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

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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.

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