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Do early-life insults contribute to the late-life development of Parkinson and Alzheimer diseases?

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Abstract

How early-life events "set the stage" for adult disease has emerged as a research focus. Historically, the epidemiology of disease risk factors has centered on adult life, with little scrutiny of early-life events. Here we review the concept that events in early life may contribute to late-life neurodegenerative disease development, with a focus on Parkinson disease (PD) and Alzheimer disease (AD). Suspect events in early life include infections, stress, poor nutrition, and environmental factors such as chemical and pesticide exposure. Adiposity appears to contribute to both PD and AD; and because early-life events contribute to the development of obesity, linkages may exist between early determinants of obesity and the subsequent development of these neurologic diseases. Many now suggest a life-course approach for determining the relative contributions of genetic and environmental factors in any chronic disease. This requires determining when during the life course that a given exposure has its greatest effect and how exposures may accumulate over the life span. The data for PD and AD suggest that a number of insults occurring early in life may lead or contribute to these diseases. More definitive knowledge of the key risk factors involved will be needed to implement intervention and preventative strategies early in life to dampen or prevent any adverse late-life outcomes.
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1. Introduction

Parkinson disease (PD) and Alzheimer disease (AD) are diseases of unknown etiology that appear late in life. Nongenetic causes are suspected in both, with most investigations of etiology centered on the adult period. However, as Wordsworth [1] noted, "The child is father of the man," and disease may be no exception to this observation. Barker [2] first espoused the controversial concept that very early life events play a causative role in disease in his articles on the fetal origins of coronary heart disease (CHD) [2-4]. The prior prevailing belief was that CHD was determined by an unhealthy Western lifestyle in combination with genetics. The "Barker hypothesis" challenged this orthodoxy by showing consistent associations of CHD with low birth weight (LBW), LBW being a surrogate and not the cause. A number of studies examining the "fetal origins of adult disease" (FOAD) hypothesis have found associations between LBW and indices of disease risk or actual disease prevalence for ischemic heart disease, hypertension, obesity, insulin resistance, and depression. The FOAD has expanded into the more general "developmental origins of health and disease" (DOHaD), allowing a consideration of infant and childhood events in adult disease etiology [5].

Although controversial, the Barker hypothesis now is more generally considered to be plausible and clinically relevant even by those initially skeptical [3,4]. Possibly, the intrauterine environment can "program the fetus" with developmental plasticity, allowing the expression of a wide range of phenotypes in response to different environments. Poor developmental conditions may cause adaptations that allow fetal survival; but this long-lasting programming may have adverse consequences in the adult. Thus, adult type 2 diabetes mellitus could be due to a "thrifty phenotype" instigated in the womb by inadequate nutrition, subsequently altering metabolic machinery and rendering it ineffective in dealing with the abundant food supply in developed countries.

The DOHaD has implications for many diseases other than cardiovascular disease, among them type 2 diabetes mellitus, obesity, depression, cancer, and osteoporosis [2,4]. The realization that adult disease may have developmental

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origins has driven a belief in the importance of a life-course approach when studying chronic disease. In determining etiology, attempts should be made to specify all factors that act across the life span and to identify periods of vulnerability for them as well [6]. Typical investigations of neurodegenerative disease etiology have concentrated on midlife factors. Although the major growth of brain occurs during the pre- and early postnatal periods, key maturation processes, marked by myelination and an increasing complexity of connectivity, continue through late adolescence. This prolonged period provides ample opportunity for various insults to interfere with brain development, although compromised function may not be expressed until later life [7]. The DOHaD hypothesis has received some attention by those interested in the etiology of PD and AD, and here we will explore the supportive evidence [8-10]. Early life encompasses fetal, infant, and early childhood; and suspect events can include poor nutrition, infections like intrauterine influenza, as well as chemical and pesticide exposure.

2. Parkinson disease

2.1. Definition

Parkinson disease or idiopathic parkinsonism is of unknown etiology, and few cases can be directly attributed to well-defined genetic or environmental causes; it is the most frequent neurodegenerative disorder after AD. There is no explicit biochemical test or progression biomarker for PD, and the diagnosis is clinical and uses the exclusion of secondary causes; this may impede epidemiologic investigation because not all persons clinically identified as having PD are found to have the disease at autopsy. Parkinson disease can be considered a dopamine (DA) deficiency disease in which the continuing decline in the amount of this major transmitter in the caudate-putamen is the cause of compromised, and eventually the loss of, motor function. Treatment with L-dopa, a compound that is converted to DA in the brain, can bolster DA amounts enough to enable and restore motor movement; but the unrelenting loss of the DA-producing cells in the substantia nigra (SN) that innervate the caudate-putamen and release DA eventually overwhelms the usefulness of this treatment. The loss of the dopaminergic cells of the SN and the presence of Lewy bodies, intracytoplasmic aggregations of α-synuclein, especially in the basal ganglia are classic histopathologic findings for PD at postmortem analysis [11]. Many suggest that PD may be caused by an interaction of genetic and environmental factors. The multiple hit hypothesis of PD suggests that the disease occurs when multiple risk factors are operating, some perhaps over a long period and others in a more episodic fashion [12].

