New Research Directions in Neuroepidemiology

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INTRODUCTION

Neuroepidemiology includes the study of a wide range of conditions of the central and peripheral nervous systems. Cerebrovascular accident (stroke), Parkinson's disease, multiple sclerosis, head injury, the epilepsies, cerebral palsy, and the dementias, especially Alzheimer's disease, are significant causes of morbidity and mortality from neurologic diseases (1). The epidemiology of many of these conditions has been reviewed recently (2-4) and is not covered here. Rather, this review focuses on two neurologic conditions, Alzheimer's disease and white matter damage in the newborn, that are likely to be important public health problems in the year 2000 and beyond because of changes in population dynamics at both the beginning and end of life and because they serve as paradigms for the role of immune response mediators in the etiology of neurologic diseases.

The aging of the US population has been well documented. It is estimated that nearly 79 million persons will be older than age 65 years in 2050, and more than 18 million will be aged 85 years or older (5). Thus, a large number of people in the United States will be entering the age range in which the incidence rates of dementing illnesses, especially Alzheimer's disease, are the highest (6). Efforts to better understand the etiology of Alzheimer's disease and to develop interventions to slow its progress or otherwise treat the disorder effectively are of immediate importance.

While few advances have been made in reducing the rate of preterm delivery (7-9), great strides in the treatment of preterm and very preterm infants have increased the number of surviving newborns who are at increased risk of adverse neurologic outcomes. In 1995, nearly 60,000 infants (81 percent of livebirths) born prior to a gestational age of 32 weeks survived the first year of life (10). This number is likely to increase with continued improvements in the care of the preterm neonate. Thus, it becomes imperative to more precisely identify factors that contribute to the etiologies of the major neurologic problems in childhood associated with preterm birth—cerebral palsy and mental retardation as well as learning, attention, behavior, and seizure disorders.

Immune mechanisms are presently a major focus of neurobiologic studies of central nervous system (CNS) damage. Immune response parameters, such as interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF-α), have been implicated in the etiologies of numerous neurologic disorders, including Alzheimer’s disease (11-14), periventricular leukomalacia (15, 16), multiple sclerosis (17, 18), and the residual damage to the brain produced by strokes (19-22) and severe head trauma (23, 24). The advent of “biomarker epidemiology” has greatly enhanced the ability of epidemiologists to investigate disease processes in human populations at the molecular level (25), and the measurement of biomarkers is now being applied to the study of neurologic disorders. Alzheimer’s disease and periventricular leukomalacia are presented here as prototypes for processes that may ultimately prove to have widespread effects in causing damage within the CNS (26).

Before discussing Alzheimer’s disease and periventricular leukomalacia separately, we offer an approach that might link our understanding of the etiology of each. One way of looking at the two disorders is to separate phenomena that incite brain damage from those that might minimize damage. This exercise in seeking links between a gray matter disorder in older adults and a white matter disorder in preterm newborns is intended to show how a biologic basis is needed for generation of hypotheses to be tested.

Final common pathway

Evidence is continuing to accrue that brain damage due to energy failure (oxygen/glucose deprivation)
may have a final common pathway. Energy failure may result from a variety of "stressors" such as ischemia and/or hypotension as well as from the toxic effects of inflammatory mediators, excitatory amino acids, or oxygen metabolites. The small number of final common pathways appears to lead to widespread programmed cell death (also known as apoptosis) and frank necrosis, which would explain diffuse impairment of functionally important parts of the CNS. These final common pathways may also help explain gray matter damage, which characterizes Alzheimer's disease, as well as white matter damage, which characterizes periventricular leukomalacia.

Inflammatory mediators can damage the CNS

Several recent studies point to the potential importance of immune response mediators, such as cytokines, acute-phase proteins, and components of the complement system, as causal factors in a number of chronic neurologic conditions in both children and adults. Most work has focused on cytokines, a broad group of soluble proteins and glycoproteins that have a high degree of biologic activity (27, 28). They are released by cells in response to some type of stimulus and act either locally or distantly to regulate cell function (29, 30). Individual cytokines can be synthesized and secreted by multiple types of cells, including monocytes, macrophages, endothelial cells, fibroblasts, and microglial cells, and can have biologic activity on a range of target cells (27, 29). Both microbial and nonmicrobial agents stimulate cytokine synthesis (29, 31).

