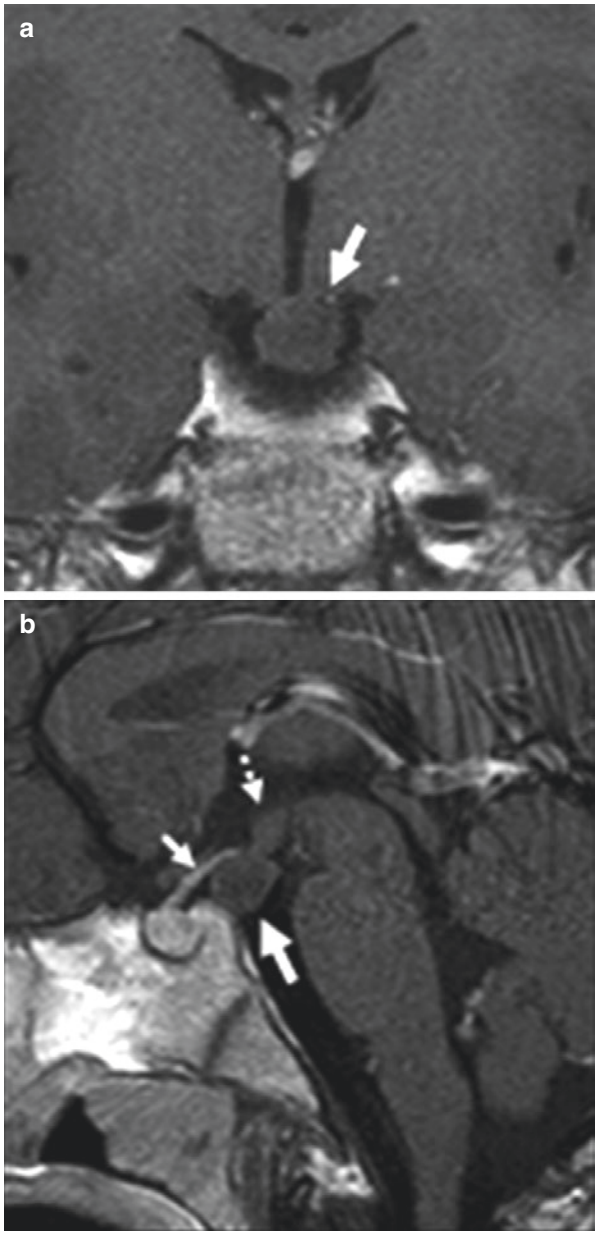

Fig. 25.1 (**a**) Coronal T1-weighted MR (with contrast administration). Arrow indicates hypothalamic hamartoma (HH) with attachment to the inferior left hypothalamus in the region of the mammillary bodies. (**b**) Sagittal T1-weighted MR (with contrast administration). Large solid arrow indicates HH. Small solid arrow indicates close anatomical proximity of HH to the contrast-enhancing tuber cinereum (consistent with the history for central precocious puberty). Small dashed arrow indicates proximity to the mammillary body (consistent with the history for gelastic seizures). Approximately 40% of HH patients with epilepsy also have precocious puberty as a result of larger lesions that attach to *both* the tuber cinereum and mammillary bodies

At 7.4 years of age, he was evaluated by neurology and neurosurgery. His foster family continued to report labile behavior and episodic aggression, usually triggered by minor situational frustration. His foster father offered that he "becomes angry at the drop of a hat." However, the history also indicated episodes of peculiar laughter five to six times per day since arriving in foster care 1.5 years previously.

In light of his history of foster care, the onset of these events could not be dated. These were unprovoked (unrelated to external circumstances) and distinct from his pattern of normal laughter with "robotic-like laughter." They were brief, usually just a few seconds in duration. In light of the recent imaging findings, these were recognized as gelastic (laughing) seizures. He did not have any history for other seizure types.

An electroencephalogram (EEG) was abnormal with sleep-activated bilaterally synchronous occipital interictal spikes with an otherwise normal awake and asleep background. Neuropsychological testing demonstrated low-average intellectual functioning (Wechsler Abbreviated Scale of Intelligence, 2nd edition [WASI-II] composite standard scores Verbal Comprehension 91, Perceptual Reasoning 83, Full Scale 85) with variability depending upon the cognitive domain. He had deficits in sustained attention and vigilance based upon standardized measures and behavioral observation. He exhibited cognitive weaknesses in aspects of executive functioning including impulse control and cognitive flexibility. Processing speed was average. His neuropsychological profile was mildly lateralizing with better performance of the language-dominant (left) cerebral hemisphere. Specifically he had relatively strong verbal compared to nonverbal reasoning and better verbal compared to nonverbal memory consolidation. He is in a self-contained second-grade class as a result of his aggression but reportedly learns quickly and can excel academically when his behavior is regulated.

Psychiatric reevaluation at 7.5 years of age showed that externalizing behaviors had decreased in the context of placement into a therapeutic foster home, a self-contained classroom, and medication treatment. However, he continued to have episodes of overt aggression toward his peers in settings that were less structured. He recognized that controlling his anger was an important goal. The recommendation was that he should continue placement in his therapeutic foster home where he had been more stable.

Preoperative evaluation also included resting-state functional MR imaging (rs-fMRI), performed in a lightly sedated state to minimize patient movement. Utilizing a seed-based approach, rs-fMRI demonstrated a greater degree of network connectivity from the HH to normal brain from the anterior region of the HH. Increased regional connectivity from HH to normal brain was most notable for enhanced activation in the lateral temporal, mesial temporal, and prefrontal regions of the cortex (see Fig. 25.2 for representative images).

James was considered to be a good candidate for surgical intervention based upon the known treatment resistance of gelastic seizures associated with HH and the disabling severity of his psychiatric comorbidity. He underwent MRI-guided stereotactic laser thermoablation of the HH (see Fig. 25.3). He was premedicated with oral dexamethasone according to our usual protocol. There were no surgical complications. He did not experience diabetes insipidus, and he was discharged home less than 48 h postoperatively.

James has had 4 months of follow-up since undergoing surgery. He has not had any seizure events (including gelastic seizures) since treatment. He has experienced significant improvement in behavior with resolution of aggressive tendencies and

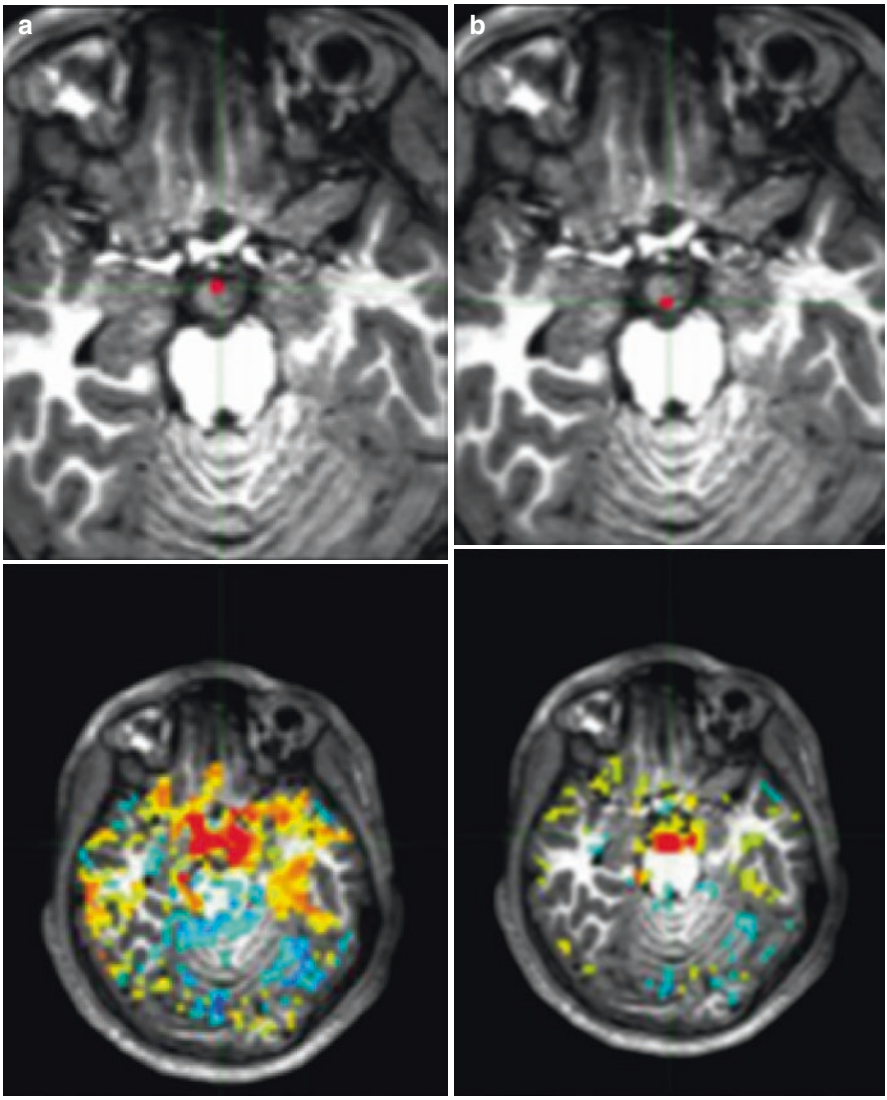

Fig. 25.2 Representative images from resting-state functional MRI (rs-fMRI) study. The patient was lightly sedated to reduce movement. This technique utilizes a seed-based approach to study whole-brain network connectivity linked to each voxel within the HH lesion (voxel of interest is indicated by the red dot in the upper panel). In the lower panels, linked *activation* of brain oxygen level-dependent (BOLD) signal is shown within the HH and in normal adjacent brain by the red-yellow signal, and linked *deactivation* of BOLD signal is shown by the blue-green signal. (**a**) Representative imaging for seed-based analysis of a voxel in the anterior region of the HH (red dot in upper panel of a). The lower panel indicates robust network connectivity between this region of the HH and normal brain, including prefrontal, lateral temporal, and mesial temporal regions of the cortex. (**b**) Conversely, seed-based analysis of a voxel in the posterior region of the HH (red dot in upper panel of b) shows much less network connectivity. Here this technique is utilized to help target the thermoablation probe within the HH volume to optimize efficacy

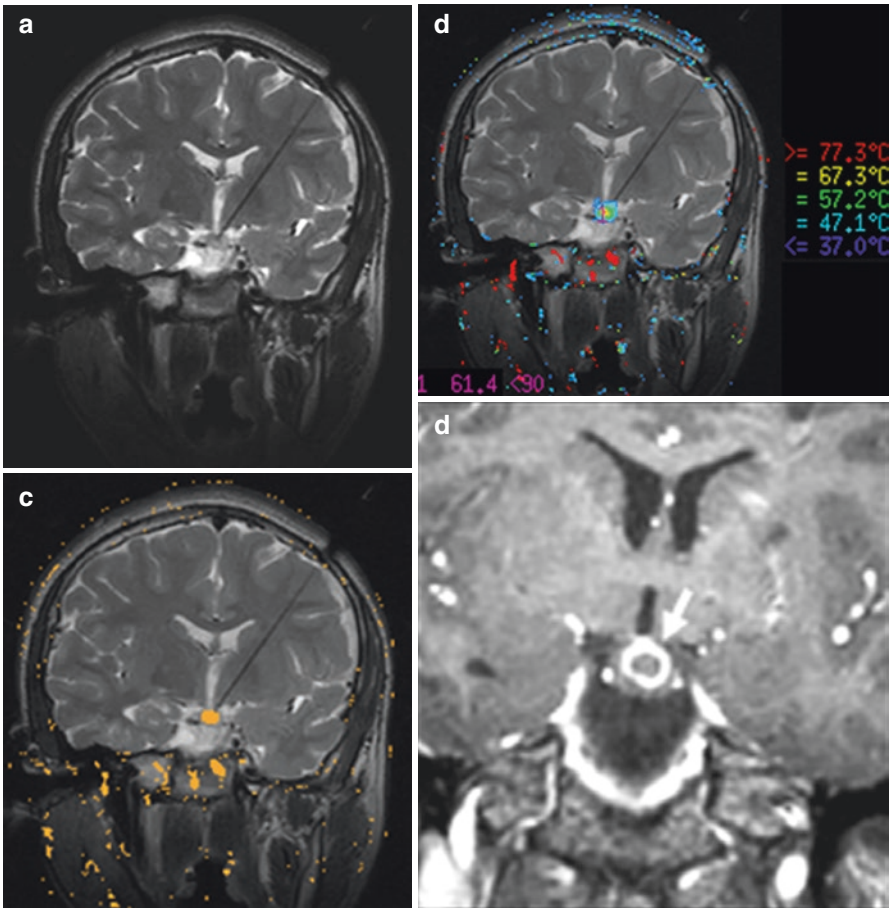

Fig. 25.3 Representative imaging acquired during surgical treatment of HH with stereotactic MRI-guided laser thermoablation. (**a**) Coronal T2-weighted image showing successful placement of the laser ablation probe into the HH, entering the skull from a burr hole over the left cerebral convexity. This trajectory is individualized to avoid major vessels and to minimize the risk of injury to sensitive structures (such as the internal capsule). (**b**) Stereotactic laser thermoablation makes use of near-real-time MR thermography to superimpose the thermal signal onto the structural imaging (coronal T2-weighted). Predetermined safety points for maximal temperature are entered into the treatment program to minimize the risk of thermal injury to normal surrounding structures (such as the optic tracts). In this way the system will shut down if one of these safety parameters is breached during treatment. (**c**) Predicted region of thermal injury (zone of predicted cell death based upon MR thermography) is represented in yellow on this coronal T2-weighted sequence. (**d**) Postoperative coronal T1-weighted image with contrast administration showing ring-enhancing region of cellular injury within the HH after thermoablation treatment

explosive behaviors. He is interacting well with the other foster children at his residence and has tolerated previously potentially triggering interactions with peers without negative or aggressive reaction which previously would have been characteristic. His foster father notes that on a recent outing to a skate park, James was in fact the center of attention among many children secondary to his pleasant demeanor.