2.2. Risk factors for PD

Parkinson disease incidence has been associated with factors that both increase and decrease the risk; a scrutiny of these factors may provide insight into how early events influence subsequent disease. Population-based studies have shown links between environmental and lifestyle attributes as well as physical characteristics and PD incidence [13,14]. Thus, rural living, drinking well water, pesticide exposure, and certain occupations (eg, health care workers, teachers), as well as midlife adiposity and high caloric intake, appear to pose increased risk. Geographic location and migratory patterns as well as head injury and a repeated loss of consciousness also are associated with increased risk. Conversely, cigarette smoking, coffee or tea consumption, and nonsteroidal anti-inflammatory drugs are associated with lower risk. Although the identification of risk factors for a disease can suggest possible avenues for future investigations into cause, the observed associations do not imply causality. For example, in the association between rural living and PD, rural or farm living may merely be a surrogate or proxy for pesticide/herbicide exposure or some particular aspect of rural or farm life that is the real cause; occupation could be a surrogate for toxin exposure or level of physical activity.

In the genesis of FOAD, geographical data provided the first clues that early-life events may shape later disease; and such data also may provide clues concerning PD etiology. Parkinson disease incidence appears to differ worldwide, with a lower incidence in Japan, whereas emigrants from Asia and western Africa to the United States have a higher incidence than in their native country. This suggests an environmental influence or an interaction between the genome and the environment, but the limited number of comparative studies and the lack of consistent diagnostic criteria across countries make further study necessary [14]. Parental PD increases the risk for PD in the offspring, but determining if this is genetic or environmental is difficult. Both are shared early in life; but most often, as the child gets older, the shared environment lessens. The risk is greatly increased the younger the child is when the parent displays symptoms, with the association being the greatest if the mother has PD, observations supporting an environmental cause [15].

2.3. Growth and PD

The role of birth weight or early growth in PD incidence has received little scrutiny. As Logroscino notes [8], Martyn and Osmond in a case-control study found no association, but the general lack of growth records for their subjects somewhat tempers the conclusion. Shorter adult height, an end point that may reflect early-life events affecting growth, is associated with greater PD risk in men [16]. Prospective population-based studies are more powerful relative to cross-sectional or case-control study designs because the entire population is studied over time and selection bias is reduced. Such prospective studies found that excess weight in midlife, as indicated by triceps skin-fold thickness or body mass index, appears to increase PD risk and low caloric intake appears to be protective regardless of weight or body mass

index [13,17]. Research has determined that obese animals are more susceptible to toxic agents that target the basal ganglia and that caloric restriction reduces the damage caused by such agents [17,18]. Furthermore, DA is important in the regulation of food intake; and early events capable of modulating the development of DA may influence adult weight. Given the recent concerns about early-life causes of adult obesity, it may be prudent to investigate the relationship(s) between early-life events affecting weight or growth, adult obesity, and the development of PD. Such work could lead to a broadening of the scope in the ongoing search for neuroprotective strategies and interventions.

2.4. Infections, chemicals, and PD

Beginning with the observation of postencephalitic parkinsonism by von Economo, many infectious agents have been mentioned in connection with PD including the influenza virus; *Nocardia*, a tuberculosis-like germ; *Helicobacter*; and others [8]. Parkinson disease cases vary or cluster by birth year; those born in the year of influenza pandemics appeared at greater risk for PD, but some question these links [8]. In a study examining early life and PD, disease incidence increased in those experiencing croup or diphtheria. Nevertheless, recall bias and the examination of a large number of childhood factors besides infections increase the potential for a chance association and may cast doubt on a role for croup or diphtheria [8].

