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HIGHLIGHT

by R. Matt Alderson, PhD and Larry L. Mullins, PhD*

Theoretical and Clinical Implications of Using an ADHD Framework to Understand Attention, Concentration, and Executive Functioning Deficits in Pediatric Cancer Survivors

(Commentary on Kahalley et al., page 110)

For the past two decades, researchers have consistently identified a pattern of neurocognitive deficits (e.g., attention/concentration difficulties and deficits in executive functioning) in many childhood cancer survivors that may significantly impact their academic performance, social/interpersonal relationships, and vocational success if left unidentified or untreated. As such, it is imperative that researchers focus on understanding the specific nature of these deficits, their precise etiology, and efficacious treatment approaches.

To better understand the nature of these deficits, a number of research teams have used an attention-deficit/hyperactivity disorder (ADHD) conceptual framework to guide their research efforts. Findings suggest that indeed many childhood survivors of leukemia [1] and brain tumors [2] evidence attentional difficulties consistent with the inattentive subtype of ADHD. In this issue of *Pediatric Blood & Cancer*, Kahalley et al. further explore rates of occurrence of ADHD and secondary ADHD (SADHD) in pediatric cancer survivors and compare those rates to that in the general population. The term SADHD refers to an ADHD-like presentation acquired from a non-developmental presentation, such as a traumatic brain injury, or for the purposes of their research, neuro-toxic cancer treatments. Importantly, they conclude that the clinical presentation of cancer survivors does not resemble that of either ADHD or SADHD, and suggest that the current DSM-IV diagnostic criteria and nomenclature may not characterize the types of deficits that pediatric cancer survivors manifest.

We would like to underscore the problems in utilizing a classic, developmental ADHD framework for understanding cognitive late effects in childhood cancer survivors, and argue that there are inherent theoretical and clinical shortcomings to this approach. Our first theoretical concerns center on the issue of diagnostic specificity. Identification of SADHD as a potential diagnosis in pediatric cancer survivors that only differs from conventional/premorbid ADHD with regard to etiology and onset, ignores the very characteristics that distinguish ADHD from other childhood disorders. That is, age of onset, pervasiveness, and impairment are particularly important in discriminating ADHD from other childhood disorders, given the characteristic symptoms of ADHD are not pathognomic. For example, attention difficulties are frequently associated with almost all diagnoses of childhood. Children with anxiety or mood disorders are often restless, fidgety, and may struggle to attend to class lectures due to the interference of persistent ruminations. Racing thoughts, pressured speech, and/or delusions associated with early onset bipolar disorder are expected to create similar interference with attentional processes, while children with autism spectrum disorders are frequently described as ''being in their own world.'' To sum, it is illogical to conclude that an ADHD framework should be invoked simply because a similar cluster of symptoms are evident in childhood cancer survivors.

A second concern revolves around the issue of e*tiological differences and underlying cognitive processes.* Neurological correlates of developmental ADHD-related deficits include the pre-frontal and frontal cortices, basal ganglia [3], and dopaminergic and noradrenergic systems [4]. Strong evidence of ADHD as a neurological disorder may mislead researchers to conclude damage to an associated brain region secondary to intrathecal chemotherapy, radiation, and/or surgery would result in the same disorder. This fails to consider the unique developmental trajectory and underlying core processes associated with developmental ADHD, as well as potential differences in neural plasticity. Within the last few decades, executive functions such as behavioral inhibition [5] and working memory [6], have been increasingly identified as potential core deficits of ADHD. Affected children with a diagnosis of SADHD are expected to exhibit similar executive function deficits if SADHD is a comparable disorder. To date, relatively few studies have examined the effect of acute lymphocytic leukemia and/or interferon-alpha and chemotherapy treatments on executive functions, and findings have been relatively equivocal [7], and/or based on parent ratings scales rather than rigorous experimental/neuropsychological methods.

