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ABSTRACT

A developmental neuropsychological model is presented to address critical factors critical to the functional outcome in children with human immunodeficiency virus (HIV) infection. In the model, which is derived from work at the Boston Children's Hospital Acquired Immune Deficiency Syndrome (AIDS) program, neuropsychological outcomes are determined by an interaction between various potential contributing risk factors and the timing of the central nervous system (CNS) disease process and treatments. The model incorporates these factors in a framework with particular emphasis on the differential impact of the disease process relative to the child's stage of brain development. CNS manifestations early in brain development result in more global neuropsychological effects due to a less differentiated state of neurological and neuropsychological development, while later manifestations result in relatively more specific and subtle effects. A better understanding of the neuropsychological profiles of children with AIDS has implications for development of specific and appropriate cognitive and academic interventions. Includes 15 references. (JDD)

A Developmental Neuropsychological Model for the Study of Children with HIV Infection

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A comprehensive developmental neuropsychological model is presented to address the factors critical to the functional outcome in children with HIV infection. Adult models are not applicable due to hypothesized differences in disease effects on the mature versus developing brain. The timing of the CNS manifestation in HIV is emphasized. The model is derived from work at the Boston Children's Hospital AIDS program and recent reports where outcome has varied widely. Neuropsychological outcomes will be determined by an interaction between non-HIV contributing risk factors and the timing of the CNS disease process and treatments. A framework is provided for the explanation of the variety of recently reported research findings. A comprehensive multivariate model is essential to predict the neuropsychological course and to direct interventions.

A Developmental Neuropsychological Model for the Study of Children with HIV Infection

Introduction

There is an increasing incidence of HIV virus in children, primarily via vertical transmission with perinatal infection. Knowledge of the developmental outcomes for these children is important to determine the nature of the disease process and appropriate remedial interventions. Patients followed by our group have ranged from those who are severely impaired at birth to others with essentially normal early development to date. Studies on similar populations have also shown variability in functional outcome. Some of the variability can be explained by non-HIV risk factors affecting development such as maternal drug use, nutritional status, and SES. None of the studies have controlled for all of these relevant contributing risk factors. Equally important, none of the studies have as yet included the issue of the developmental timing of the HIV-related CNS manifestations and treatments upon structural and neurobehavioral outcomes. A developmental neuropsychological model is proposed to incorporate these factors in a comprehensive framework with particular emphasis on the differential impact of the disease process relative to the child's stage of brain development. This model is derived from data gathered by regular neuropsychological examinations of patients with HIV infection (natural history and AZT treat) in a pediatric AIDS program.

Developmental Neuropsychological Model of Children with HIV Infection

The present state of knowledge regarding the neuropsychological outcome of AIDS has largely been established with adult populations (e.g., AIDS dementia complex) which reflects the disease process affecting a fully developed central nervous system. Application os this knowledge base to children is not necessarily appropriate because insult to the developing system is clearly different than insult to the mature, fully developed system (Isseroff, Schwartz, and Bugbee, 1983; Kolb, 1985; Spreen, Tupper, Risser, Tuokko, and Edgell, 1984). The child's neurological and neuropsychological development proceeds from a relatively undifferentiated state to a highly differentiated and integrated system. Like other disorders (e.g., lead toxicity-Shaheen, 1984; cranial radiation for ALL - Waber, in press), the developmental timing of the CNS manifestations of HIV infection will determine the degree and type of functional outcome (illustrated in primate research by Goldman-Rakic, 1985).

With respect to the model illustrated below specific neuropsychological outcomes will be determined by an interaction between the various potential contributing risk factors and the timing of the CNS disease process and treatments.