The owners of the skate park were additionally impressed by his outgoing and engaging behavior to the extent that they provided him a new skateboard as a gift. He continues in a special education program at school but has made significant gains since surgery. He is awaiting follow-up with psychiatry and neuropsychology for postoperative evaluation and testing.

Discussion

Clinical Overview

Hypothalamic hamartomas (HH) are rare congenital lesions of the ventral hypothalamus. HH are associated with two widely recognized clinical phenotypes, depending upon the location of the HH lesion within the hypothalamus [1]. HH lesions with a base of attachment posteriorly in the hypothalamus in the region of the mammillary bodies are highly associated with epilepsy, cognitive dysfunction, and psychiatric symptoms [2]. This subtype is often termed *intrahypothalamic*, since these lesions are within the third ventricle, with a base of attachment that includes the ventricular surface of the hypothalamus. Conversely, HH lesions located anteriorly in the hypothalamus, in close proximity to the tuber cinereum and pituitary stalk, are highly associated with endocrine dysfunction, specifically central precocious puberty [3]. These lesions are termed *parahypothalamic*, as they have a base of attachment to the inferior (ventral) surface of the hypothalamus, often with a narrow peduncle or stalk. Large HH with a base of attachment that includes both the anterior and posterior regions results in both the neurological features and central precocious puberty. Approximately 40% of HH patients with epilepsy also have a history of central precious puberty [4].

The neurological features associated with HH are highly variable from patient to patient and often evolve over time [5]. Gelastic seizures are the prototypical seizure type associated with HH, usually the initial symptom for patients with the intrahypothalamic form of HH, often beginning during infancy. Gelastic seizures consist of brief, stereotyped behaviors resembling laughter, typically lasting 5–20 s in duration, without a sense of enjoyment (mirthless laughter). Some HH patients exhibit seizures that resemble crying rather than laughter with similar lack of true emotionality, termed dacrystic seizures. This is a continuum of expression, as many patients have gelastic seizures that simultaneously combine the appearance of laughing and crying. Parents learn to easily differentiate gelastic seizures from normal emotion in their children. Gelastic seizures are highly resistant to conventional anti-epileptic drugs (AEDs).

The majority (80%) of patients with HH and gelastic seizures develop additional seizure types over time [5]. This occurs most commonly around 4–7 years of age, but there is a great deal of variability to the clinical course in terms of seizure type and severity. Localization-related seizures, often mimicking temporal lobe epilepsy, are most common, but generalized seizures can also occur [6]. Other seizure types

may or may not be preceded by gelastic features. AEDs may be helpful in reducing the frequency of these additional seizure types, but they are almost universally treatment-resistant, and surgical treatment of the HH is required [7]. Standard scalp-recorded EEG features are also highly variable and have limited utility for evaluating subcortical forms of epilepsy [8].

The natural history of epilepsy associated with HH is complex with important changes that occur over time [9]. The HH lesion is intrinsically epileptogenic, that is, gelastic seizures arise from within HH tissue [1]. As additional seizure types develop, these also originate from the HH lesion, but over time, a process of secondary epileptogenesis occurs. In many patients seizures may begin to originate in other brain regions and ultimately may become completely independent of the HH lesion. Secondary epileptogenesis likely explains why HH surgery is less successful in older patients and supports the premise that earlier surgery is advised in HH patients with uncontrolled seizures [10].

Neuropsychiatric Features

Much like the clinical features of seizures and epilepsy, the cognitive and psychiatric symptoms associated with HH are very diverse from patient to patient and can represent a moving target with clinically significant changes over time.

Cognitive impairment was identified as an early and prominent problem for patients with HH by Berkovic and colleagues in 1988 [11]. This important paper crystallized the clinical triad of major symptoms for the intrahypothalamic type of HH, consisting of epilepsy (beginning with gelastic seizures and then advancing to additional types of seizures), cognitive impairment, and psychiatric symptoms (manifesting most commonly as rage behaviors). Additionally, Berkovic and colleagues identified that the emergence of cognitive deficits and psychiatric symptoms usually coincided with the emergence of the additional, non-gelastic, seizure types and that cognition and behavior can progressively worsen in a manner that parallels the increase in the severity of the epileptic seizures [11, 12]. Approximately 50% of patients with HH associated with early childhood-onset epilepsy demonstrate this deteriorating clinical course [13]. Few publications document this deterioration in the same cohort in a longitudinal fashion, but the available detailed case studies are compelling [14, 15].

This natural history with deterioration in neurobehavioral function coincident with worsening seizures (termed epileptic encephalopathy) can be observed with other severe forms of pediatric epilepsy. HH is an important human model for epileptic encephalopathy since it is a single disease entity, whereas other pediatric epilepsy syndromes associated with epileptic encephalopathy, such as infantile spasms and Lennox-Gastaut syndrome, result from a long list of underlying etiologies [9]. The basic cellular and molecular mechanisms responsible for epileptic encephalopathy associated with HH or any other epilepsy syndrome are not understood.

Cognitive impairment, with or without superimposed deterioration, occurs in 80% or more of patients with HH and epilepsy [16, 17]. Cognitive deficits are exclusive to those HH patients with epilepsy: patients with HH and CPP only (the parahypothalamic subtype) do not have neuropsychological deficits [18].

Prigatano and colleagues evaluated 49 patients with HH and treatment-resistant epilepsy with neuropsychological testing during presurgical evaluation [19]. Age at time of testing was 16.3 years (range 5–55 years; patients less than 5 years of age were not included in this cohort; 59% male). Mean age for first seizure onset was 0.9 years, with 45% of subjects with onset of first seizure before 1 month of age. These patients were taking a mean of 2.3 AEDs at time of testing. Six patients (12%) had only gelastic seizures, and 42 (86%) had at least 1 other seizure type. Patients with a prior history of epilepsy surgery were excluded. Test results were highly variable across the study group. Seven patients (14%) had severe intellectual disability and could not complete any standardized testing. For the testable patients (86%), mean full-scale intelligence quotient (FS IQ) was 86. These authors describe four patterns of neuropsychological results: *Pattern 1* (35% of entire cohort) having essentially normal intellectual functioning for age, although deficits in one or more subscales may be observed; *Pattern 2* (18%) with clinically significant cognitive deficits in either verbal or performance domains, but without global intellectual disability as judged by FS IQ; *Pattern 3a* (33%) with intellectual disability (FS IQ <70) but testable with standardized scales; and *Pattern 3b* (14%) with intellectual disability not testable with standardized scales.

Quiske and colleagues evaluated cognitive function in 13 adolescent and adult patients with HH and epilepsy (mean age 25.7 years; 54% male) undergoing presurgical evaluation [17]. Mean age for first seizure onset was 4.5 years, and patients were taking mean 1.8 AEDs at time of testing. FS IQ was 81 for the entire cohort with 7 of 13 (54%) in the subnormal range and only 2 (15%) normal in all domains. Deficits in verbal and visual learning and memory were most common.

Clinical features predictive for a greater degree of cognitive impairment have been identified in presurgical cohorts undergoing neuropsychological testing. Statistically significant correlation with worse cognitive performance was observed for HH patients with earlier age at onset of seizures (of any type) [13], longer lifetime duration of additional (non-gelastic) seizures [20], more frequent seizures [16], larger HH lesion size [19, 21], intrahypothalamic HH lesion subtype [20], and higher number of anti-epileptic drugs (AEDs) at the time of testing [19, 20]. Taking more AEDs may be a proxy for seizure severity, but the AEDs themselves may adversely impact neuropsychological testing results.

In contrast to cognitive issues, research on behavioral symptoms and psychiatric functioning of HH patients with epilepsy has been limited. However, behavioral and psychiatric symptoms are common, potentially disabling, and can represent the most significant issue influencing quality of life for the patient and family. The clinical importance of psychiatric symptomatology is readily apparent to medical providers in regular contact with this patient population, and there is abundant descriptive literature (often consisting of individual case reports or small series)

documenting psychiatric comorbidity [11–15]. Our case illuminates the problems with self-control and frustration tolerance commonly encountered in these patients.

Mood lability and rage attacks are the most problematic symptoms. Patients have poor frustration tolerance, with acting-out behavior and excessive reactivity to relatively minor stimuli, sometimes with destructive and aggressive features. Here again, there is significant symptom diversity and severity between patients. Weissenberger and colleagues reported on the psychiatric comorbidity in 12 patients with HH and epilepsy [22]. All patients had HH and treatment-resistant epilepsy with an age range of 3–14 years at the time of evaluation. Patients were assessed by structured interview with comparison to one sibling (closest in age) as a control for psychosocial factors unrelated to HH. Behavioral problems, consisting of significant difficulties with rage, aggression, temper tantrums, and other signs of emotional lability, were reported by 83% of families. *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR) diagnoses included oppositional-defiant disorder (83%), attention deficit/hyperactivity disorder (75%), conduct disorder (33%), and mood disorder (17%). These diagnoses were significantly less common in the control sibling.

Veendrick-Meekes and colleagues report psychiatric symptoms for five adults with HH and epilepsy [23]. The history for all five patients suggested progressive cognitive decline. Four of the five (80%) had aggression, often unprovoked, but a wide spectrum of other psychiatric symptoms was also present, including anxiety, depression, and thought disorder. These authors stress the diversity of psychiatric comorbidity with HH and epilepsy, such that symptoms from virtually every DSM category can be encountered. These reports notwithstanding, there is a disheartening lack of basic descriptive data with systematic psychiatric evaluations and consistent use of diagnostic criteria and terminology in this population. Pharmacotherapy for psychiatric comorbidity associated with HH and epilepsy is completely unexplored.

Killeen and colleagues have recently reported a systematic review of the English-language literature in an effort to identify clinical features associated with a higher risk of aggression and rage behaviors in HH patients with epilepsy [24]. They identified peer-reviewed publications in which HH subjects were individually described and could be clearly segregated into cohorts *with* (51 patients) and *without* (68 patients) comorbid symptoms of aggression. The presence of aggression showed a statistically significant positive correlation (based upon univariate analysis) with (1) male gender, (2) younger age at time of first seizure (regardless of seizure type), (3) the presence of intellectual disability, and (4) the presence of multiple seizure types (versus gelastic seizures only).

Taken together with the predictive factors for cognitive impairment (see above), these findings provide evidence that seizure severity and duration of epilepsy are linked with neuropsychiatric dysfunction in HH patients, supporting the concept of epileptic encephalopathy as originally formulated by the clinical observations of Berkovic and colleagues. The cellular mechanisms and brain networks responsible for epileptic encephalopathy in HH patients are unknown.

Surgical Treatment As previously noted, HH are intrinsically epileptogenic and the appropriate target for surgical treatment for most patients. There has been a rapid pace of development for surgical therapies for HH over the past 15–20 years, so that a previously untreatable condition now has a complicated array of possible therapies. The aim of these surgical treatments is to remove, disconnect, or destroy HH tissue with a variety of strategies. A detailed presentation of each surgical approach is beyond the scope of this chapter, but detailed reviews are available [25, 26]. Clinical experience and published open-label treatment studies have established the principle that the choice of technique should be tailored to the individual clinical features of each patient, most importantly the surgical anatomy of the HH lesion (position, size, and planes of attachment, among other considerations) and the clinical course (stable versus deteriorating). Ideally, evaluation and treatment for HH are carried out at multidisciplinary centers specializing in this disease [27]. Table 25.1 lists the currently available surgical modalities with selected outcome indicators. The reader should be aware that outcome measures between the techniques are not directly comparable since the patient cohorts are dissimilar. Randomized treatment studies have not been performed.

