NEURODEVELOPMENT AND CHRONIC ILLNESS: MECHANISMS OF DISEASE AND TREATMENT

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Successful treatment of many childhood diseases once considered terminal has resulted in the emergence of long-term effects of the disease or consequences of treatment that were previously unrecognized. Many of these long-term effects involve the central nervous system (CNS) and are developmental in the way that they emerge over time. Because we are now able to observe the natural history of childhood diseases such as sickle cell anemia or HIV, or the consequences of treatment of disease such as leukemia, brain tumors, or kidney disease, we are also able to study a number of biological mechanisms that result in long-term neurocognitive impairment. While some of the neurodevelopmental outcomes can be directly linked to structural damage of the CNS, other systems (e.g., hematologic, immunologic, pulmonary) appear to play crucial indirect roles in the development of the CNS and neurocognitive abilities because of the way that they affect the course of brain development and activity of the brain across time. Important interactions between acute disease factors, biological mechanisms, age at the time of disease or treatment effect, and disruptions in patterns of development after successful treatment or management all provide support for a neurodevelopmental model of childhood chronic illness. Testing this model may make it possible to more accurately predict the timing and degree of severity of long-term neurodevelopmental consequences, provide guidance for improved treatment and prevention, and offer better understanding of neurodevelopmental disruptions that occur in other non-chronic illness related disabilities.

Key Words: neurocognitive impairment; childhood chronic illness; childhood disease late effects; neurodevelopmental disability

Improvements in imaging techniques, diagnostic genetics, pharmaceutical development, and availability of well-designed clinical trials have resulted in a relative explosion in both understanding and successful treatment of many diseases of childhood that were, as recently as the late 1970s, either usually terminal, unrecognized, or severely understudied. Childhood cancer now enjoys an overall survival rate of nearly 80% [National Cancer Institute, 2006]. HIV/AIDS has gone from being a devastating disease for children who acquired the virus by vertical (mother to child) transmission to one that is prevented in about 98% of the cases [Centers for Disease Control and Prevention, 2006] or managed as a chronic illness for many children well into the late teen and early young adult years [McConnell et al., 2005]. A 15-year, multi-center natural history study of sickle cell disease in newborns [Gill et al., 1995] has led to new treatments that have nearly eliminated early death due to bacterial infection in young children [Falletta et al., 1995], and has opened up many new treatment options that were not available as recently as the early 1990s [Iannone et al., 2003; Kratovil et al., 2006]. As exciting as these advances in treatment have been, an unexpected and undesired outcome has begun to be recognized. As these children survive past childhood, we are becoming increasingly aware of the degree that the natural history of the disease and the consequences of treatment can adversely affect brain development and emergence of cognitive abilities after treatment. With the recognition of neurodevelopmental mal-outcomes, we have also begun to consider some of disease- and treatment-related mechanisms that lead to these outcomes.

This issue of Mental Retardation and Developmental Disabilities Research Reviews includes reviews of studies of the cognitive outcomes of childhood cancer, sickle cell disease, HIV, and kidney disease [Butler and Haser, this issue; Gerson et al., this issue; Schatz and McClellan, this issue; Willen, this issue], as well as reviews of studies of the biological mechanisms associated with these outcomes [Cole and Kamen, this issue; DeBaun, this issue; Mitchell, this issue]. This article builds on these disease-specific reviews to describe an integrated model of neurodevelopment for children treated for chronic illness that (a) describes biological mechanisms associated with these diseases and treatments that lead to neurodevelopmental challenges, (b) examines the relationship between timing of disease or treatment-related CNS impairment and ability- and age-specific neurodevelopmental disabilities over the course of child’s life, and (c) suggests how this model can be applied to treatment of existing disabilities, prevention of later disabilities, and translation of the principles of the model to other neurodevelopmental disabilities not associated with childhood chronic illnesses.
TYPICAL NEURODEVELOPMENT AND CHRONIC ILLNESS