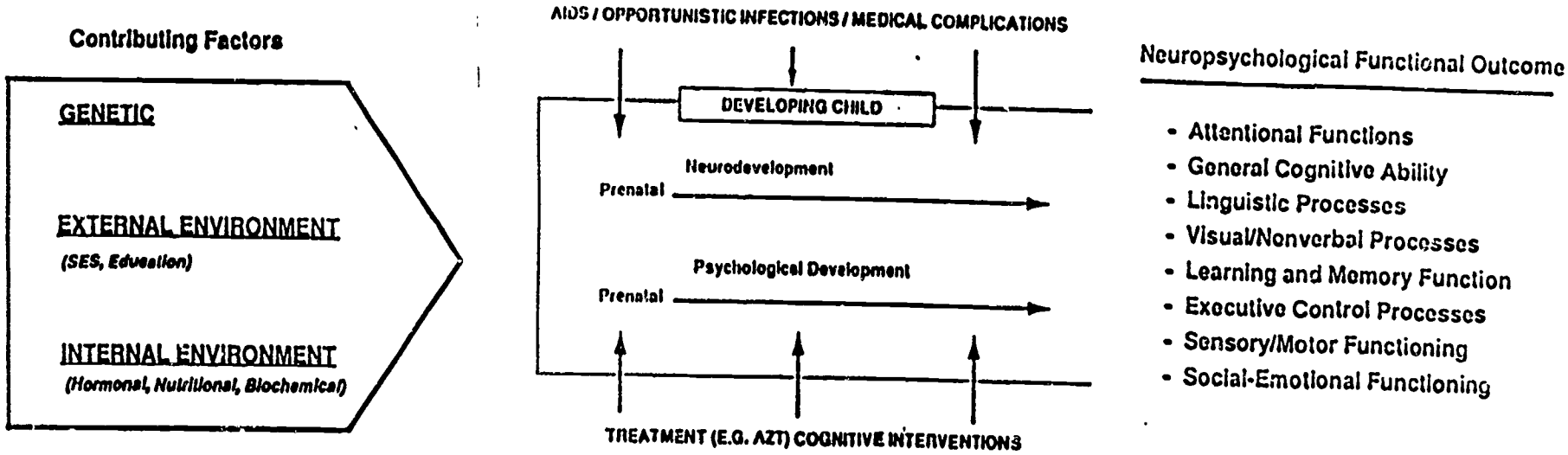

Figure 1. Developmental Neuropsychological Model of HIV Infection in Children.

Contributing risk factors found in certain groups of AIDS patients include the non-AIDS variables that are known to independently impact on development including: genetic composition, internal environment (e.g., hormonal, nutritional, prematurity, and maternal drug use) and external environment (e.g., SES, education experience).

Timing of the CNS disease process and treatments in development is critical to both neurological and neuropsychological outcome. Specific neurologic abnormalities found in adults are also reported in children (e.g., brain calcifications, white matter abnormalities, and cerebral atrophy). However, in children normal neurodevelopmental processes (e.g., synaptogenesis, programmed cell death, myelinization) will be adversely affected; the timing of the CNS disease manifestation will be critical in determining the type and degree of abnormality. Such compromise of normal neurodevelopmental processes will be associated with abnormal neuropsychological development differential outcomes depending upon timing as well. For example, inadequate myelinization during certain neurodevelopmental periods could lead to functional deficits associated with white matter disorders as described by Rourke (1987, 1988).

Specific neuropsychological functional outcomes will be observed based on the above outlined factors. Detailed neuropsychological examinations must include analysis of multiple age-relevant domains of functioning in order to precisely specify the scope of effects. Global IQ indices alone do not provide an adequate description of specific compromise and sparing of functions associated with the timing of HIV-related CNS insult.

Predicted Effects of HIV Disease During Development

CNS manifestations early in brain development result in more global neuropsychological effects due to a less differentiated state of neurological and neuropsychological development as illustrated by the Case 1 that we report with neonatal CNS involvement. In contrast, CNS manifestations after some period of brain and cognitive development will have less devastating global neuropsychological effects as illustrated in the cases of a four and five year old child. CNS manifestations relatively late in brain and cognitive development may result in relatively more specific and subtle effects as seen in Case 4- older case example. In the absence of effective treatments, the progressive nature of the HIV-related CNS disorder will result in more severe and eventually global detericration in all of the situations described above, irrespective of the developmental timing factor.

Implications

Given the multivariate nature of the problem of HIV infection in children, a comprehensive neuropsychological model is essential to understand the various potential outcomes, to predict the

neuropsychological course, and to direct therapeutic management. Additionally, this model is able to provide a general framework for the explanation of the various pediatric HIV research findings recently reported on developmental neuropsychological outcome (Brouwens, Pizzo et. al, 1989; Hittelman, et. al, 1989; Kletter, et. al, 1989; Scott, et.al, 1989;) and treatment effects (e.g., Pizzo et. al, 1988). The range of non-HIV related contributing factors and their interaction with neurological and neuropsychological developmental timetable must be considered to better understand the variable outcomes associated with HIV infection in children. More precise definition of the effects of the AIDS disease process on the developing brain will help to elucidate the neuropsychological outcomes and vice versa. Ultimately, a better understanding of the neuropsychological profiles of children with AIDS will lead to more specific and appropriate cognitive and academic interventions.

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