Table 25.1 Surgery for hypothalamic hamartoma

			Outcome: efficacy	Outcome: complications	
Surgical approach	Year of first publication	Centers reporting	100% seizure-free	Transient decreased short-term memory	Permanent decreased short-term memory
Gamma knife radiosurgery	2000	4	37–40%	0%	0%
Pterional resection	2002	3	15–40%	40%	30%
Transcallosal interforniceal resection	2003	3	52–77%	48–58%	8–14%
Stereotactic radiofrequency thermoablation	2003	2	20–71%	10%	NA
Transventricular endoscopic resection	2006	4	36–49%	14%	0–8%
Stereotactic interstitial radiosurgery	2008	1	38%	NA	11%
Stereotactic laser thermoablation	2013	2	44–85%	NA	22%

Data shown are derived from peer-reviewed open-label surgical outcome reports with at least ten patients treated with the identified surgical approach. A range is provided if there is data provided by more than one center. *NA* not available. An expanded version of this table and a complete list of citations are available in reference [26]

Neuropsychiatric Outcome with Surgical Treatment HH associated with epilepsy are universally located in close proximity to the mammillary bodies [2]. The mammillary bodies, in association with their primary white matter tracts, the fornices and the mammillothalamic tracts, are important structures supporting learning (short-term memory). Open microsurgical approaches, including transcallosal interforniceal and pterional, often cause transient deficits in short-term memory, as indicated in Table 25.1. Fortunately, most (but not all) improve.

Long-term (usually considered to be at least 1 year after surgical intervention) cognitive outcome, utilizing standardized pre- and postoperative neuropsychological scales, has been investigated by several groups. Wethe and colleagues have reported postoperative neuropsychological testing for patients undergoing HH surgery in comparison to preoperative results [28]. In this cohort of 32 patients, 63% underwent endoscopic resection. For the entire cohort, there was a statistically significant improvement in full-scale intelligence quotient (FS IQ), with a preoperative mean of 83.0 and postoperative mean of 91.3 ($p < 0.001$). For the entire group, there was no significant difference between preoperative and postoperative scores relating to learning and memory, although individual patients did demonstrate diverse (some favorable and others unfavorable) changes between pre-and postoperative testing. Improvement in cognitive functioning was most likely to occur in patients who were younger at the time of surgery (and had a shorter lifetime duration of epilepsy) and in those with *lower* scores on preoperative testing ($p < 0.05$).

Wagner and colleagues have reported standardized neuropsychological outcomes in 26 patients undergoing stereotactic interstitial radiosurgery [29]. On a group-wise basis, there were no statistically significant changes between preoperative and postoperative testing in any of the scales used in this study, which placed particular emphasis on learning and memory. However, like the study reported by Wethe and colleagues, there was a great deal of variation in memory outcome between individual patients. Those with higher preoperative scores appeared to be at particular risk for postoperative decline.

Kameyama and colleagues have recently provided an updated report on their cohort of 100 patients undergoing stereotactic radiofrequency thermoablation [30]. With at least 1 year of follow-up (median duration of follow-up 3 years), they reported 71% of patients are completely seizure-free. For those patients with both pre- and postoperative neuropsychological testing (69% of the entire treatment group), there was a statistically significant group-wise improvement in full-scale IQ (mean increase in postoperative full-scale IQ 6.1 points; $p < 0.001$).

In summary, group-wise cognitive performance, as determined by full-scale IQ, *improves* after HH surgery for the three interventions that have been studied to date. Improvement correlates with surgical success for controlling seizures [31]. Short-term memory is at risk, and some individual patients experience clinically significant deficits, but the group-wise studies available thus far have not shown a significant change from pre- to postoperative testing.

Psychiatric outcome with HH surgery is poorly studied. Systematic attention to psychiatric diagnoses and severity assessment scales are universally absent in the

available open-label surgical outcome studies. The likelihood of reporting bias in these studies is high. Based upon their review of the literature, Killeen and colleagues found that of 48 HH patients with epilepsy *and* aggression, 45 (94%) were reported to be improved, 1 patient (2%) as unchanged and 2 patients (4%) as worse [24]. These authors viewed this result as unlikely to hold up to studies conducted with rigorous psychiatric assessment protocols but concluded that the risk for *worsening* of psychiatric symptoms with HH surgery appears low.

A small number of patients have been reported after undergoing surgery principally to improve disabling psychiatric symptomatology (rather than to treat epilepsy). Du and colleagues report one patient in their treatment series with rage attacks (but without epilepsy) with over 2 years of follow-up after undergoing stereotactic laser thermoablation of the HH lesion [32]. This patient did not improve.

Ng and colleagues have reported a small series of four patients undergoing HH surgery for psychiatric indications [33]. One had no history of seizures and three had seizures that were well-controlled. The mean age at the time of surgery was 11.9 years (range 9.8–15.0 years). Three were male. All four patients had severe rage behaviors, often destructive to property and placing themselves and others at risk of injury. Three were diagnosed with oppositional-defiant disorder and one with bipolar disorder. Two had mild intellectual disability. The surgical approach was individualized for HH anatomy: two underwent transventricular endoscopic, one transcallosal, and one pterional resection. Mean duration of follow-up was 2.8 years (range 1.3–6.6 years). All four patients had striking improvement in psychiatric symptomatology with ability to resume school and restore family relationships. Postoperative neuropsychological testing showed stable or improved intellectual function compared to preoperative results. These authors recognized the checkered history regarding neurosurgery for psychiatric indications and made the point that HH surgery for behavioral indications should be regarded as investigational and should be conducted under institutional review board-approved protocols with informed consent.

Perspective on Further Research The availability of surgically resected HH tissue has enabled significant progress over the past 15 years with our understanding of intrinsic epileptogenesis of HH tissue. There is sufficient discovery of basic cellular and molecular mechanisms that a working model for HH epileptogenesis has been developed [1]. Similar progress has been possible with discovery of the somatic mutations responsible for HH [34].

Conversely, the understanding of the basic mechanisms and cellular networks related to the neuropsychiatric comorbidity of HH and epilepsy, both cognitive and psychiatric, is limited, and progress has been slow. The nature of neuropsychiatric problems requires a “whole-brain” rather than tissue-based approach, and progress is perhaps most likely to be derived from innovative developments in brain imaging. This may be the most rewarding area for HH-related research over the next 10 years. Many of these imaging technologies have yet to be leveraged for HH-related research, representing an opportunity for centers that treat these patients.

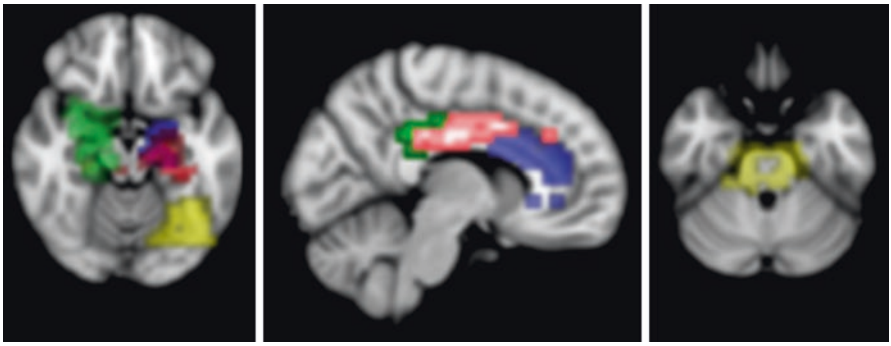

Fig. 25.4 Representative imaging derived from resting-state functional MRI (rs-fMRI) studies on a cohort of patients with HH and treatment-resistant epilepsy. These studies utilized a seed-based approach with determination of network connectivity by correlating brain oxygen level-dependent (BOLD) signal between the HH and other brain regions during resting state. Group data (12 HH subjects) is superimposed upon an idealized brain. Regions showing significant correlation indicating network connectivity are shown in color. These results suggest network connectivity between HH and limbic regions and brainstem. The axial image to the left shows activation of mesial temporal regions. The sagittal image in the middle demonstrates activation of cingulate gyrus. The axial image to the right shows activation of the pons. Mesial temporal and cingulate network connectivity may be mediated through the limbic circuit by HH projections to the mammillary bodies and then via the mammillothalamic tracts to downstream structures including cingulate gyrus and hippocampal formations. Brainstem connectivity may be mediated by the mammillotegmental tract. Direct experimental evidence confirming these pathways is lacking. (This figure modified from Boerwinkle et al. [35]. Reproduced with permission of the Publisher Mary Ann Liebert, Inc.)

One such imaging technology currently of interest is resting-state functional MRI (rs-fMRI). Boerwinkle and colleagues have utilized this technique to identify regional brain networks that are functionally linked to HH lesions [35]. Their work confirms that there is robust connectivity between HH and the component regions of the limbic circuit as originally formulated by Papez [36]. This includes the anterior thalamus, cingulate gyrus, and hippocampus as shown with representative imaging results in Fig. 25.4. There is hope that this technique can be used to address important questions regarding epileptic encephalopathy and HH, perhaps looking for differences between clinical cohorts (e.g., groups *with* and *without* a history for oppositional-defiant disorder) and changes over time.

Case Reflections

The rage behaviors and poor frustration tolerance exhibited by James prior to surgical treatment are typical of many HH patients. He has only one of the clinical risk factors that are associated with higher likelihood of aggression (male gender) identified by Killeen and colleagues (as discussed above). Conversely, the hypersexualized behavior is not typical for this patient population based upon the experience of the authors, although this clinical issue has not been subjected to systematic study.

Additional risk factors for emotional distress and psychiatric symptoms, not directly related to HH, are present in this patient's life story, including foster placement under state custody due to parental neglect and frequent turnover in foster home placement (which in turn, of course, may have been influenced by behavioral problems related to his HH resulting in foster parent inability or unwillingness to handle him). There is little information regarding his biological family, and consequently genetic influences potentially increasing his susceptibility to behavioral health problems are unknown. We were also motivated to present James in order to highlight the favorable neuropsychiatric response to surgical treatment that is experienced by many HH patients undergoing surgery for control of epilepsy. Admittedly, in his case follow-up after surgery has been brief, but feedback from his caregivers is encouraging.

Clinical Pearl #1

Psychiatric comorbidity associated with treatment-resistant epilepsy is common [37]. Attention deficit/hyperactivity disorder (ADHD), depression, anxiety, and autism are common comorbidities in children with epilepsy, and psychosis may also be encountered in adults [38, 39]. These internalizing psychiatric symptoms are common across all forms of epilepsy and are usually not specific to different epilepsy syndromes.

Conversely, externalizing symptoms such as rage behaviors and reactive (but not predatory) aggression are hallmark clinical features for patients with HH and epilepsy. They are infrequently associated with other forms of epilepsy [40]. HH stands out as rather unique among the epilepsies for its association with externalizing symptoms.

Clinical Pearl #2

Rage attacks are the hallmark behavioral symptom associated with HH. Rage attacks are usually reactive to external (often minor) stimuli and consist of explosive anger, sometimes associated with violence. These are impulsive manifestations of aggression. Patients with HH do not have predatory or premeditated aggression. There is a lack of uniformity in the literature with regard to diagnostic terms.

In the absence of other psychiatric features, these episodes may be diagnosed as intermittent explosive disorder or episodic dyscontrol syndrome, diagnoses in the impulse-control disorder category. Alternatively, they may be considered as comorbid symptoms of other psychiatric diagnoses, including attention deficit hyperactivity, conduct, mood, or anxiety disorders. As a consequence, diagnostic terms are not consistently applied in this group of patients [33]. Oppositional defiant disorder is a frequently encountered diagnosis, but is also not a perfect fit for this patient population.

Lessons Learned About Neuropsychiatry

The hypothalamus is a key structure for many regulatory functions that do not require constant conscious attention, including homeostatic mechanisms relating to temperature, thirst, appetite, and sleep. The hypothalamus also has an important role for behavioral regulation. Disorders in the posterior hypothalamus including HH can result in disorders of impulse control and result in excessive reactivity and rage. Electrical stimulation experiments in normal cats show that reactive (but not predatory) aggression localizes to the ventral hypothalamus in a zone that extends posteriorly to the level of the mammillary bodies [41]. The specific details of these posterior hypothalamic networks remain unknown.

