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Role of apolipoprotein E4 in protecting children against early childhood diarrhea outcomes and implications for later development

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Summary

Our group and others have reported a series of studies showing that heavy burdens of diarrheal diseases in the formative first two years of life in children in urban shantytowns have profound consequences of impaired physical and cognitive development lasting into later childhood and schooling. Based on these previous studies showing that apolipoprotein E4 (APOE4) is relatively common in favela children, we review recent data suggesting a protective role for the APOE4 allele in the cognitive and physical development of children with heavy burdens of diarrhea in early childhood. Despite being a marker for cognitive decline with Alzheimer's and cardiovascular diseases later in life, APOE4 appears to be important for cognitive development under the stress of heavy diarrhea. The reviewed findings provide a potential explanation for the survival advantage in evolution of the thrifty APOE4 allele and raise questions about its implications for human development under life-style changes and environmental challenges.

Introduction

The vicious cycle between diarrhea and malnutrition is well known and may even occur with enteric infections without overt diarrhea [1]. Recent data from Brazil and Peru document a lasting impact of diarrhea (as with malnutrition and intestinal helminthic infections) on child development with ill-effects on cognition, growth, and educational performance [2,3]. Early post-natal malnutrition is associated with significantly retarded

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central nervous system growth, reduced brain weight, thinner cerebral cortex, deficient myelinization, poor neuritic arborization, and changes in features of dendritic spines such as reduction in their width and number [4–6].

Accumulating evidence reveals novel early gene–environment interactions, which play dynamic roles in developing brains of children experiencing repeated enteric infections and diarrhea [7–10]. The genetic contributions may determine differential susceptibilities to infection or their outcomes, by affecting host–parasite responses, placing certain children at particularly high risk. Furthermore, these interactions may hold throughout life despite ever-changing environmental challenges that present themselves, although our understanding of how these interactions occur is limited.

We now recognize that early childhood diarrheal illnesses, often acquired from water-borne pathogens and poor sanitation, lead to lasting cognitive deficits [11]. Although several studies address their impact on children's health worldwide [12], study of the effects of diarrhea on intellectual function is impeded by the scarcity of long-term surveillance from birth in developing countries.

Recent findings suggest that early cognitive development under the stresses of environmental toxins, early childhood diarrhea and malnutrition is modulated by apolipoprotein E (APOE) genotype, although not in healthy children in resource-rich countries [13], nor in favela children with low diarrhea burdens [14]. The single structural locus of APOE has three alleles on chromosome 19: APOE2, APOE3, the most frequent allele in populations studied to date [15], and APOE4.

Herein, we review findings from our ongoing cohort Brazilian studies and novel hypotheses on APOE epidemiology in children from the developing world, highlighting the possible protective role of the apolipoprotein E4 (APOE = gene; ApoE = protein) in children afflicted with enteric infections and heavy diarrhea, which could explain the evolutionary retention of this allele among populations worldwide, especially those with high rates of childhood infection. In addition, we note that APOE4 bearers raised in poor urban areas of the developing world and afflicted with heavy diarrhea and enteric infections early in life would be under a high risk for developing cardiovascular and Alzheimer's diseases.

ApoE-cholesterol complex and cognitive development: a differential role during aging and childhood?

Apolipoprotein E (ApoE), a 35 kDa, 299-amino acid secretory plasma protein synthesized mainly in the liver, facilitates cholesterol transport from somatic cells to the liver to be metabolized via the low density lipoprotein (LDL) receptor pathway [16,17]. As a key determinant of plasma cholesterol homeostasis, ApoE binds with high affinity to lipoprotein particles in the plasma compartment and acts as a ligand for receptor-mediated endocytosis via multiple members of the LDL receptor family [18,19,16,20]. ApoE is also expressed in other tissues, notably the brain, the second most prolific tissue in terms of ApoE production [21,22].

ApoE also appears to play a pivotal role in the redistribution of lipid and cholesterol during membrane repair, and has been postulated to be important for maintaining synaptic plasticity, especially after neuronal injury in the CNS [23–25]. Synthesis, transport, or uptake of cholesterol in the CNS may directly affect the development and plasticity of the synaptic circuitry. The formation of synaptic contacts is a critical phase during brain development that is crucial to long-term synaptic plasticity in the adult CNS [26]. New lines of evidence indicate that cholesterol produced by glial cells and secreted in apoE-containing lipoproteins is the glial factor involved in regulation of synaptogenesis [27,28].