In contrast to children with neurodevelopmental disabilities resulting from genetic conditions or prenatal adverse events associated with exposure to toxins or other trauma, children with chronic illness, as a rule, have no predisposing factors for neurodevelopmental disabilities. Unless there is a concurrent and unrelated genetic or environmental risk, most children with chronic illness can be assumed to follow a typical pattern of development, meeting milestones within normative ranges and progressing from skill to skill in a predictable fashion. We can expect that early development (through the first 3 years of life) will be dominated by advances in gross motor abilities (e.g., standing, walking, throwing a ball) and both receptive and expressive language abilities (e.g., babbling, first words, expanding vocabulary, and short sentences to express needs). Verbal memory and processing of oral language will dominate development during this period. Between 3 and 7 years of age, we can anticipate that regulation of attention and emotion will begin to solidify, along with development and refinement of fine motor coordination, visual processing, including visual memory, visual-spatial skills, and visual–motor coordination, and the ability to process complex information quickly and accurately. Between 7 and 30 years of age, development of cognitive abilities would be expected to include advancement of organizational and planning skills, ability to rapidly process complex visual and auditory information, increased capacity for storage and retrieval of complex content [Green and Palfrey, 2002].

Underlying the developmental course of these functional abilities is a concurrent process of brain development. Brain structures associated with language and gross motor abilities have primacy during the first 3 years of life, accompanied by processes of dendritic pruning [Huttenlocher, 1979], myelination (primarily in the frontal cortex) [In- der and Huppi, 2000; Volpe, 2000], and development of an extensive system of complex connecting structures in the basal ganglia and throughout the frontal cortex [Huttenlocher, 1979; Lenroot and Giedd, 2006] that accelerates during the preschool years and continues through the third decade of life [Yakovelev and Lecours, 1967]. Along with this structural development, a network of vasculature, consisting primarily of micro-vascular, expands throughout the brain to support metabolic activity and ongoing growth of the brain [Lee et al., 2006]. All of this may also be concurrently affected by developmental changes in the neuroendocrine system [Creyghton et al., 2004].

Other systems, not usually directly associated with CNS development and function, are additionally critical to this typical neurodevelopmental process. Pulmonary function and oxygen delivery are essential for brain development and metabolic function, and disruption in these functions is associated with greater risk for cognitive impairment [Beebe et al., 2004; Hogan et al., 2006; Kurnatowski et al., 2006]. Hematologic factors, such as normal platelet function and red cell function, assure efficient oxygen delivery to the CNS unencumbered by thrombotic events (e.g., bleeding or excessive clotting) that are related to increased risk for vascular infarct [Armstrong et al., 1996; Lynch et al., 2005]. A functional immunologic system appears to prevent infectious processes that might damage the CNS, and there is evidence that disruptions in immune function may contribute substantially to abnormalities in CNS development [McAllister et al., 1997; Epstein and Gelbard, 1999].

A typical neurodevelopmental pattern of both brain development and function is anticipated for most children with chronic illness. For those whose disease and/or treatment affects any of the systems that contribute directly or indirectly to typical brain development, alterations in these systems or developmental processes may have either immediate, noticeable effects on functional abilities, or the effects may be delayed and not detectable until the functional abilities associated with the disruption are detectable in typically developing children.

ATYPICAL NEURODEVELOPMENT IN CRONICALLY ILL CHILDREN

Acute Changes

Atypical brain development and neurodevelopmental cognitive challenges in children treated for chronic illnesses may, therefore, be quite complex. These children may experience acute brain dysfunction due to (a) structural injury (e.g., neurosurgery to treat a brain tumor) [Beebe et al., 2005; Vinchon et al., 2005; Scarzello et al., 2006] (b) acute disruption of brain metabolism due to vascular injury (e.g., stroke) [Chadduck et al., 1995], or (c) acute alterations in hormonal function [Agha and Thompson, 2006]. Similarly, an acute hypoxic event (e.g., upper airway obstruction or acute chest syndrome in sickle cell disease), abnormal production of platelets, or severe anemia can produce changes in the brain that are evident immediately and may constitute life-threatening emergencies [Henderson et al., 2003]. Some of these acute changes result in changes in cognitive, emotional, or social function that are of short-term duration and resolve after acute treatment is provided [Doxey et al., 1999; Santoro et al., 2005]. However, some of these acute events may result in permanent injury that is associated with loss of previous abilities, progressive loss of function, or disruption in continued development of abilities along a typical trajectory [Minn et al., 2005; Schwartz and Major, 2006]. Any of these events can have a lasting impact on brain function that persists long after the acute episode is resolved.