References

1. Kerrigan JF, Parsons A, Tsang C, Simeone K, Coons S, Wu J. Hypothalamic hamartoma: neuropathology and epileptogenesis. Epilepsia. 2017;58(Suppl 2):22–31.
2. Parvizi J, Le S, Foster B, Bourgeois B, Riviello JJ, Prenger E, Saper C, Kerrigan JF. Gelastic epilepsy and hypothalamic hamartomas: neuroanatomical analysis of brain lesions in 100 patients. Brain. 2011;134:2960–8.
3. Chan YM, Fenoglio KA, Paraschos S, Muhammad L, Troester MM, Ng YT, Johnsonbaugh RE, Coons SW, Prenger EC, Kerrigan JF, Seminara SB. Precocious puberty associated with hypothalamic hamartomas correlates with anatomic features but not with expression of GnRH, TGFα, or KISS1. Horm Res Paediatr. 2010;73:312–9.
4. Harrison VS, Oatman O, Kerrigan JF. Hypothalamic hamartoma with epilepsy: review of endocrine comorbidity. Epilepsia. 2017;58(suppl 2):50–9.
5. Kerrigan JF, Kahane P, Fohlen M, Arzimanoglou A. Hypothalamic hamartoma. In: Arzimanoglou A, Cross JH, Holthausen H, Kahanem P, editors. Pediatric epilepsy surgery. 1st ed. Surrey: John Libbey Eurotext; 2016.
6. Freeman JL, Harvey AS, Rosenfeld JV, Wrennall JA, Bailey CA, Berkovic SF. Generalized epilepsy in hypothalamic hamartoma: evolution and postoperative resolution. Neurology. 2003;60:762–7.
7. Cross JH, Spoudeas H. Medical management and antiepileptic drugs in hypothalamic hamartoma. Epilepsia. 2017;58(Suppl 2):16–21.
8. Troester M, Haine-Schlagel R, Ng YT, Chapman K, Chung S, Drees C, Prenger E, Rekate H, Kerrigan JF. EEG video-EEG seizure monitoring has limited utility in patients with hypothalamic hamartoma and epilepsy. Epilepsia. 2011;52:1137–43.
9. Kerrigan JF, Y-T N, Chung SS, Rekate HR. The hypothalamic hamartoma: a model of subcortical epileptogenesis and encephalopathy. Semin Ped Neurol. 2005;12(2):119–31.
10. Ng YT, Rekate HL, Prenger EC, Chung SS, Feiz-Erfan I, Wang NC, Varland MR, Kerrigan JF. Transcallosal resection of hypothalamic hamartoma for intractable epilepsy. Epilepsia. 2006;47:1192–202.
11. Berkovic SF, Andermann F, Melanson D, Ethier RE, Feindel W, Gloor P. Hypothalamic hamartomas and ictal laughter: evolution of a characteristic epileptic syndrome and diagnostic value of magnetic resonance imaging. Ann Neurol. 1988;23:429–39.
12. Striano S, Striano P. Clinical features and evolution of the gelastic seizures-hypothalamic hamartoma syndrome. Epilepsia. 2017;58(suppl 2):12–5.
13. Nguyen D, Singh S, Zaatreh M, Novotny E, Levy S, Testa F, Spencer SS. Hypothalamic hamartomas: seven cases and review of the literature. Epilepsy Behav. 2003;4:246–58.
14. Deonna T, Ziegler A-L. Hypothalamic hamartoma, precocious puberty and gelastic seizures: a special model of “epileptic” developmental disorder. Epileptic Disord. 2000;2:33–7.

15. Savard G, Bhanji NH, Dubeau F, Andermann F, Sadikot A. Psychiatric aspects of patients with hypothalamic hamartoma and epilepsy. Epileptic Disord. 2003;5:229–34.
16. Frattali CM, Liow K, Craig GH, Korenman LM, Makhlouf F, Sato S, Biesecker LG, Theodore WH. Cognitive deficits in children with gelastic seizures and hypothalamic hamartoma. Neurology. 2001;57:43–6.
17. Quiske A, Frings L, Wagner K, Unterrainer J, Schulze-Bonhage A. Cognitive functions in juvenile and adult patients with gelastic epilepsy due to hypothalamic hamartoma. Epilepsia. 2006;47:153–8.
18. Cukier P, Castro LHM, Banaskiwitz N, Teles LR, Ferreira LRK, Adda CC, da Costa Leite C, Arnhold IJP, Mendonca BB, Latronico AC, Brito VN. The benign spectrum of hypothalamic hamartomas: infrequent epilepsy and normal cognition in patients presenting with central precocious puberty. Seizure. 2013;22:28–32.
19. Prigatano GP, Wethe JV, Gray JA, Wang N, Chung S, Ng Y-T, Prenger E, Kerrigan JF. Intellectual functioning in presurgical patients with hypothalamic hamartoma and refractory epilepsy. Epilepsy Behav. 2008;13:149–55.
20. Sonoda M, Masuda H, Shirozu H, Ito Y, Akazawa K, Asano E, Kameyama S. Predictors of cognitive function in patients with hypothalamic hamartoma following stereotactic radiofrequency thermocoagulation surgery. Epilepsia. 2017;58:1556–65.
21. Kameyama S, Murakami H, Masuda H, Sugiyama I. Minimally invasive magnetic resonance imaging-guided stereotactic radiofrequency thermocoagulation for epileptogenic hypothalamic hamartomas. Neurosurgery. 2009;65:438–49.
22. Weissenberger AA, Dell ML, Liow K, Theodore W, Frattali CM, Herna D, Zametkin AJ. Aggression and psychiatric comorbidity in children with hypothalamic hamartomas and their unaffected siblings. J Am Acad Child Adolesc Psychiatry. 2001;40:696–703.
23. Veendrick-Meekes MJBM, Verhoeven WMA, van Erp MG, van Blarikom W, Tuinier S. Neuropsychiatric aspects of patients with hypothalamic hamartomas. Epilepsy Behav. 2007;11:218–21.
24. Killeen Z, Bunch R, Kerrigan JF. Psychiatric comorbidity with hypothalamic hamartoma: systematic review for predictive clinical features. Epilepsy Behav. 2017;73:126–30.
25. Mittal S, Mittal M, Montes JL, Farmer JP, Andermann F. Hypothalamic hamartomas. Part 2. Surgical considerations and outcome. Neurosurg Focus. 2013;34(6):E7.
26. Dorfmuller G, Ferrand-Sorbets S, Fohlen M, Delalande O, Kerrigan JF. Surgical procedures for epilepsy-associated hypothalamic hamartomas. In: Arzimanoglou A, Cross H, Gaillard WD, Holtshausen H, Jayakar P, Kahane P, Mathern G, editors. Pediatric epilepsy surgery. 1st ed. Surrey: John Libbey Eurotext; 2016.
27. Jayakar P, Gaillard WD, Tripathi M, Libenson MH, Mathern GW, Cross JH, on behalf of the Task Force for Paediatric Epilepsy Surgery, Commission for Paediatrics, and the diagnostic Commission of the International League Against Epilepsy. Diagnostic test utilization in evaluation for resective epilepsy surgery in children. Epilepsia. 2014;55:507–18.
28. Wethe JV, Prigatano GP, Gray J, Chapple K, Rekate HL, Kerrigan JF. Cognitive functioning before and after surgical resection for hypothalamic hamartoma and epilepsy. Neurology. 2013;81:1044–50.
29. Wagner K, Buschmann F, Zentner J, Trippel M, Schulze-Bonhage A. Memory outcome one year after stereotactic radiosurgery in patients with epilepsy due to hypothalamic hamartoma. Epilepsy Behav. 2014;37:204–9.
30. Kameyama S, Shirozu H, Masuda H, Ito Y, Sonada M, Akezawa K. MRI-guided stereotactic radiofrequency thermocoagulation for 100 hypothalamic hamartomas. J Neurosurg. 2016;124:1503–12.
31. Wagner K, Wethe JV, Schulze-Bonhage A, Trippel M, Rekate H, Prigatano GP, Kerrigan JF. Cognition in epilepsy patients with hypothalamic hamartomas. Epilepsy. 2017;58(suppl 2):85–93.
32. Du VX, Gandhi SV, Rekate HL, Mehta AD. Laser interstitial thermal therapy: a first line treatment for seizures due to hypothalamic hamartoma? Epilepsia. 2017;58(Suppl 2):77–84.

33. Ng YT, Hastriter EV, Wethe J, Chapman KE, Prenger AC, Prigatano GP, Oppenhiem T, Varland M, Rekate HL, Kerrigan JF. Surgical resection of hypothalamic hamartomas for severe behavioral symptoms. Epilepsy Behav. 2011;20:75–8.
34. Hildebrand MS, Griffin NG, Damiano JA, Cops EJ, Burgess R, Ozturk E, Jones NC, Leventer RJ, Freeman JL, Harvey AS, Sadleir LG, Scheffer IE, Major H, Darbro BW, Allen AS, Goldstein DB, Kerrigan JF, Berkovic SF, Heinzen EL. Mutations of the sonic hedgehog pathway underlie hypothalamic hamartoma with gelastic epilepsy. Am J Hum Genet. 2016;99:423–9.
35. Boerwinkle VL, Wilfong AA, Curry DJ. Resting-state functional connectivity by independent component analysis-based markers corresponds to areas of initial seizure propagation established by prior modalities from the hypothalamus. Brain Connect. 2016;6:642–51.
36. Papez JW. Visceral brain, its component parts and their connections. J Nerv Ment Dis. 1958;126:40–56.
37. Lin JJ, Mula M, Hermann BP. Uncovering the neurobehavioral comorbidities of epilepsy over the lifespan. Lancet. 2012;380:1180–92.
38. Ekinci O, Titus JB, Rodopman AA, Berkem M, Trevathan E. Depression and anxiety in children and adolescents with epilepsy: prevalence, risk factors, and treatment. Epilepsy Behav. 2009;14:8–18.
39. Tellez-Zenteno JF, Patten SB, Jette N, Williams J, Wiebe S. Psychiatric comorbidity in epilepsy: a population-based analysis. Epilepsia. 2007;48:2336–44.
40. Bronsard G, Bartolomei F. Rhythms, rhythmicity and aggression. J Physiol Paris. 2013;107:327–34.
41. Gregg TR, Siegel A. Brain structures and neurotransmitters regulating aggression in cats: implications for human aggression. Prog Neuropsychopharmacol Biol Psychiat. 2001;25:91–140.

More Than Just ADHD: Evaluation of Sleep Disorders with Inattention

26

Janet Lam

Case

Brianna is a nearly 7-year-old girl who presents to clinic for difficulty with her attention span. Overall, she has typical early development and is a bilingual Spanish and English speaker whose first language is Spanish. She is overactive in comparison with her peers and easily distracted by background noise and does not listen well or sit still in place. As early as in kindergarten, there were concerns at school that she could not concentrate and tended to be impulsive. There are no safety concerns such as running into the street, wandering in crowds, or unbelting herself in the car. She is not a "daredevil." At home, she understands requests made from her family but either will not or cannot comply with them. Brianna's mother estimates that she acts like a 4-year-old in terms of her attention to requests. Her tantrums are excessive for her age, and she has difficulty with organization. She leaves items strewn about the house, and her mother cleans her room because it would otherwise be an intolerable mess.

Brianna exhibits no repetitive behaviors, dependence on routines, perseverations, tics, or aggression. She tends to argue with siblings or with peers and often does not want to share. Brianna has a good appetite; however, she stands up and leaves the table repeatedly during meals. She goes to bed at 8PM on school nights and is up at 6:30AM. While sleeping, she snores and does some mouth breathing but otherwise demonstrates no snorting, gasping, or pauses in her breathing. She has been noted to be somewhat restless while sleeping with frequent movements during sleep.

Brianna is in a typical classroom setting without special education services. She describes liking books but is disinclined to read them, mentioning that she does not have the energy to read. At one point, she expressed wanting to be a doctor or nurse when she grows up but then changed her mind because she heard that "they have to

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read a lot." She typically takes a very long time to complete homework, often twice as long as would be expected in comparison with peers. School reports were inconsistent; some teachers reported significant inattention and hyperactivity, and others reported no concerns.

Pregnancy and birth history were essentially uncomplicated, notable for some meconium aspiration and 7-day neonatal intensive care unit hospitalization. Birth weight was 6 lb 14 oz, and she was described as a calm baby. She walked around 11 months of age and said her first words in Spanish at 1 year of age. Brianna lives with her parents, and younger brother and sister. There is a report of an extended family member who was noted to have ADHD, learning disability, and required special education services. Brianna had no medical illness except for tympanostomy tubes placed at the age of 5 for frequent ear infections. At the time of her initial evaluation, Brianna had a body mass index at the 77 percentile though was at the 98 percentile for height and weight. Her neurological examination was non-focal, except for mildly decreased tone in all extremities.