These isoforms influence serum lipid levels, cardiovascular disease, and neuronal repair [16]. Individuals with the APOE 4 allele have a markedly increased risk for developing early and late-onset Alzheimer's disease and poor recovery after brain injury [29,30], however APOE polymorphisms' influences on brain plasticity in pediatric populations remain uncertain [31].

Recently, Hirayama et al. measured CSF levels of apoE-HDL, which are believed to affect brain plasticity [32]. These levels were similar among individuals with E2, E3 and E4 during childhood but higher in adulthood. CSF-ApoE4 then declines more than other isoforms later in life, which may explain predispositions to neurodegenerative diseases with aging [32]. These new findings suggest that APOE polymorphisms might have a different role during early development and aging. We hypothesize that enriched cholesterol diets and increased cholesterol absorption, which is mostly regulated by apoE isoforms early in life [33] in weanling malnourished children, might have a critical role during long-term brain maturation [34,35].

ApoE4 and intestinal development: adaptations against enteric infection and malnutrition?

Impaired brain development may result from intestinal damage or dysfunction because of impaired nutrient absorption caused by enteric infection in the first two years of life [36]. Starvation and malnutrition are known to jeopardize small bowel development, affecting intestinal permeability [37], biomechanical properties [38], the gut mucosal immune system [39], and causing mucosal atrophy [40], all effects that may be potentially ameliorated with early intervention [41,42]. The weaning period is a critical time of rapid remodeling and adaptation of the gut to a new diet regimen, resulting in dramatic changes in the intestinal morphology and cell kinetics [43]. Consequently, this is a period when the brain may be particularly vulnerable to the effects of malnutrition.

ApoE mRNA abruptly increases in rat livers at birth and rises again during the suckling period, suggesting that it plays a significant role during post-natal development. Liver apoE mRNA rises in 10-h-fasted suckling rats, suggesting that APOE expression in rat hepatocytes changes during development in relation to insulin and glucagon levels [44]. ApoE also appears to establish the integrity of tight junctions in intestinal cell lines. Since APOE null mice exhibit blood–brain barrier disruption, especially after injury [45,46], and because the blood–brain barrier is mainly composed of tight junctions between endothelial cells, similar to the barrier formed by enterocytes, they might conceivably have disrupted intestinal barrier function as well. Finally, a role for the apolipoprotein E-cholesterol complex in the intestine is also suggested by the finding that ApoE is secreted by

enterocytes in response to 25-OH cholesterol induction in differentiated, polarized Caco-2 cells and this secretion is reduced by LPS [47]. Furthermore, increased apolipoprotein gene expression accompanies the differentiation in intestinal cell lines in vitro [48]. Shedding light on these findings, our group has documented blunted IGF-1 expression and poor intestinal adaptations in malnourished weanling apoE-knock out mice following refeeding (Nutr Res 2006;26:427–35).

Interestingly, in our pilot studies with Brazilian shantytown children, we found that children with APOE4 had fewer *Giardia* infections (measured by positive stools), suggesting a possible role of APOE4 reducing *Giardia* and overall infection rates [49]. Therefore, we raised the hypothesis that the cholesterol bioavailability might be shifted from the parasite, which cannot synthesize cholesterol per se, to the developing brain. Additionally, since apoE4 knock-in mice have increased activity of the arginine cationic transporter in glial cells, we postulate whether a similar transport within enterocytes may enhance intestinal immune defenses against infection, by elevating NO levels [50].

Early environmental challenge might determine genetic programming throughout life

The theory assembling a role for a modified genetic programming early in life in determining ultimately the fate of development has come from several studies worldwide but still lacks a strong validation other than some epidemiological findings [51,52].

The malnutrition challenge early in post-natal development might influence the genetic programming and therefore the distribution, number, and function of various receptors, transporters and signaling pathways within targeted tissues [52,53]. It has been postulated that enteric infection and diarrhea as major stressors may activate on–off key genetic regulators, such as gene pathways controlling apoptosis, cell growth, and survival and inflammatory responses, altering predisposition to neurodegenerative and cardiovascular diseases late in life [54–57].