The multiple hit hypothesis of PD etiology [12] drives concern that abnormal development of the nigral-striatal pathway due to infection or toxic insult may make it more vulnerable to later insults. The subsequent reduction in SN cell number or neurochemical function would hasten the onset of symptoms that are not apparent until a threshold loss has occurred [8]. In humans, early-life trauma may cause a mild rigid akinesia that is reversible by L-dopa; findings suggestive of an alteration in DA systems [19]. Lipopolysaccharide is a bacterial endotoxin that causes an inflammation similar to that of infection. Intrauterine exposure to lipopolysaccharide in rats decreases the number of nigral DA cells present at birth—a deficit that persists in the adult and is accompanied by a compromised function of the DA pathway [20]. Producing brain inflammation in these compromised animals when they were adults caused more damage in them than those rats experiencing the inflammatory condition for the first time. This supports the idea that exposure to an infection or chemical during early life can compromise the nigral-striatal pathway at critical developmental stages, resulting in an increased mid- or late-life susceptibility to chemicals targeting this system.

Epidemiologic studies frequently report that living in a rural setting increases risk for PD, observations suggestive of a link to pesticide or herbicide exposures, and suggest that pesticide or herbicide exposure may be involved in the increased risk, although early-life exposures to these agents have not yet received a great deal of scrutiny. Farming involves exposure to many environmental factors, but pesticide exposure is frequently singled out as a risk factor for development of PD. Nevertheless, no specific farm chemicals have been identified as contributory, much less causative, for PD, although organochlorines and paraquat are among the most frequently mentioned [21]. At first glance, paraquat seems a likely culprit because it is structurally similar to the toxic metabolite of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyriden (MPTP) (MPP^+ 1-methyl-4-phenylpyridinium), a chemical capable of causing a PD phenotype in humans. Emphasis on paraquat for its possible connection to PD risk, however, remains controversial [8,21,22]. Animal studies show that chemicals, like infections, can compromise the development of the nigral-striatal pathway; early developmental exposure to drugs such as cocaine or pesticides such as dieldrin increases vulnerability to dopaminergic neurotoxicants [23,24]. If such losses of reserve occur in humans, it could predispose them to PD if later insult causes further loss [8,25].

2.5. Lifestyle factors and PD

That cigarette smoking strongly reduces the risk of PD has been reported consistently in case-control as well as prospective epidemiologic studies [13,14,26]. Risk is reduced by about half in current smokers, and the reduced risk is still present in former smokers relative to never smokers; the protection is related to smoking duration, intensity, and recentness, all suggestive of a biological effect. The association is considered not to be due to a greater survival of nonsmokers or differences in the behavioral characteristics of smokers [8]. Such a consistent and dramatic impact of smoking on PD risk prompts one to ask if maternal cigarette smoking or coffee/tea consumption, another lifestyle factor capable of reducing risk, impact PD incidence in the offspring. There appears to be little examination of this question despite reports that either behavior during pregnancy causes LBW and may have other developmental effects [27-29]. Cigarette smoke and coffee contain many active substances including nicotine and caffeine, respectively. Experimental work has demonstrated the neuroprotective properties of both. Given the evident biological actions of smoking, nicotine replacement therapy, and caffeine, as well as the suspected links between maternal smoking and other disorders involving DA systems (eg, attention-deficit/hyperactivity disorder), it remains crucial to determine if exposure to these drugs during early life impacts the risk for PD.

3. Alzheimer disease

3.1. Definition

Sporadic AD, the most common cause of dementia in the elderly (50%-60% of the cases are older than 65 years, with a doubling of risk every 5 years after 65 years), has been described for over a century; but its cause is still unknown and widely debated [9,30,31]. AD, like PD, is a progressive neurodegenerative disorder; it is characterized

by an ever-worsening memory impairment accompanied by a declining ability to perform important daily behaviors. AD is complex; to date, there are no broadly validated biomarkers for its diagnosis. Neuritic plaques, extracellular deposits of amyloid β, and neurofibrillary tangles consisting of hyperphosphorylated tau proteins are found in the brain areas responsible for learning, memory, and emotion. Although these features are considered characteristic pathologic hallmarks of the disease, they are by no means unique to AD. Some studies have identified individuals at autopsy with a significant plaque load but little evidence of dementia, findings that call into question the idea that there is a direct relationship between plaque load and the degree of impairment [30]. The characteristic loss of cholinergic brain cells important for cognition has resulted in merely palliative symptomatic treatments focused on modifying cholinergic neurochemistry.

3.2. Risk factors for AD

As with PD, population-based observational studies have identified factors that both increase and decrease the risk of AD, providing clues into the ways early events may contribute to its etiology. A limited education, rural living during childhood, and major head trauma all increase the risk of AD [7]. Interestingly, AD and cardiovascular disease appear to share many of the same risk factors including obesity and minimal physical activity, among others. Furthermore, anti-inflammatory drugs like nonsteroidal anti-inflammatory drugs and statins appear to be protective, implicating vascular pathology in both. Many of these conditions when measured in midlife are predictive for late-life AD [31].