In the office, Brianna was quietly, constantly fidgeting and wiggling her arms in and out of her shirt but was otherwise cooperative with cognitive testing. On digit span, she was able to repeat three digits forward, which is at a 3-year-old level, but was not able to consistently repeat four digits forward. She could reverse two digits, which is at a 5-year-old level. She had difficulty with sentence repetition and made errors with sentences at a 4-year-old level. On the Durrell oral reading test, she was able to read a third-grade level paragraph but was slow and had pronunciation errors. She was able to comprehend fully. On the Ayres Scale for handwriting speed, her speed was at the 2.2 grade. Her Goodenough Draw-A-Person test resulted in an age equivalent of 7 years. She correctly copied a 6-year-old figure on Gesell Figures. On block construction, she was able to accurately copy a 6-year block staircase. On the Wide Range Achievement math subtest, she had a raw score of 19 (1.7-grade level equivalent). Behavioral observations at this time were particularly notable for ongoing fidgeting during testing and easy distractibility. On the NICHQ Vanderbilt Parent ADHD scale, she had 6/9 symptoms of inattention and 4/9 symptoms of hyperactivity/impulsivity, suggestive of the diagnosis of ADHD, inattentive type. Although many functions were on level for age, the subjective impression of the examiner was that her performance was adversely affected by her attention.

Clinical Course

A polysomnogram (PSG) was ordered due to the history of snoring, suggestive of possible obstructive sleep apnea. The overnight sleep study revealed obstructive airflow, with an apnea-hypopnea index of 3.1 events per hour, which is in the mildly abnormal range. She was noted to have 100 periodic limb movements with a limb movement index of 13.3. She had 33 periodic limb movement sequences with a periodic limb movement sequence of 4.4, which is borderline for periodic limb movement disorder. Hematologic evaluation showed normal ranges of hemoglobin and hematocrit. Serum iron level was 97 mcg/dL, transferrin 277 mg/dL, TIBC 346 mcg/

dL, %sat 28, and ferritin 16 ng/ml. Otolaryngology consultants did not recommend surgery to remove her tonsils and adenoids. However, the family was contacted due to low ferritin level and advised to start an iron supplement at 3 mg/kg/day.

Case Reflections

Brianna is a child who has symptoms of inattention and hyperactivity at home and at school which appear to meet criteria for attention deficit hyperactivity disorder, though symptoms appear inconsistent based on the reporting at school. ADHD in females can have a variable presentation; teachers of a large classroom of children may not notice symptoms if hyperactivity is less prominent. In addition to ADHD, in this case, sleep problems may impact daytime functioning, resulting in the appearance of inattention and short-term memory problems which may affect school performance. The link between her sleep apnea, periodic limb movements, and ADHD is based on possible disruption of sleep due to sleep fragmentation. There is evidence that untreated sleep apnea results in cognitive deficits and there is a clear association between periodic limb movements and ADHD [1]. She did not endorse symptoms related to restless legs syndrome, but it's likely that she was unable to provide that history. For diagnostic purposes in this case, the differential diagnoses needed to be expanded to include restless legs syndrome and periodic limb movement disorder.

Restless Legs Syndrome

Restless legs syndrome (RLS) is a sensorimotor disorder described as uncomfortable leg sensations and an irresistible urge to move the legs. The leg sensations are worse when sitting or lying and are relieved by movement, particularly at night. There are no standardized diagnostic criteria for the diagnosis of RLS. Eighty percent of patients with RLS have characteristic leg movements during sleep that meet diagnostic criteria for periodic limb movement disorder [1]. RLS is challenging to diagnose in children because of their difficulty in describing the abnormal sensations in their legs and lack of understanding in younger children of the connection between the abnormal sensations and urge to move their legs.

Periodic Limb Movement Disorder

Periodic limb movement disorder (PLMD) is a disorder of repetitive movements, usually in the lower limbs, that occur every 20–40 s during sleep. These movements may appear as brief muscle twitches, jerking movements, or flexion of the feet. They occur in clusters lasting from a few minutes to hours. These movements are identified and quantified as part of the polysomnogram. The prevalence of periodic leg movements in children with ADHD is estimated to be 26% [1].

Neuroanatomy

Much of our understanding regarding structural deficits related to ADHD derives from neuroimaging studies. Fronto-striatal models of ADHD pathophysiology are

supported by findings of altered gray matter volume in the basal ganglia on MRI [2]. Other structural abnormalities noted in ADHD may include gray matter volume reduction in the bilateral visual cortex and cerebellum [2]. Still, ADHD may also be considered a disorder of altered neural connectivity. Diffusion tensor imaging studies of ADHD show anomalies of white matter tracts in the right anterior corona radiata, left cerebellar white matter, and internal capsule [3]. Positron emission tomography (PET) imaging has found disruption of the brain dopamine reward pathway in adults with ADHD compared to controls [2].

Links Between Iron Deficiency, ADHD, and Sleep

Iron deficiency may play a significant role in the pathophysiology of ADHD. Iron is an essential trace metal which is involved in many essential brain functions. First of all, iron is a cofactor of enzymes necessary for the synthesis and catabolism of monoaminergic neurotransmitters, which may be involved in the pathophysiology of ADHD. Additionally, iron deficiency is associated with decreased dopamine transporter expression; and alteration of the dopamine transporter gene has been linked to genetic vulnerability for ADHD [2]. Lastly, iron deficiency may lead to dysfunction in the basal ganglia, also implicated in the pathophysiology of ADHD [2]. In an MRI study comparing brain iron levels between children with and without ADHD, children with ADHD had lower estimated iron levels in the bilateral thalamus and right caudate [4].

In ADHD, the thalamus is a critical component of the cortico-striato-thalamocortical circuit that serves regulatory processes. In sleep, on the other hand, the thalamus is involved in the thalamocortical connections involved in processes related to arousal. It has been hypothesized that, since children with ADHD have longer sleep latencies and more arousals, they may have inadequate sleep duration. As a result, they may be more fatigued during the day and may appear inattentive as a result [5]. Further, they may exhibit increased motor activity in an attempt to stay awake and alert. If, in fact, iron deficiency results in impaired thalamic activity, there may be an impact on alertness [2].

Similarly, iron deficiency plays a role in restless legs syndrome (RLS). This is also based on the role of iron in dopamine synthesis and the association between low serum ferritin levels and RLS severity. More specifically, iron is a cofactor for tyrosine hydroxylase, the rate-limiting enzyme for dopamine synthesis. Iron deficiency has been recognized as altering dopamine D2 receptor density and dopamine transport activity [6]. Furthermore, treatment of RLS with iron therapy or dopamine agonists results in an improvement of symptoms.

Treatment Strategies

Brianna clearly had both inattentive and hyperactive symptoms with reported difficulties in reading. In milder cases, referrals to cognitive-behavioral therapy and neuropsychological testing are reasonable first steps. Obtaining accommodations at school may alleviate the burden associated with poor school performance and improve the negative impression she has about school.

Brianna was found to have mild obstructive sleep apnea, but was not a surgical candidate for an adenotonsillectomy or to warrant other nonsurgical interventions such as continuous positive airway pressure (CPAP) therapy. Continued monitoring with repeat polysomnograms is necessary as the tonsils and adenoids may enlarge over time, resulting in more severe symptoms. Furthermore, she was noted to be very restless with frequent periodic limb movements, though still borderline in meeting diagnostic criteria for PLMD. Iron treatment (3–5 mg/kg/day) is the first line of therapy for children with periodic limb movement disorder or restless legs syndrome. Given its clinical bioavailability, brain iron levels are often approximated with serum ferritin levels. So even though serum iron levels were within the normal range, low serum ferritin level generally reflects necessity for treatment. Recommended ferritin levels are above 50 ng/mL. Treatment with iron supplementation may not only improve sleep problems but also attention and alertness.

Following appropriate diagnosis and treatment with iron supplementation, Brianna is currently stable with school accommodations and with consistent iron treatment. To date, her attentional symptoms and fatigue have improved such that she does not require additional medications.

Clinical Pearls

1. Children with ADHD should also be evaluated for sleep problems. Parents of children with ADHD commonly report bedtime resistance, sleep-onset difficulty, night awakenings, sleep breathing problems, and daytime sleepiness. Additionally, sleep problems may mimic ADHD symptoms [7, 8]. Children who are sleepy may appear inattentive and have difficulty with behavioral regulation and memory. Unlike adults, children can become more hyperactive when they are tired, which could lead observers to think that they are not tired at all.
2. Iron treatment may alleviate symptoms of both ADHD and sleep problems. There is an association between ADHD and PLMD or RLS which suggests that all three disorders may utilize similar neural pathways of dopamine transmission.

Lessons Learned About Neuropsychiatry

Sleep disorders have an important place in the diagnosis and management of ADHD. Clinically, both cause behavioral problems and impact academic performance. The frequent association between these disorders may be linked to a shared neurobiology. Both disorders utilize common neurotransmitter systems and overlap in their neuronal networks [9]. Genetic studies support the involvement of catecholamine systems in both ADHD and sleep regulation. Brain regions involved in the regulation of arousal (e.g., dorsolateral and ventrolateral prefrontal and dorsal anterior cingulate cortices) are sensitive to sleep deprivation and implicated in ADHD pathophysiology.

Circadian rhythm disruption may be relevant for many conditions, including sleep apnea, restless legs syndrome, and even ADHD. Obstructive sleep apnea disrupts the circadian rhythm, based on measurements of decreased melatonin secretion in the middle of the night [10]. Treatment of obstructive sleep apnea restores the circadian rhythm, based on normalization of melatonin secretion after 3 months of CPAP therapy [10].

RLS and PLMD also demonstrate a circadian pattern, with worsening of symptoms during the beginning of sleep at night. There is some evidence that RLS can occur during the day, which may also be misinterpreted as hyperactivity in children with suspected ADHD. It is important to identify whether the excessive movements during the day are due to RLS by asking children if they experience uncomfortable sensory symptoms when they are sitting still.

Sleep problems may also impact the course and outcome of ADHD. Children with both ADHD and RLS had more severe ADHD symptoms compared to children with ADHD alone, possibly due to sleep fragmentation associated with RLS that impacts daytime behavior [11]. Treatment of sleep problems may then result in resolution or reduction of ADHD symptoms.

References

1. Pockett C, Kirk V. Periodic limb movements in sleep and attention deficit hyperactivity disorder: are they related? Paediatr Child Health. 2006;11(6):355–8.
2. Cortese S, Azoulay R, Castellanos FX, et al. Brain iron levels in attention-deficit/hyperactivity disorder: a pilot MRI study. World J Biol Psychiatry. 2012;13:223–31.
3. Cortese S, Castellanos FX. Neuroimaging of attention-deficit/hyperactivity disorder: current neuroscience-informed perspectives for clinicians. Curr Psychiatry Rep. 2012;14(5):568–78.
4. Adisetiyo V, Jensen JH, Tabesh A, Deardorff RL, Fieremans E, Di Martino A, Gray KM, Castellanos FX, Helpern JA. Multimodal MR imaging of brain iron in attention deficit hyperactivity disorder: a noninvasive biomarker that responds to psychostimulant treatment? Radiology. 2014;272(2):524–32.
5. Herman JH. Attention deficit/hyperactivity disorder and sleep in children. Sleep Med Clin. 2015;10:143–9.
6. Burhans MS, Dailey C, Beard Z, Wiesinger J, Murray-Kolb L, Jones BC, et al. Iron deficiency: differential effects on monoamine transporters. Nutr Neurosci. 2005;8(1):31–8.
7. Efron D, Lycett K, Sciberras E. Use of sleep medication in children with ADHD. Sleep Med. 2014;15:472–5.
8. Weiss MD, Salpekar J. Sleep problems in the child with attention-deficit hyperactivity disorder: defining aetiology and appropriate treatments. CNS Drugs. 2010;24(10):811–28.
9. Bassetti CL, Ferini-Strambi L, Brown S, et al. Neurology and psychiatry: waking up to opportunities of sleep. State of the art and clinical/research priorities for the next decade. Eur J Neurol. 2015;22(10):1337–54.
10. Barnas M, Maskey-Warzechowska M, Bielicki P, et al. Diurnal and nocturnal serum melatonin concentrations after treatment with continuous positive airway pressure in patients with obstructive sleep apnea. Pol Arch Intern Med. 2017;127(9):589–96.
11. Konofal E, Cortese S, Marchand M, et al. Impact of restless legs syndrome and iron deficiency on attention-deficit/hyperactivity disorder in children. Sleep Med. 2007;8:711–5.