Although the CNS once was considered an "immunologically privileged" site, it is now viewed as having a wide range of immune functions and response capabilities (32-35). This understanding has led to a focus on inflammatory responses rather than on inciting agents (11, 12, 15, 35). Selected cells in the CNS, particularly microglia and astrocytes, can produce a vast array of immune mediators in response to injury, infection, ischemia, and other types of tissue "stressors" (11, 35). As in the systemic immune response, these mediators include inflammatory cytokines, components of the complement cascade, and acute-phase proteins (11, 35). These agents have complex interactions with each other and with cells in the CNS that are substance specific and dose dependent. They play a primary role in the host's response to external agents, but they are also capable of damaging neurons and glia (28). Although some of the inflammatory mediators that damage the CNS apparently arise there, others originate elsewhere and cross a poorly functioning blood brain barrier, gaining access to vulnerable areas of the CNS (15, 35). Noninfectious stimuli, such as trauma, and ischemia can initiate production of cytokines, thereby accommodating hypotheses involving nonmicrobial risk factors.

Vulnerability and protectors

Some cytokines in the CNS, whether or not they originate there, can function as response modifiers. Some modulate (turn down) the inflammatory response, reducing the probability of damage. Cytokines that act as receptor antagonists do so by blocking the action of other agents. Other cytokines, which satisfy criteria for growth factors, are able to sustain neurons and glia under adverse conditions. Those known for sustaining neurons are called neurotrophins; those capable of protecting oligodendrocytes are called oligotrophins. For simplicity, we have labeled these response modifiers "protectors." People who have inadequate amounts of these modulators or protectors may be at increased risk of CNS disorders.

One view of the common vulnerability of both very immature and aging brains is that they are relatively deprived of protectors. Some infants born preterm appear to be incapable of synthesizing adequate amounts of (protective) polypeptides and proteins provided by the mother or placenta before birth (36). It seems that synthesis of these protectors, exemplified by thyroxine (37, 38), is regulated by phenomena that vary with gestational age, warranting the term "developmental regulation" (39). The possibility exists that with senescence, adults lose some of their ability to synthesize adequate amounts of protectors. If so, developmental regulation would link the very immature, who have not yet gained the full ability to synthesize these neurotrophins and oligotrophins, with the elderly, who have lost some of their ability to synthesize these protectors.

Some of the variation in vulnerability may also be explained by genetic polymorphisms of the synthesis of damage promoters or protectors. For example, the presence of a "high producer TNF-α allele" in mother and fetus might modify the risks for preterm delivery and white matter damage (40). At the other end of the age spectrum, apolipoprotein E polymorphisms have been shown to influence the risk of Alzheimer's disease, such that persons with the type 4 allele are at increased risk of Alzheimer's-type dementia (41-43).

ALZHEIMER'S DISEASE

Dementia is a syndrome characterized by a decline in memory and other cognitive functions compared with the person's previous level of functioning (44, 45). Alzheimer's disease comprises about two-thirds of all cases of dementia in Europe and North America.
The diagnosis of Alzheimer’s disease is based on clinical criteria and excludes other specific causes of dementia (46). No agreed-upon pathologic criteria exist for diagnosing Alzheimer’s disease (6), although some definitions include histopathologic features (45). The neurofibrillary tangles and neuritic plaques seen in persons with Alzheimer’s disease are not pathognomonic and can also be found in persons without apparent Alzheimer’s disease (47).

The epidemiology of Alzheimer’s disease was reviewed recently by Breteler et al. (6). Incidence and prevalence rates of this disease increase dramatically with age, with incidence rates of nearly 2 percent and prevalence rates of 30 percent or higher in those aged 80 years or older (48). It is estimated that because of the aging of the population, the prevalence of Alzheimer’s disease in the United States will quadruple in the next 50 years, such that more than 8 million people will be affected (49).