Developmental Changes

Besides acute changes, there is growing evidence that children treated for a number of chronic illnesses may experience injury to brain processes and functions that are not immediately detectable at the time of the injury. In these cases, the disease and treatment appear to have minimal effect on the brain structures and processes that are developed and in place prior onset of disease and treatment. Instead, the primary effect is disruption of the development of brain structure and processes that typically occur after the time the treatment is provided, a disruption that may influence the emergence of functional abilities across the life of the child. These kinds of disruptions are much more subtle than acute injury.

Some of the more common examples of disease and treatment processes associated with these neurodevelopmental mal-outcomes include disease mechanisms and treatments that (a) disrupt myelin formation and development of networks of connecting structures (e.g., cranial radiation therapy for brain tumors) [Reddick et al., 2000; Mulhem et al., 2001], (b) produce immunologic changes that usually support typical brain development and function (e.g., HIV infection, prolonged immuno-suppression associated with stem cell or solid organ transplantation) [Escobar et al., 2005; also see Mitchell, this issue, for a review], (c) destroy microvasculature through calcification or atrophy (e.g., calcifications following treatment for leukemia or microvascular infarctions associated with sickle-related vascular occlusion) [Hertzberg et al., 1997;
Prengler et al., 2005), (d) disrupt biochemical pathways that support typical brain development and function (e.g., anti-folates used in the treatment of leukemia) [see Cole and Kamen, this issue, for a review], or (e) interfere with the biological processes that support brain development (e.g., poor pulmonary function resulting in sleep hypoxia; chronic anemia that leads to chronic inadequate brain oxygen profusion) [Pickett et al., 1999; Armstrong, 2005; Kheirandish and Gozal, 2006; Kunatowski et al., 2006]. Most of these consequences of chronic illness and treatment are not evident acutely; they only emerge over time, and are only seen at the point in time when the neurodevelopmental trajectory reaches the point when a typically developing child displays the ability and the child with a chronic illness does not [Armstrong and Horn, 1996; Armstrong et al., 1999; Armstrong and Briery, 2004]. Investigators working in the field of childhood cancer have used the term “cognitive late effects” to label neurodevelopmental disruptions in brain structure, process, and function that follow cancer treatment because they are often detected long after the treatment is administered [Landier et al., 2004]. This concept of cognitive late effects can be applied to many chronic illnesses besides childhood cancer.

Treatment Specific Factors Influencing Neurodevelopmental Outcome

A number of other specific disease and treatment factors influence the intensity and scope of neurodevelopmental late effects. Diseases that directly affect the CNS (e.g., brain tumors, stroke, CNS infections) may produce a range of neurodevelopmental late effects based on (a) the size and location of the CNS tissue change [Mulhern et al., 2004] or (b) indirect effects of the primary disease (e.g., injury to sensory nerves because of direct pressure or increased/sustained intracranial pressure) [Kortmann et al., 2003]. Genetic variation in the severity of the underlying disease (e.g., HbSS versus HbSC genotype in sickle cell disease) [Armstrong et al., 1996; Hoppe et al., 2003] may also contribute to variation in late effects. Treatment for these diseases may produce late effects of differing severity because of (a) inadvertent consequences of surgical treatment [Doxey et al., 1999; Beebe et al., 2005], (b) treatment intensity (e.g., dose of radiation therapy in the treatment of brain tumors) [Mulhern et al., 1998; Mulhern et al., 2004], or (c) delivery schedule and chronicity of medication exposure (e.g., dose and schedule of methotrexate in treatment of acute lymphoblastic leukemia) [Mahoney et al., 1998; Montour-Proulx et al., 2005].