Part VII

The Pediatric Neuropsychiatric Examination

Introduction

> There is only one cardinal rule: One must always listen to the patient
> Oliver Sacks, MD

Having now explored many instantiations of the clinical approach to diagnosis and treatment, this final chapter provides an organized overview to the evaluation of the child or adolescent with concerns for neuropsychiatric illness. This broad approach can be utilized by practitioners from a variety of training backgrounds and levels of experience and may be tailored to different clinical scenarios and contexts. This approach urges multidisciplinary involvement, careful establishment of a therapeutic alliance, and utilization of a broad range of clinical and diagnostic skills.

Nuances of the Pediatric Neuropsychiatry Evaluation

27

Aaron J. Hauptman, Haley Duncanson, and Jay A. Salpekar

Introduction

Our aim in this chapter is to summarize a thorough pediatric neuropsychiatric examination that can be tailored to a variety of clinical needs. A range of referral types can come to those open to receiving children and adolescents with neuropsychiatric conditions. Sometimes, there is a known neurological illness that is thought to be contributing to psychiatric symptoms. An example of this might be an identified epilepsy, traumatic brain injury, or encephalitis that has been complicated by psychiatric symptoms either secondary to or comorbid with the underlying illness. At other times, the clinician will be asked to assist in work-up and diagnostic clarification for a child who presents with symptoms that cross disciplines, such as atypical psychosis, treatment-refractory attentional and dysexecutive symptoms, unusual abnormal movements, etc.

The neuro*psychiatric* evaluation is different from the neuro*psychological* evaluation. The evaluations can be used to supplement one another, but the methodology, approach, and goals will differ. The latter is a psychological sub-specialty, while the former is a medical one. Both are interested in the structure and function of the brain and how they correlate with psychological, cognitive, sensory, behavioral, and emotional function. The goal of neuropsychological testing is to utilize detailed psychometric testing within a clinically informed framework to characterize the

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nature and extent of cognitive and emotional difficulties, delineate strengths and weaknesses, assist with differential diagnosis, and provide treatment recommendations. The neuropsychiatric examination, on the other hand, is a medical examination that relies less on formalized testing and, instead, focuses on clinical evaluation, neurobehavioral observations, medical history, and physical examination and will often include a focus on medical aspects of diagnosis and treatment such as interpreting lab or imaging data and prescribing psychotropic medication, respectively.

A range of practical issues will dictate details of the evaluation which itself may require significant modification based on the treatment setting. For example, if the patient is being seen by a pediatrician for routine follow-up, the examination approach will necessarily differ from that where a child is being seen in an outpatient psychotherapy session. Often, time for the neuropsychiatric examination is limited, particularly in comparison with the more generous allotments available for neuropsychological testing. As a result, many clinicians will be constrained to a 1 or 2 h appointment at best, and in more common medical settings, such as in general pediatrics, a much shorter span of time is available. Here, we outline a more ideal evaluation, where certain luxuries of time and resources are assumed. This is not to say that these techniques cannot be brought to bear in other contexts. The ultimate goal is in appreciating the conceptual approach of an integrated examination.

Clinicians may or may not have the time, training, or opportunity to complete a full neurological evaluation or a full psychiatric evaluation based on the nature of the consultation. However, the clinician should be able to at least provide a basic neurologic exam and an accurate assessment of mental status. For clinicians uncomfortable with these aspects, we recommend including consultants from other subspecialties, such as in-office psychiatric consultants integrated in a general neurology clinic who can be informally consulted. The nature of neuropsychiatry is cross-disciplinary and team-based; by necessity, clinicians interested in these illnesses will work toward deeper understanding of the surrounding disciplines.

Examination

Pre-evaluation

The same rule for a neuropsychiatric evaluation stands for that of any other subspecialty or consultation-liaison assessment: first, characterize as best as possible the goal of the consultation and the clinical question to be answered. At times, there will be no specific referral question, just a vague sense that the patient's diagnosis does not seem quite to match their symptom cluster, or new symptoms may conflict with the original primary psychiatric diagnosis. We suggest that for such complex patients, the evaluation process should involve active development of hypotheses that are then gradually tested by subsequent data gathering. As such, even without a formal consultation question, clinicians may develop their own internal series of queries based on new data as it is gathered. An example of this may be a patient who is referred for panic attacks but does not describe phenomenology classic for panic.

The clinician may suspect that the events are actually seizures and initially move forward in diagnostic assessment exploring this possibility, obtaining clinical and laboratory data along the way, and then proving or disproving hypotheses as appropriate.

A record review is essential prior to seeing the patient and includes a review of neuroimaging data, neuropsychological evaluations, and any previous psychiatric, neurological, and other sub-specialty evaluations. Most of the time, patients presenting to a pediatric neuropsychiatrist have seen many other clinicians, and insight may be obtained from detailed records. Geneticists, developmental pediatricians, or other medical specialists may have noted subtle findings that could suggest a possible syndrome that has not yet been appreciated or early-life complications that might hint at a predisposing set of risk factors.

Formal aspects of assessment can begin prior to the patient even being in the room. It is advisable that clinics have a standardized set of history forms or formalized rating scales that can be sent to patients and families before the evaluation begins. Data from multiple resources and environments is valuable and diagnostically necessary in the case of attention deficit hyperactivity disorder (ADHD), where symptoms must be present in at least two different settings. In pediatrics, multiple informants may be the only way to understand stressors that could be setting-specific and alternative viewpoints of a child's behavioral inconsistencies. In many instances, use of pre-evaluation history forms streamlines the evaluation process and provides necessary information without having to return for multiple points of contact after the session. Standardized data from rating scales can also be particularly helpful for symptom monitoring and comparison of treatment effects from a pre-intervention baseline. Establishment of a quantifiable set of target symptoms that can be routinely monitored can help focus the evaluation when multiple categories of symptoms are present.

Basic pediatric psychiatry symptom rating scales may be useful, but it cannot be overstated that the goal of these forms is not to make a diagnosis but, rather, to provide additional data. Sometimes, pre-evaluation forms create more problems than they solve, as when a patient marks off symptoms on a bipolar disorder screening form that could be interpreted as mania when, in fact, they are describing developmentally appropriate behaviors, ADHD, or an exacerbation of depressive, anxiety, or compulsive behaviors in the setting of a stressor. Clinical correlates for rating scales are necessary as is the case with any lab test or other diagnostic study encountered in other fields of medicine. A table of a small selection of screening forms is included at the end of this chapter.

After the preexamination paperwork, the first step of the interview happens in the waiting room. What are the interactions like? Is the child sitting on the parent's lap? Is the adolescent withdrawn to the corner? Is the patient appropriate with the administrative staff: is there aggression, inappropriate degrees of friendliness, or dysregulated behavior? Furthermore, what are the physical characteristics of the individual? Do they have morphological features suggestive of a particular syndrome such as fragile X, Down syndrome, or another common syndrome? Are visible scars present from craniotomy or other neurosurgical procedures? Is the individual displaying

obsessional or compulsive behavior or signs of Tourette's syndrome? One can observe gait and station, gross motor coordination, dystonic posturing, and many other abnormal movements on the way to the interview room. The process of examining speech starts as soon as the patient is greeted.

Evaluation

The nature of the evaluation will be governed by context and specific referral questions. First, the question is whom to have in the room and how to gather information effectively and efficiently. With an older adolescent, sometimes the parental input will be minimal; with a young child, it is possible that the entire history will be obtained from the parent and the time with the child can be spent engaging in diagnostic play that both builds rapport and offers opportunity for more subtle assessment.

It is important to know at the beginning, what the presenting complaint of the family is and how it may differ from that of the referring physician. Furthermore, it is also useful to know the child's understanding of the purpose of the evaluation and how it might differ from that of the family.

History of Present Illness

Once the formal appointment begins, one should start with thorough psychiatric, neurological, and other medical histories. It is usually prudent to adhere to the common practice of beginning with medical history, then moving on to any formalized neurobehavioral status examination that may be done, and then shifting to a physical examination.

The history of present illness will generally provide the main substance of the assessment. Here, the family and individual are asked to describe specific symptoms of concern, when they began, how they have evolved over time, what diagnoses and treatments have already been considered or tried, what interventions are helpful, and what exacerbates symptoms of concern. In complex pediatric neuropsychiatry cases, often it is more efficient to pursue a linear narrative because of the number of different diagnoses and treatments that are intermingled. Sometimes, the traditional history of present illness must be abandoned and replaced by a stepwise chronologic history from the prenatal period through the present day.

In gathering the past historical details, one should include psychiatric and medical details and use specifics whenever possible rather than generalities. Sometimes, multiple prompts are necessary to elicit this information as patients or families may not categorize problems the way that clinicians do. For example, "Have you ever had any neurological problems?" can elicit a "No" even though the child has an identified genetic syndrome that can impact neurocognitive and emotional development. Standard past medical and psychiatric historical details necessary to include are any prior medical and psychiatric diagnoses, treatments and hospitalizations,

and psychiatric or other mental health encounters (however brief and in whatever setting). It is important to be wary of past symptoms of failure to thrive, muscular weakness or altered tonicity, focal neurological symptoms, seizures, periods of altered consciousness or memory, spontaneous behavioral and emotional changes, significant changes in weight, and regression in skills or abilities.

Pregnancy and Birth

Prenatal and very early-life histories are crucial. Some psychiatric disorders can be the direct result of in utero exposures; others have characteristic signs in the first days of life. Still other conditions may not be directly causally related to perinatal events but may increase risk of illness later in life. For pre- and perinatal histories, inquiries of prenatal exposures should include licit and illicit substances, antibiotics, and other medications as well as herbal remedies. History of maternal infections (e.g., HIV, syphilis, and rubella), nutritional deficiencies, medical complications (e.g., gestational diabetes, preeclampsia, eclampsia, opioid withdrawal), and stressors including physical and emotional abuse should all be noted. Details of routine screening tests are also important; in particular, any abnormalities on ultrasound, amniocentesis, etc. should be reviewed.

A detailed birth history includes gestational age at birth, whether the birth was spontaneous or induced, vaginal delivery or cesarean section, heart rate abnormalities, birth weight, length and head circumference, jaundice, meconium aspiration, APGAR scores, and whether a prolonged hospital stay for the child or the mother was required. Also notable is the presence of other complications soon after birth necessitating a return to hospital such as high fever, frequent infection, meningitis, or febrile seizures.

Developmental History

Developmental and educational histories are core parts of the pediatric neuropsychiatric evaluation and are very important to establish whether the concerns being addressed are longstanding or acquired in the context of previously neurotypical development. Some underlying conditions can put one at increased risk for another neuropsychiatric disorder, such as autism increasing risk for epilepsy or early traumatic brain injury putting one at greater risk for anxiety and mood disorders. At other times, history may reduce risks of subsequent illness.

Many reference charts and formalized assessments are available to assist in determining whether a patient's development follows typical patterns. As a first step, it is important to know whether delays are global or domain-specific. Typical developmental domains include gross and fine motor, sensory systems, speech and language, social and communication, feeding, toileting, and sleeping. If there is a known neurological insult, the history can also include how the developmental trajectory in each domain may have subsequently changed. Similarly, any history of developmental regression following previously typical development should be noted. Potential early-life exposures to toxins through paint, toys, water

supply, etc. should be included in questioning, as well as consideration of other exposures through breast milk during feeding in infancy. As part of the developmental history, screening for core symptoms of autism spectrum disorder should be done. Assessment of social reciprocity, stereotypy, and restricted ranges of activities and interests is relevant as autism may be present in many genetic and developmental disorders and can overlap with complex conditions including catatonia, schizophrenia, obsessive-compulsive disorder, or specific learning and language disabilities.

School History

In the context of evaluating early development, the patient's history of early intervention services can provide a bridge to the evaluation of education. If early intervention or other special education services were provided, then formal designations and service details may be available. Other details worth pursuing include school transfers between public and private schools, presence of an individualized education program (IEP) or a section 504 plan, push-in or pull-out services, counseling, use of alternative communication methods such as a picture board or computer-facilitated system, and if the services utilized were deemed helpful.

Whether the child or adolescent is typically developing or not, a sense of how they do in school, including areas of strength, weakness, and interests, is important. Details of their social interactions especially during lunch and recess may provide important clues of their social skills. A child's understanding of friendship and whether any friends can even be named may provide a window into social pragmatics.

Safety Assessment

Safety concerns are always an important part of a psychiatric assessment. In addition to the standard questions about self-injury, suicidal thoughts, attempts, and high-risk behaviors, a pediatric neuropsychiatric examination should also include repetitive behaviors and compulsive behaviors such as skin or hair-picking, eye-gouging, and self-soothing behaviors (such as rocking and headbanging).