3.3. Growth, lifestyle, and AD

Limited education, lower income, and lower occupational status increase the risk for AD; all can be related to an impoverished early-life environment and poor growth [7]. Poor growth can result in short stature, which is associated with AD [32]. Low birth weight can cause deficient maturation and is also related to poor cognitive ability that is evident in early life and may result in less schooling. Limited linguistic ability in young women increased the likelihood of meeting neuropathologic criteria for AD in old age. Deficient maturation may cause a less well-developed brain with diminished reserve capacity and serve as a way the various modifiers of growth can contribute to the development of AD [7,33].

Although LBW children may continue to weigh less, intrauterine growth restriction often leads to rapid weight gain after birth. With this "catch-up," there is a higher ratio of fat to lean mass with greater central fat and insulin resistance. Rats subjected to intrauterine growth restriction display similar metabolic abnormalities [34,35]. Obesity and diabetes are associated with a several-fold increase in AD risk, implicating insulin resistance in both. Indeed, AD may be linked to a unique form of insulin deficiency in brain. Rats made deficient in brain insulin by killing insulin-producing brain cells during early life displayed AD-like pathology, suggesting that AD may be a brain-specific neuroendocrine disorder, a type 3 diabetes mellitus. In transgenic mouse models of AD, a high intake of sucrose water hastened amyloidosis and cognitive deficits, whereas caloric restriction is protective. A growing consensus suggests that the early-life events linked to growth and metabolism may be important in understanding AD etiology [7,9,31,36-39].

3.4. Infections, chemicals, lifestyle, and AD

The potential relationship between early-life infections and the risk of AD has not been examined. Nevertheless, fetal and childhood infections can interfere with brain development, especially in LBW and premature infants; and a diminished cognitive reserve may result from compromised brain development. A more developed and perhaps larger brain will have a greater reserve providing a buffer against the neuronal and synaptic losses of AD, resulting in its possible delay or even prevention [7]. Certain viruses can lie dormant in neurons for decades; the virus from varicella-zoster infection in early childhood leads to painful shingles in late life. Accordingly, a provocative but untested hypothesis suggests that AD is due to late-life activation and transmission through cholinergic neural circuits of a subclinical infection by *Borrelia*, the spirochete causing Lyme disease [40]. *Helicobacter pylori* has been linked to AD; HIV and TB are widespread, and the offspring of infected mothers may have altered inflammatory processes. Whether there is a link between aberrant inflammation in early life and the inflammatory process considered to be important in AD is unknown [41,42].

Despite the finding of a consistent association between a childhood spent in a rural setting and an increased risk for AD, there has been no examination of early-life chemical exposure and risk; but recent experimental work provides some evidence. Notably, the brains of old monkeys exposed to dietary inorganic lead as infants displayed AD-like brain pathology despite having no signs of overt toxicity or ill health during exposure. Amyloidosis is observed in rodents treated in the same way but not in those receiving lead as adults [43].

Head trauma is clearly associated with AD, but it is not known if the risk is greater if the insult occurs during early life. However, adult head circumference is correlated with cognitive performance; and childhood traumatic brain injury reduces head size [7,44].

4. Conclusions

The available evidence strongly suggests the need for further study of early-life events that affect the development of late-life neurodegenerative diseases like PD and AD. This is a challenging task because of (1) the long latency between early-life insult and disease manifestation; (2) the limited

number of complete birth, growth, and other life-stage records for epidemiologic evaluation; (3) the lack of homology within groups, for example, infants with the same birth weight may have achieved that weight by different paths (compromised fetal or maternal nutrition, timing of inadequate nutrition [45]); and (4) the great likelihood that a nonoptimal early life may result in many changes capable of altering disease susceptibility. It is quite sobering to consider that the seeds of late-life disease like PD and AD can be sowed so early in life. Indeed, this possibility would seem to warrant therapeutic pessimism that may in part be justified. For example, rescue through adequate nutrition can make up for some but not all the deficits in brain development and function engendered by poor early nutrition. A LBW followed by rapid postnatal catch-up growth appears to set the stage for later glucose mishandling and obesity [17]. Conversely, a risk factor like low education is modifiable. The data suggest that intervention and prevention should start early in life, and direction for this strategy will be fostered by a greater understanding of just how early-life deprivations and insults set the stage for late-life disease. As suggested at a recent conference on early-life and late-life neurodegenerative disease, this task would be made easier by establishing long-term prospective epidemiologic studies that follow individuals from conception to old age [37].

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