While the term chronic illness encompasses a class of diseases of childhood, in reality there is tremendous variation in the natural history of each illness and the complexity of the treatment involved for each. Some diseases have an acute onset and a set course of treatment with subsequent surveillance follow-up (e.g., cancer, solid organ failure requiring transplantation), while others have an unpredictable natural history that is influenced by adherence with a medical regimen (e.g., HIV) [Raeda et al., 2006; Willen, this issue], changes in the medical regimen as new treatments become available (e.g., HIV, sickle cell disease) [de Montalembert et al., 2006; Kratovil et al., 2006], or variations in the natural progression of the illness over time (e.g., sickle cell anemia) [Pegelow et al., 2002].

Other Non-Disease Factors Influencing Neurodevelopmental Outcome

The fact that a child has a chronic illness does not ensure that other risk factors for neurodevelopmental disability are eliminated. Family history for neurodevelopmental conditions associated with genetic factors (e.g., attention deficit hyperactivity disorder; dyslexia), birth complications (e.g., prematurity), other complex disorders (e.g., autism spectrum disorder), or environmental factors (e.g., head trauma, substance exposure during pregnancy, or lack of opportunity for educational opportunities because of hospitalizations or isolation requirements) may contribute to neurodevelopmental outcomes in children who also have an identified chronic illness, even though these factors are unrelated to the chronic illness or its’ treatment.

A NEURODEVELOPMENTAL MODEL OF CHRONIC ILLNESS

In 1991, Cousens and her colleagues [Cousens et al., 1991] described four specific deficits in survivors of childhood acute lymphoblastic leukemia (ALL) associated with cranial radiation therapy and intrathecal chemotherapy. These included deficits in the areas of attention, visual-spatial skills, memory, and arithmetic. Missing from this list were deficits in language abilities and gross motor abilities. This led to a series of studies over the next 15 years that confirmed the hypothesis that treatment for ALL resulted in neurodevelopmental impairment, but that some functions appeared largely protected from the effects of treatment and factors such as age at time of diagnosis or onset of treatment, gender, and intensity of treatment had a significant effect on the scope and severity of impairments [see Armstrong and Mulhern, 1999; Armstrong and Briery, 2004; Mulhern et al., 2004 for reviews]. From these observations and similar observations of children with other chronic illnesses, a model for understanding cognitive late effects in many chronic illnesses was developed [Armstrong and Horn, 1996].

This model has four core components:

(a) Most chronic illnesses and treatment of chronic illness primarily affect growth and development of the brain, and are largely not associated with injury to and deterioration of existing structures, processes, and functions. Brain structures, processes, and functions that are developed prior to the onset of the illness generally appear to be intact and continue on a relatively typical developmental course. There are exceptions. Ineffectively treated perinatally acquired HIV often results in a progressive loss of function [Nozyce et al., 1994; Gay et al., 1995], leukencephalopathy following cranial radiation therapy is also associated with loss of white matter [Reddick et al., 2000; Mulhern et al., 2001], and repeated inductive events in sickle cell disease can result in cumulative injuries that appear to produce progressive loss of function [Schatz et al., 2002]. These situations all involve a disease process that is not controlled by treatment and is actively progressing or producing new insults to the CNS. For diseases or treatments that have a time-limited injury, the late effect appears to be primarily developmental and not a result of progressive loss.

(b) The age of the child at the time of onset of disease or treatments that affect the CNS is a critical feature in determining the scope and severity of late neurocognitive effects. Brain structures, processes, and functions that typically develop after the age that treatment is administered appear to be most
predict what abilities are likely to be impaired at what age for children with different chronic illnesses, but this requires prospective studies that test the current assumptions about typical and disrupted trajectories of neurodevelopment.