If a child has a history of suicidal thoughts or attempts, it is important to understand specifically how close the individual has ever been to completing suicide and the planning involved in making the attempt. The methods potentially used in suicide attempts are relevant parts of the history as well as what safeguards have been placed at home to prevent future self-harm. With children, as with older, developmentally disabled individuals, it is important to assess their understanding of what it means to die and whether they believed their actions, regardless of actual lethality risk, would lead to death. Sometimes a relatively benign form of self-injury may have been believed by the child to have potentially resulted in fatal injury. In another instance, a dangerous suicide attempt might have been employed in order to result in some perceived gain, like reincarnation or to be with a deceased relative, without the deeper understanding of the permanence of death and mortality.

Parents should be interviewed regarding their own history of depression, anxiety, and substance use as well as other mental health concerns. Intimate partner violence, substance exposure in the home, parental abuse history, social supports, and parental perception of family functioning, all can play a significant role in a child's suicidality and should be evaluated. Appropriate ancillary referrals for parental diagnosis and treatment may be placed as needed.

Review of Systems

A general neuropsychiatric systems review includes screening questions related to depression, bipolar disorder, psychotic phenomena, anxiety spectrum disorders, obsessional and compulsive symptomatology, eating habits and disordered behavior, social engagement and pragmatics abnormalities, and symptoms and behaviors associated with personality disorders. It should also include changes in awareness and consciousness, cognitive and memory changes, attentional and hyperactive symptoms, balance problems and clumsiness, muscular and other motor changes, alterations in speech, sensory changes, headache, dizziness, and autonomic changes. A detailed discussion of sleep habits including latency to fall asleep, frequent waking, snoring, early waking, frequent movements, dream enactment, and daytime sleepiness are all relevant.

The review of systems will also be dependent on the patient's history. For example, if the patient has a history concerning for epilepsy or psychogenic non-epileptic episodes, a detailed history of the semiology of the episodes should be taken. This might include events surrounding onset, auras, signs of lateralization, and postictal symptoms. The neuropsychiatrist will wish to delve further into each of these, to elicit from the patient and collateral informants regarding staring spells, unusual posturing or motor automatisms, sudden behavioral or emotional changes, feelings of deja vu and jamais vu, rising or falling epigastric sensations, marching sensory and motor changes, intense feelings of anxiety or fear, etc. These questions do not need to be used in screening all patients; however, they may be useful in a range of differential diagnoses. One should be similarly prepared to systematically inquire about neurological details of other common symptoms that are seen in pediatric neuropsychiatry such as headaches, pain, tics and other abnormal movements, post-concussive symptoms, and others.

In addition to evaluation of neuropsychiatric symptoms, the review of symptoms should also include a general medical review of symptoms. This includes constitutional, ear/nose/throat, cardiovascular, respiratory, gastrointestinal, urinary, dermatologic, hematologic, endocrine, and musculoskeletal symptoms and changes. These can sometimes be provided to the child and family as a checklist before the appointment to rule out broad categories of symptoms so that, in the appointment, the focus can go to the most relevant symptomatology. Neuropsychiatric illnesses are by definition very often multi-system, and so clues to an underlying disorder or to symptom exacerbation or progression may lay in symptomatology that is not specifically neurological or psychiatric.

There are some in-person formal assessments that can be utilized as part of the clinical interview, if appropriate. This can include the Abnormal Involuntary Movement Scale (AIMS), a formalized assessment usually checked when patients are taking neuroleptics. Similarly, there are certain validated rating sheets that not only make the clinician's job easier but that can help the quality of the interview. For example, in patients with concern for obsessive-compulsive symptoms, a full Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) will include questions that are difficult to conduct without a formalized method. Questions such as sexual obsessive thoughts or uncomfortable compulsions can sometimes be more easily elicited when it is an aspect of a routine screen. Some clinicians, particularly in research settings, will base their interviews on semi-structured testing, such as the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children (KSADS), which can be useful in structuring the interview and approaching difficult questions with helpful partially formalized language arranged by age. This could be helpful to peruse, particularly for the non-psychiatrist, to get a sense of appropriate language for different symptoms based on patient age.

Social History

Social history is an important source of information that, among other things, can contribute to understanding of underlying stressors that can impact a medical condition or may explain the trigger for new, medically unexplained symptoms. Simply having a complex medical illness, unfortunately, does not immunize one against significant life stressors. Thus, social history should include, at very least, living situation, parental marital status, occupants of the home, recent changes and stressors, and trauma history (including abuse, neglect, domestic violence exposure, sexual trauma history, and homelessness). It is important to evaluate for current safety screening as well as child protective services involvement.

Substance use can be screened here if not done at other points of the interview. In addition to traditional drugs of abuse, misuse of prescription medications should be considered. Age of first substance use, details of use pattern, and the subjective benefit of the substance are all useful information to obtain. Specific substances and their use will depend on time and region. For example, prior to 2012, synthetic cathinones ("bath salts") were legal in many states and could be readily purchased. This often would not come up unless teens were specifically asked. Other substances, such as kratom, have shifting legality based on region, and the clinician should be aware of substance use patterns and legalities in their local area. It is increasingly common for patients and their families to utilize nonprescribed medications for management of conditions (such as epilepsy) either with or without their doctors' recommendation (such as cannabidiol or medical marijuana). Finally, use of specific diets should be discussed. This is relevant as some highly restrictive diets can put one at risk of specific vitamin deficiencies unless carefully monitored.

Others, such as ketogenic, gluten-free, casein-free, and other diets are sometimes used as alternative treatments for a range of disorders.

A gender and sexual history is important. The patient's gender history and status are crucial not only because depression, suicide, and sexual victimization risk are elevated in circumstances of gender identity dysphoria or in transgender individuals but also because appropriate use of preferred pronouns and name assists in the establishment of good therapeutic alliance. Additional factors to be aware of include use of pubertal blockers or other hormone treatments and family support of the child's experience. Sexual history should include sexual activity, menstruation, use of birth control, relationship status, abuse or trauma, and sexually transmitted disease history.

Use of media, including smartphone application usage, video gaming, and other electronics utilization, is an important detail and may offer insight into social interaction. Finally, determination of whether the child is being bullied or is involved in the bullying of others is of relevance.

Family History

Family histories can sometimes be best completed with a family genogram, particularly if there is a specific disorder, symptom, or trait being tracked. Standard family histories of psychiatric and neurological disorders are crucial given the heritability of many disorders. It can be important to know histories of autoimmune, dermatologic, endocrine, cardiac, and a range of other categories of medical disorders that can be associated with psychiatric syndromes. Family history of psychiatric treatment and diagnoses and hospitalization, suicidality, and substance use are relevant factors. Often, symptomatic individuals will not have received formal diagnoses, so lifestyle patterns and symptom exacerbations may need to be specified independent of formal psychiatric care. History of adoption, nonpaternity, having a twin, nontraditional parentage, and other factors that may impact the patient's genetic history are relevant. As in any pediatric evaluation, there can be very complex issues of living situation, caregiver status, parental rights, child protective services involvement, medical decision-making rights, and other legal circumstances that may require clarification.

Physical Examination

The physical examination is a complicated aspect of the evaluation because of variability in clinician experience and care goals. In many circumstances, psychiatrists or psychotherapists, for example, should not be engaging in a complete physical examination due to maintenance of appropriate therapeutic boundaries. In urgent or emergent care settings or in neurology and pediatrics clinics, the physical examination will form a key part of any routine examination. Psychiatrists are also trained in physical examination, and, in some settings, this can be an appropriate aspect of their routine evaluation.

The detailed neurological examination of the child and adolescent by age and developmental level is beyond the scope of this chapter. But, if an examination is to be completed, it should necessarily include a number of components. These include height, weight, head circumference, and vital signs. Skin exam should be done to evaluate for any signs of neurocutaneous syndromes. Similarly, one should observe for hair whorl location and palmar crease as well as the quality of hair, eyebrows, joints, nails, and signs of atypical facial features and other dysmorphologies. Neurological examination should include the cranial nerves, gross and fine motor function, coordination, tone, gait, station and sensory function, sensory examination, cerebellar testing, and reflexes (including pathological reflexes). The details of these will necessarily depend on age and developmental status.

If the physical examination is not completed, there are certain observations that must be made since some physical characteristics can suggest the presence of specific genetic disorders that can impact neuropsychiatric functioning. The family should be asked if there are any skin lesions, axillary and other freckling, birth marks, or discolorations. A dysmorphology evaluation should include facial features (face and head shape, eye location and shape, flattening of philtrum and nasolabial folds, visible freckling, etc.), hand and foot shape, finger length and number, flexibility, palmar crease, and webbing. In addition to dysmorphology, a clinician can readily include aspects of a physical examination without doing a formal examination. For example, in the process of play therapy for either diagnosis or treatment, most cranial nerves, handedness, strength, gross sensation, gait, and station can all be assessed.

Age-appropriate balance and fine and gross motor development and coordination should be evaluated, with a focus on typicality of developmental milestones. Speech and language milestones can be evaluated with particular attention to receptive and expressive milestones. These can also be evaluated either formally, as in a clinical pediatric appointment or bedside examination, or informally, as in a psychotherapeutic setting (e.g., play therapy or an initial psychiatric appointment).

The Neuropsychiatric Mental Status Examination

In contrast to adult neuropsychiatry or behavioral neurology clinics, where formal standardized testing is often done routinely by the physician, in children this is much less often the case. For example, it is routine for the primary care doctor, geriatrician, psychiatrist, neurologist or other specialist to give a Mini-Mental Status Examination, Montreal Cognitive Assessment, or another well-validated clinical examination to screen for cognitive impairment in adult patients. These measures offer a cutoff score at which performance below this threshold would suggest the presence of cognitive impairment. In pediatric populations, this is much less common. This is in large part due to the variable nature of developmental stages in children; that is to say, it would be unwise to administer a single screening measure with one cut score that could reliably assess cognitive status in a 4-year-old, a 12-year-old, and an 18-year-old.

Adult neuropsychiatrists and behavioral neurologists oftentimes will not necessarily utilize the complex scoring approaches or the statistical methods that neuropsychologists are trained in. This can be reasonable in many circumstances but sometimes can result in confusion and should be done with particular caution in children, because the integrity of various cognitive functions changes rapidly across the developmental period, sometimes in the order of months. Although the gold standard for the neurocognitive assessment of children is to refer patients for a comprehensive neuropsychological evaluation, during which the neuropsychologist is able to select appropriate measures that assess all domains of functioning and compare the patient's performance against age, education, and/or gender-based norms, it is still important for the neuropsychiatrist to gain an understanding of the child's level of cognitive functioning during the evaluation. This requires a strong foundational knowledge of the typical developmental trajectory of neurocognitive skills and emotional function. Many children coming to a neuropsychiatry appointment may have already had psychoeducational testing as part of a school evaluation. This often is a good start to gain a sense of specific learning difficulties, overall intelligence, and specific school needs. There are also developmental screening measures available to physicians that can provide indicators of potential delays in functioning. Finally, behavioral observations of neurocognitive skills and mood states are important aspects of the neuropsychiatric mental status exam and should be documented during the assessment.

Behavioral Observations

In general, observations should be made about the major domains of neurocognitive and socioemotional functioning including attention, executive functioning, language, memory, interpersonal skills, affect, and mood. With regard to attention and executive functioning, observations about activity level, temperament, impulsivity, initiation, distractibility, cooperation, persistence, level of alertness, ability to shift between activities or objects of interest, and ability to self-soothe should be made. For example, does the child have difficulty remaining seated and appear fidgety or restless? Does the child become overly upset when the clinician removes an object and have difficulty shifting interest to a new object? Does the child impulsively take items off the clinician's desk or interrupt frequently? Does the interviewer need to repeat instructions due to inattention or slow the rate of speech due to processing speed deficits? Are the child's thought processes tangential or does he or she often lose a train of thought? In young children, object permanence is suggested to be one of the earliest signs of working memory capacity and should be observed roughly around 12 months of age. This can be tested by engaging a child's interest in an object, covering it with a blanket, and seeing if the child attempts to look under the blanket for the toy.

Language formulation, including observations about word retrieval, organization of syntactic output, and grammatical errors atypical for age, should be observed. Difficulties with word retrieval may appear as frequent pauses in speech as the individual searches for the word and/or frequent use of non-specific or incorrect word

choice (such as "thing" or "the duck what went in the woods"). Problems with language comprehension should be suspected when the neuropsychiatrist must use simpler language than is typical for the child's age. Oftentimes, language comprehension difficulties are also apparent when the child responds to a question in a related, but incorrect, manner. For example, when asked, "What did you eat for breakfast this morning?," the child with comprehension issues may respond with, "Fork." Clearly the child can comprehend some words in the question (i.e., "eat") but is not yet able to comprehend at the syntactic level. If there is a concern about memory, asking a child about a recent memorable event such as his or her birthday, a recent field trip, or a family vacation can give clues about his or her ability to recall autobiographical information as well as proving a language sample. By ages 3–4, children should be able to verbally recall familiar experiences.