Importantly, studies indicate that the phenotype of developmental ADHD changes over time such that affected individuals tend to exhibit fewer problems related to hyperactivity in adulthood [8]. This finding likely reflects that ADHD results from delayed maturation of cortical areas involved in motor control and attention, and treatments modalities often change (e.g., change from MPH to Adderal) according to changes in symptoms. It is not clear if childhood cancer survivors exhibit a similar change in their symptoms over time, particularly since the etiology is a traumatic insult to their brain (e.g., chemotherapy), rather than a complex interaction of genetics and environmental influences. Recent studies of the Cogmed working memory training reveal promising findings that suggest the neural plasticity of children

[1]Department of Psychology, Oklahoma State University, Stillwater, Oklahoma

*Correspondence to: Larry L. Mullins, Professor, Department of Psychology, Oklahoma State University, Stillwater, OK 74078.
E-mail: larry.mullins@okstate.edu

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with ADHD may allow for improved working memory that generalizes to other non-WM executive functions associated with the disorder [9]. However, it is not clear if childhood cancer survivors would exhibit similar neural plasticity. Grouping children with developmental ADHD and SADHD implies a shared etiology that would benefit from similar treatment modalities, an implication that may have little basis in current science.

Finally, using an ADHD framework for late effects in pediatric cancer survivors may be quite problematic as it concerns the use of clinical interventions that are based on such a model. Indeed, this conceptualization has led a number of researchers (and who knows how many medical and psychological providers in the community) to recommend the use of stimulant medications. Although some research has demonstrated improvement in childhood cancer survivors on measures of attentional functioning with pharmacological interventions used traditionally for the treatment of ADHD, rates of improvement are far lower than in children diagnosed with developmental ADHD. The practice of ''diagnosis by medication response'' is inappropriate and scientifically unsound. The literature suggests most children benefit from some dose of psychostimulants, so this is not unique to SADHD, or developmental ADHD for that matter. Similarly, use of the ADHD framework for childhood cancer survivors has implications for undermining successful interventions within the classroom context. Inappropriate accommodations may be made or appropriate accommodations not made, when a classroom teacher is led to believe that a pediatric cancer survivor has developmental ADHD, and does not understand the unique nature of cognitive late effects.

In summary, we encourage researchers to resist the temptation to use a theoretical and diagnostic framework that may have proven somewhat fruitful in understanding the behavior of typically developing children, but may not be appropriate for children who have undergone treatment for cancer.

REFERENCES

1. Krull KR, Brouwers P, Jain N, et al. Folate pathway genetic polymorphisms are related to attention disorders in childhood leukemia survivors. J Pediatr 2008;152:101–105.
2. Patel SK, Lai-Yates JJ, Anderson JW, Katz ER. Attention dysfunction and parent reporting in children with brain tumors. Pediatr Blood Cancer 2007;49:970–974.
3. Crosbie J, Pérusse D, Barr CL, Schachar RJ. Validating psychiatric endophenotypes: Inhibitory control and attention deficit hyperactivity disorder. Neurosci Biobehav Rev 2008;32:40–55.
4. Rieger M, Gauggel S, Burmeister K. Inhibition of ongoing responses following frontal, nonfrontal, and basal ganglia lesions. Neuropsychology 2003;17:272–282.
5. Barkley RA. Behavioral inhibition, sustained attention, and executive functions: Constructing a unifying theory of ADHD. Psychol Bull 1997;121:65–94.
6. Rapport MD, Alderson RM, Kofler MJ, Sarver DE, Bolden J, Sims V. Working memory deficit in boys with attention-deficit/hyperactivity disorder (ADHD): The contribution of the central executive and subsystem processes. J Abnorm Child Psychol 2008;36:825–837.
7. Scheibel RS, Valentine AD, O'Brien S, Meyers CA. Cognitive dysfunction and depression during treatment with interferon-alpha and chemotherapy. J Neuropsychiatry Clin Neurosci 2004;16:185–191.
8. Biederman J, Mick E, Faraone SV. Age-dependent decline of symptoms of attention deficit hyperactivity disorder: Impact of remission definition and symptom type. Am J Psychiatry 2000;15:816–818.
9. Klingberg T. Training and plasticity of working memory. Trends Cogn Sci 2010;14:318–324.