Children with chronic illnesses may present with a neurodevelopmental learning profile that is dramatically different from those generally encountered in the educational system. Since many chronic illnesses have their onset of symptoms or require treatment after during or after the preschool period [e.g., Gay et al., 1995; Pegelow et al., 2002], these children often have significant strengths in verbal abilities and oral language, but may have significant and change weaknesses in processing speed, visual-spatial-motor abilities, and other attention and emotion regulation abilities [Armstrong and Briery, 2004; also see Butler and Haser, this issue]. Addressing the educational needs of these children can be challenging. Many academic programs emphasize weaknesses (e.g., reading and writing) while minimizing strengths (e.g., listening and speaking), making successful academic progress challenging for children treated for chronic illnesses. Providing appropriate accommodations emphasizing areas of strength while reducing emphasis on areas of weakness may ensure that children have academic progress consistent with their areas of strength [Armstrong and Briery, 2004].

Interventions focused on correcting areas of neurocognitive weakness may benefit from the neurodevelopmental model. Cognitive remediation is an intervention based on the concept that using mass-practice and assisted skill development to address areas of deficit can promote brain plasticity and improve skills in the areas where late neurocognitive effects are detected [Butler and Copeland, 2002; Yerys et al., 2003; Butler and Mulhern, 2005]. This approach is initially promising in its ability to improve attention and some areas of academic achievement, but it requires significant effort and cost to achieve these gains. The neurodevelopmental model suggests that the best time for use of cognitive remediation may not be when deficits are detected, but in anticipation of their occurring. This may require testing intervention components that support the sequence of brain development at the onset of disease or treatment when brain injury is assumed to first occur.

Another important implication of this model is its application to how childhood chronic illnesses are treated. Recognition of the delayed neurodevelopmental effects of cranial radiation therapy significantly altered approaches to treatment of children with CNS tumors in the mid-1980s. Chemotherapy regimens were successfully shown to prevent tumor progression and permit delay of radiation for very young children [Duffner et al., 1999], and subsequent protocols have focused on further reducing radiation therapy to the brain to prevent neurocognitive late effects [Duffner, 2004]. Clinical investigations using transcranial Doppler ultrasonography to evaluate developmental changes in the vasculature of the CNS that are associated with subsequent stroke have lead to early intervention with chronic transfusion [Lee et al., 2006], hydroxyurea [Gulbis et al., 2005; Kratoval et al., 2006], and bone marrow transplantation [Walters et al., 2005] for children with sickle cell disease and thalassemia. Understanding the mechanisms involved in neurodevelopmental late effects of many childhood chronic illnesses can lead to modifications in treatment that provide the same disease management or cure benefits, while reducing the long-term neurodevelopmental mal-outcomes.

With ongoing advances in genetic diagnostics and establishment of genome relationships to clinical outcomes, continued development of the empirical foundation for this neurodevelopmental model in childhood chronic illness may have implications for other neurodevelopmental disabilities. Since it is possible, with many of the chronic illnesses, to determine the point at which brain injury occurs and the mechanisms involved in that injury, it also becomes possible to design studies that precisely describe the neurodevelopmental course. Well designed, prospective neuroimaging and neuropsychological studies may provide information that can be applied more directly to children with neurodevelopmental disabilities that do not have an onset that can be precisely determined. By understanding more precisely how CNS development in children with chronic illnesses is altered by specific genetic risk, changes in structure, and physiological processes, we may gain an understanding of how these changes occur for children with neurodevelopmental disabilities that are not the result of a chronic illness. This kind of transdisciplinary exchange is already taking place in some specific areas such as using cord blood transplantation to treat children with metabolic disorders that typically lead to severe developmental disability and early death [Escobar et al., 2005].
the complex mechanisms of neurodevelopment related to childhood chronic illness and treatments are further defined, the opportunities will expand quickly to apply this knowledge to all children with neurodevelopmental disabilities, regardless of whether the etiology is because of disease, genetic factors, environmental exposures, or trauma.

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