Informal observation of play skills in younger children can reveal a wealth of information about both a child's ability to learn and his or her social skills. Imitation is observed in as young as 12-day-old infants. Children who cannot imitate the behaviors of adults (e.g., children with autism) are at significant risk for problems with social skills and learning. Informal assessments include observing if the child waves "bye-bye" or asking the child to mimic hand movements and/or facial expressions. Joint attention involves the coordinated attention between a person and an object or event of interest in the environment. Joint attention is a social skill that develops early (around 9 months of age) and is problematic in children with autism or other developmental disabilities. This skill can be assessed in the office simply by having the clinician state the child's name, direct their own gaze and point toward an object, and then direct their gaze back toward the child. The child should follow the clinician's gaze toward the object and then return their gaze back to the clinician in order to make eye contact.

In typically developing children, relational play skills should be mastered around age 2 years of age. Imaginary play, in contrast, tends to develop around 3 years of age. These skills are early indicators of theory of mind and ability to generalize social routines. The neuropsychiatrist concerned about delays in these areas can simply provide the child with toys and observe whether or not the child is able to pretend to take a sip from an empty cup (relational play) or pretend to give a baby a bath with an imaginary bar of soap (imaginary play) after providing nondirective prompts (e.g., "The baby is hungry!" *not* "Give the baby a drink.").

In older children, social skills can be informally tested by observing whether or not the child makes appropriate eye contact, initiates and/or maintains conversations, takes social bids, and/or has an understanding of friendships and social relationships. The neuropsychiatrist suspicious of social skill delays may ask the child questions such as, "Do you have a best friend? Why is he/she your best friend? What do you like to do together? Do you ever do anything that makes him or her angry? Why do you think that he/she gets mad about that? Have you ever been bullied or anyone you know been bullied? Why do you think they were bullied?" and so on. Questions such as these attempt to gauge the child's understanding of social

relationships and the emotional reactions of others and can provide a surprising wealth of information. One way to test a child's ability to take social bids and initiate and maintain conversation is to make a nondirective statement that attempts to encourage the child to reciprocate and maintain conversation. For example, if the child states that he or she recently went to Florida, the examiner might respond with, "Oh! I have been to Florida." A typically developing child will often follow the lead by asking questions about the clinician's experience.

Behavioral observations of visuospatial and fine motor skills can be informally assessed by asking the child to scribble and draw simple (straight lines, circles, etc.) and complex shapes (a triangle, diamond, square, etc.). By 2–3 years of age, a child should be able to scribble with a crayon, and by 3–4 years of age, a child should be able to imitate a circle. The ability to copy more complex shapes typically do not develop until after first grade. Attention to pencil grasp and hand dominance also provide clues as to whether or not fine motor delays may be present. A pincer grasp should be observed around 12 months of age. In first graders, a tripod (holding the pencil with the index finger and thumb, resting against the middle finger) or modified tripod pencil grip (holding the pencil with the index finger, middle finger, and thumb resting against the ring finger) should be well established. Awkward grasps or grasps that are immature for age (e.g., a palmer or fisted grasp in a first grader) may indicate poor motor control or low muscle tone that requires an occupational therapy evaluation.

Developmental Screening Measures

Formal measures can be useful to objectively quantify and monitor the status of children at risk for developmental delays. Screening measures can estimate a developmental age equivalent at which the child is currently functioning, while patterns of impairment may suggest potential underlying etiologies. For example, a child who performs poorly on tasks assessing social and language functioning may be at risk for autism. Similarly, a child who performs poorly on tasks of letter and sound identification, despite adequate teaching of these skills at school, may be at risk for the development of a reading or writing disorder. However, it needs to be emphasized that screening measures generally lack the strong psychometric properties of neuropsychological measures. Screeners are not diagnostic tools or IQ tests. If a screening test identifies a potential problem, based on the nature of the difficulty, further consultation with a neuropsychologist, speech and language therapist, and/or occupational therapist is indicated. Screening tools do not provide conclusive evidence of developmental delays or lack thereof, and the clinician suspicious of delays despite a normal screening exam should still refer for consultation by a specialist. The measures listed below require direct administration of a series of tests that require use of manipulatives by the clinician. Tasks include activities such as requiring the child to reproduce structures built with blocks, providing writing samples, copying figures, matching symbols, naming pictures of objects, answering comprehension questions, repeating digits of increasing length, performing calculations, and so forth.

Table 27.1 Selected screening questionnaires and approximate age ranges

General or cross-diagnostic symptoms, function, and parental or child concerns		
CBCL	Childhood Behavior Checklist	1.5–18 years
PMC	Progress Monitoring Checklist	3–17 years
PSC-17 or -35	Pediatric Symptoms Checklist	4–16 years
SDQ	Strengths and Difficulties Questionnaire	4–17 years
BASC	Behavior Assessment for Children	2–21 years
BITSEA	Brief Infant Toddler Social Emotional Assessment	12–36 months
PHQ-A	Patient Health Questionnaire for Adolescents	13–18 years
ESI	Early Symptom Inventory	3–6 years
CSI	Child Symptom Inventory	5–12 years
CASI	Child and Adolescent Symptom Inventory	5–18 years
ASI	Adolescent Symptom Inventory	12–18 years
BYI	Beck Youth Inventory	7–18 years
Developmental screeners		
ASQ-3	Ages and Stages Questionnaire	0–36 months
ASQ-SE	Ages and Stages Questionnaire: Social-Emotional	6–60 months
CDI	Child Developmental Inventory	0–6 months
SIB-R	Scales of Independent Behavior-Revised	birth to 80 years
Autism		
M-CHAT	Modified Checklist for Autism in Toddlers	16–30 months
ASSQ	Autism Spectrum Screening Questionnaire	7–16 years
SCQ	Social Communication Questionnaire	4+ years
SRS	Social Responsiveness Scale	2.5–18+ years
GARS	The Gilliam Autism Rating Scale	3–22 years
Anxiety		
SCARED	Screen for Childhood Anxiety-Related	
	Emotional Disorders	8–18 years
SCAS	Spence Children's Anxiety Scale	3–12 years
RCMAS	Revised Children's Manifest Anxiety Scale	6–19 years
Trauma/PTSD		
CTSQ	Childhood Trauma Screening Questionnaire	7–16 years
TESI-C	Trauma Events Screening Inventory for Children	8–18 years
CPSS	Child PTSD Symptom Scale	8–18 years
CATS	Child and Adolescent Trauma Screen	3–6 years
		7–17 years
UCLA-PTSD-RI	University of California at Los Angeles	
	Post-traumatic Stress Disorder Reaction Index	7–18 years
TSCC	Trauma Symptom Checklist for Children	8–12 years
TSCYC	Trauma Symptom Checklist for Young Children	3–12 years
Depression		
MFQ	Moods and Feelings Questionnaire	8–18 years
BDI	Beck Depression Index	14+ years
ADHD and frontal/executive function		
Vanderbilt	NICHQ Vanderbilt Assessment Scale	6–12 years
SNAP	Swanson, Nolan, and Pelham	6–17 years
Connors CBRS	Connors Comprehensive Behavior Rating Scale	6–18 years

Table 27.1 (continued)

BRIEF	Behavior Rating Inventory of Executive Function	2–18+ years
Bipolar disorder		
CBQ version 2.0	Childhood Bipolar Questionnaire	5–17 years
CMRS	Child Mania Rating Scale	9–17 years
Substances		
CRAFT	Car, Relax, Alone, Forget, Friends, Trouble	Lifetime use
Parental function screens		
PHQ-2	Patient Health Questionnaire-2	Adult
PHQ-9	Patient Health Questionnaire-9	Adult
MGFS	McMaster General Functioning Scale	Adult
PSQ	Parent Screening Questionnaire	Adult
In-person formal tests		
KSADS-PL 5	Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children	6–18 years
CY-BOCS	Children's Yale-Brown Obsessive-Compulsive scale	6–17 years
YGTSS	Yale Global Tics Severity Scale	6–17 years
AIMS	Abnormal Involuntary Movement Scale	Lifetime use
CAPS-CA-5	Clinician-Administered PTSD Scale for DSM-5-	
	Child/Adolescent Version	7 years+

A few screening batteries that are approved for use by a range of practitioners, including medical doctors, are highlighted in Table 27.1. The Denver II Developmental Screening Test (DDST-II) is a developmental screener that is designed to be administered to children from birth to age 6. The total test requires 10–20 min to administer. Four developmental areas are addressed: personal-social, fine motor-adaptive, language, and gross motor. The normative population for the DDST-II is based on a sample of 2096 children from Colorado. Results allow examiners to classify children as in the normal range, suspect, or delayed. Children can score "delay" on an item if they fail to do an item that is at or below their age level, whereas they can score "normal" on an item that they complete correctly and is indicated to be at their age level. A score of "caution" is provided on an item if a child fails to answer it correctly, and 75–90% of children their age can complete the item. Training in the instrument is available through the publishers.

The Gesell Developmental Observation-Revised (GDO-R; © 2013 Gesell Institute of Child Development) is another developmental screener that uses direct observations to evaluate a child's cognitive, language, motor, and social-emotional responses in five domains: developmental, letter/numbers, language/comprehension, visual/spatial, and social/emotional/adaptive. Normative data was collected from a nationwide sample of 1287 children. One can expect to spend 45 min administering the test. A child's performance in each domain corresponds to a rating of either age-appropriate, emerging, or concern. A developmental age can also be determined. Purchase and use of the kit requires attendance at a training workshop held by the publishers. The Gesell Early Screener (GES; © 2013 Gesell Institute of

Child Development) is an early screener, based on selected GDO-R items, that is intended for use with children age 3 to 6 years. The benefit of the GES is that it is substantially quicker to administer (taking on average about 15 min to complete). One disadvantage is that a developmental age is not provided.

Post-evaluation

After the core of the appointment is complete, the majority of cases will require coordination with the patient's other providers in order to best determine diagnosis, any necessary follow-up studies, and treatment planning. Often, the initial appointment, even for a single consultative evaluation, is just the beginning. In many cases, exploring potential overlap in treatments can in itself be a powerful intervention; for example, if a child is experiencing greater agitation or dysregulated behavior in the setting of levetiracetam or perampanel initiation for epilepsy, working with other specialists to cross-titrate to an alternative antiepileptic drug is preferable to the addition of another medication to manage what may be a side effect to the original medicine. Other examples might be the use of a tricyclic antidepressant for comorbid depression and migraines, treatment of comorbid fatigue and attentional difficulty in traumatic brain injury with stimulants, or use of a mood stabilizer for aggression in an individual with developmental disabilities and seizures.

Specific laboratory, imaging studies and specialist referrals will often be necessary. Some investigations may fall outside of the realm of the specialist's comfort level, such as ordering and interpreting functional neuroimaging for the psychiatrist or interpreting ideal therapeutic psychiatric drug levels for the neurologist. Thus, collaboration may be necessary for these aspects of work-up as well. The investigations to be utilized will depend heavily on the specific condition suspected and patient presentation. Other chapters throughout this book explore specific work-up recommendations and interpretation of test results in a wide range of conditions. It is common for patients who present to neuropsychiatry services to have a sense that aspects of their diagnosis have been missed or have not been fully investigated by clinicians. Thus, evaluations should be as extensive as possible to thoroughly explore a wide range of potentially relevant conditions before arriving at a high index of suspicion for a particular disorder. This is especially the case if a diagnosis of "conversion disorder" or "psychological factors affecting other medical conditions" is being considered.

By definition, parents who bring their children for neuropsychiatric evaluation are struggling to assess complex symptoms that cross medical disciplines. They often feel that their concerns have not been heard or that their child's symptoms have not been adequately explored or explained. Often, a detailed and honest discussion of the clinician's hypothesis after all of the data has been collected can be a very powerful intervention in and of itself. Often parents and patients feel abandoned by medical practitioners who are intimidated by complexity and ambiguity.

Clinicians will have a range of comfort levels in how to provide feedback, but at the very least, reassurance that the clinician will be supportive even if rapid answers are not at hand can go a long way to build a treatment alliance and enhance the evaluative process. It may be helpful, if the clinical situation warrants it, to set up a second appointment 1–2 weeks later specifically for feedback so that any imaging, laboratory studies or other tests as well as clinician discussions can be completed in the interim. Empathic listening, unconditional positive regard, careful multidisciplinary collaboration, and consistent communication between providers, caregivers, and families form important foundations for the medical care of the neuropsychiatrically complex child. Diagnosis, in neuropsychiatry, is often a therapeutic intervention.

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