The causes of Alzheimer’s disease remain elusive, and, other than increasing age, no factors have been identified that contribute substantially to risk. An increased risk has been consistently reported in association with a family history of dementia (50) and Down’s syndrome (6, 50) and with the apolipoprotein E type 4 allele (43). Other factors that have been investigated, but for which there is no convincing evidence regarding their relation to risk, include aluminum (6), lead (51), viruses, and CNS infection (52). Lower risks of Alzheimer’s disease have been reported in some studies of women who use postmenopausal estrogens (53, 54) but not in other studies (55). These results remain controversial and may reflect selection or information biases (56, 57).

Several investigators recently proposed that chronic activation of immune response mediators, including cytokines, and resultant CNS damage may become self-perpetuating, leading to the development and progression of Alzheimer’s disease (11, 12). These mediators are produced in the CNS, and, in the case of Alzheimer’s disease, systemic immune involvement may be minimal or absent. In this model, IL-1 derived from microglia activates astrocytes to induce expression of S100β, an astrocyte-derived cytokine. S100β has been implicated in the formation of the plaques characteristic of Alzheimer’s disease. IL-1 also increases expression and processing of β-amyloid precursor proteins and induces production of other proteins present in neuritic plaques (12, 34).

IL-1 and S100β, and the processes they induce, can become self-propagating, leading to chronic overexpression of glial cytokines and other immune response mediators that results in progressive neurodegeneration (11, 12). Whether elevated levels of these cytokines reported in CNS tissue homogenates, microglia, and cerebrospinal fluid of patients with Alzheimer’s disease are involved in the pathogenesis of the disease or merely mark a response to other etiologic agents requires further study.

The insults to the CNS that initiate production of acute-phase glial cytokines such as IL-1 and S100β are not understood clearly. One such insult may be head trauma. Most epidemiologic studies that have assessed head trauma as a risk factor for Alzheimer’s disease have reported a positive association, typically for relatively recent trauma (i.e., within 10 years of diagnosis) (58). Problems of recall bias in obtaining injury histories were reduced in studies that included only severe head trauma with loss of consciousness (58–60). Boxers, who experience repeated head trauma, have been shown to have histopathologic changes in the brain similar to those seen in Alzheimer’s disease (61). Increased production of IL-1 in the CNS in response to brain injury has been reported (12, 62). IL-1, in turn, increases production of amyloid precursor protein, the precursor of β-amyloid, a constituent of the senile plaques of Alzheimer’s disease. Cytokines can also disrupt the blood-brain barrier (34, 63), resulting in exposure of the brain to damaging agents.

The observation from epidemiologic studies that persons chronically exposed to nonsteroidal anti-inflammatory drugs are at a lower risk of Alzheimer’s disease supports the hypothesis that chronic inflammation plays a role in the etiology of this disease (54, 64). These drugs are known to reduce production of IL-1 and other inflammatory mediators (65). Randomized, controlled trials of other anti-inflammatory agents such as prednisone, hydroxychloroquine, and colchicine in the treatment of Alzheimer’s disease are currently under way (13).

**WHITE MATTER DAMAGE IN THE NEWBORN**

Each of the disorders described as a developmental disability is probably heterogeneous, which adds to the complexity of epidemiologic studies. One approach to this problem has been to look for more homogeneous entities that comprise each of these developmental disabilities. For example, periventricular leukomalacia is one of the underlying disorders accounting for much of the cerebral palsy among children who were very preterm and for perhaps a fraction of cerebral palsy in infants born at term. Periventricular leukomalacia may also account for some of the cognitive limitations, including mental retardation, as well as perceptual and behavioral disorders in infants born much before term.

Factors that consistently have been shown to increase the risk of periventricular leukomalacia include delivery at a very low gestational age and...
maternal or placental infection (66, 67). Interest has
focused on the inflammatory response to infection as a
primary initiator of processes that could lead to both
preterm delivery and white matter damage (15, 68).
The idea that an infection remote from the CNS can
damage the CNS developed decades ago but only now
is gaining attention (69). Several studies have reported
an association between increased cytokine levels in
amniotic fluid or umbilical cord blood, particularly IL-
1α, IL-1β, IL-6, and TNF-α, and risk of preterm labor
(70–75) and of periventricular leukomalacia and other
cranial sonographic entities considered correlates of
cerebral white matter damage (16, 76, 77). Yoon et al.
found that preterm infants who later developed cere-
bral palsy had higher levels of several inflammatory
cytokines in their amniotic fluid than their peers who
did not develop cerebral palsy (76).

Now it appears that infants born at term who
develop cerebral palsy might be similar to preterm
infants who develop cerebral palsy in that they are
exposed to potentially damaging proinflammatory
cytokines. Recently, IL-1α, IL-6, IL-8, IL-13 and
TNF-α were reported to be elevated in blood spots
obtained in the early neonatal period from full-term
children who subsequently developed cerebral palsy
compared with children who did not (78). Differences
in autoimmune and coagulation factors were also
observed between cases and controls. Autoantibodies
may affect risk through direct stimulation of cytokine
production (31).

Questions remain as to whether the elevated inflam-
matory mediators in amniotic fluid, umbilical cord
blood, and even early postnatal blood are of maternal
or fetal origin. Increasingly, however, some of the ele-
vation appears to be of fetal origin (79). This conclu-
sion leads to the inference that the fetus damages its
own brain.

Observations of increased levels of cytokines in the
absence of detectable infection (71, 80) suggest either
that indicators of infection in those studies were insen-
sitive or that nonmicrobial agents may also be respon-
sible for stimulating cytokine production. The role of
nonmicrobial agents in stimulating cytokine production
during gestation has not been examined ade-
quately.

Thyroxine can function as an oligotrophin (37, 38).
Adrenocorticosteroids are also capable of functioning
as oligotrophins, and they can modulate the inflamma-
atory response. Support for the hypothesis that depriva-
tion of such oligotrophins increases the risk of brain
damage is now coming from epidemiologic studies.
Infants with hypothyroxinemia of prematurity are at
increased risk of periventricular leukomalacia (81),
disabling cerebral palsy, and mental retardation (82).
In addition, compared with their very preterm peers,
those infants exposed to a course of antenatal corticos-
teroids (intended to enhance lung maturity and reduce
the risk of respiratory distress and chronic lung dis-
ease) are at lower risk of periventricular leukomalacia
(81) and cerebral palsy (83).

SUMMARY

Many of the risk factors previously identified for
disorders such as Alzheimer’s disease, periventricular
leukomalacia, multiple sclerosis, stroke, cerebral
palsy, mental retardation, and acquired learning and
attention disorders ultimately may be shown to dam-
age the central and peripheral nervous systems through
activation of inflammatory mediators. The challenge
to epidemiologists in the future is to expand use of epi-
demiologic methods to explore how immune-mediated
insults produce CNS disorders in human populations.
Studies of the association of use of nonsteroidal anti-
inflammatory drugs with risk of Alzheimer’s disease
and those of the association of immune parameters
with risk of cerebral palsy are excellent examples of
how epidemiology can contribute to our understanding
of the causes of neurologic and/or neurodevelopmental
disorders. Many of the immune parameters of interest
have short half-lives and are difficult to measure out-
side of the laboratory setting. Questions also remain as
to the proper timing of measurements in relation to the
initial insult and, in some cases, which tissue is the
most appropriate to sample. These measurement issues
will need to be resolved before use of immune bio-
markers in epidemiologic studies of the etiologies of
neurologic disorders can be fully realized.

Epidemiologists are most likely to help identify
ways to prevent neurologic disorders if they are
knowledgeable about the molecular biology of inflam-
mation, modulators of CNS vulnerability, and genetic
polymorphisms that influence both inflammation and
CNS vulnerability and are prepared to become adept at
biomarker epidemiology. This does not necessarily
compel them to gain extensive knowledge of neuro-
biology. Rather, neuroepidemiology in the 21st cen-
tury will require increased collaboration between epi-
demiologists, neurologists, and neurobiologists.

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