It has been postulated that long-term changes in behavior and neuroendocrine signaling (leptin and other hormones that modulate appetite) in early childhood might occur under the pressures of malnutrition and dehydration that threaten to impair normal development and survival in order to protect body mass index and to hasten recovery [58,59]. However, when living conditions improve, high-fat and high caloric diets might have a negative impact on health, as seen in developing countries (via increased cardiovascular and neurodegenerative diseases), since those changes may become inappropriate and potentially dangerous with the advent of more affluent life-styles. Early markers of altered phenotypes during infancy and early childhood might give a clue about what would be established later on.

Studies conducted in poor urban areas of Brazil [60–62] and elsewhere [63] have shown that the severity and timing of diarrhea and poor somatic growth in the first two years of life are associated with profound long-term effects on cognitive test performance during childhood. Our group has found that early childhood diarrhea associates with lasting growth shortfalls [64]. The best surrogate measure of early childhood diarrhea and marker for later fitness (and cognitive impairment) is the height-for-age z score (HAZ), namely that at 2 years of age (HAZ-2) [65,66], thus strengthening the links made between early childhood growth and

cognitive development and helping to identify children at risk in more need for intervention. Somatic growth deficits due to poor nutritional status would additionally have an impact in the brain structure which would endow increased risk for developing neurodegenerative diseases.

Children carrying APOE4 show a developmental benefit against environmental stress

In our studies of favela children in Northeast Brazil, we found that early childhood diarrhea and enteric parasitic infections are associated with significant, long-term cognitive deficits in higher executive function, such as verbal fluency and coding, and that the APOE4 allele is associated with protection against these deficits [11]. These differences were not seen in favela children with low diarrhea burdens.

In a recent study, Wright et al found that APOE4 in Mexico City children associates with >4.4 pts better Bayley Mental Developmental Index (MDI) scores at 24 months of age and with a 4-fold protection from the adverse effects of lead. Supporting the hypothesis that APOE polymorphisms may regulate the responsiveness to malnutrition, with lasting effects throughout the life span, a recent study has convincingly demonstrated an association of APOE4 with schizophrenia only in a group with a history of severe food shortage during early development [67]. Like others, we speculate [55,68,54] that shantytown children with APOE4, previously suffering from heavy diarrhea and malnutrition, would be at greater risk for acquiring Alzheimer's disease, type II diabetes, atherosclerosis and maladies triggered by life-long high fat consumption and progressive life-style improvements, as foreseen by Prentice and colleagues [69]. That is to say, biological switches once triggered by host–pathogen interaction, immune response, and recovery from enteric infections would ultimately enhance the likelihood of certain diseases and cognitive decline, thus reducing longevity, when genetic predispositions, such as APOE4, prevail [56].

Hence the associations of APOE4 with protection against diarrhea and its subsequent cognitive decline seen in our studies and in those Mexican infants [70] bolster the need for experimental documentation of these relationships, their causality, and the ability of specific micronutrients to ameliorate the lasting effects of malnutrition in individuals lacking APOE4.

Evolutionary advantage of the thrifty APOE4?

Studies have examined the importance of the APOE4 allele during embryonic development [71–73], which would be expected to enhance cholesterol involvement in signaling pathways during embryonic differentiation [74].

An evolutionary advantage of the E4 allele is also suggested by its greater prevalence in pre-industrialized societies and in those with greatest fertility [75] and especially in populations (ancestral and present) affected by heavy diarrhea burdens in early childhood [76]. Some have suggested that E4 is the ancestral APOE allele [77,78]. The APOE4 allele has been suggested to be a “thrifty” allele, since APOE4 is much more common (24–40%) in pre-industrialized societies (Papuans, Aborigines, Pigmies; Khoi San; Lapps), and APOE4 associates with fertility in pre-industrialized African Ecuadorian women with 9–17 children, who are 3-fold more likely to have E4 (50%) than women with <8 children. Our laboratories

are now addressing whether APOE4 and specific micronutrients are protective against the intestinal, brain, and cognitive effects seen with malnutrition, seeking potential and relevant mechanisms as proposed by the model shown in Box 1.

Novel studies from Prentice and colleagues have attributed a critical role to enriched-fat diets during the anabolic stage required for physical recovery following enteric infections and malnutrition [79]. In a cohort study in Gambia, Prentice et al. reported that fat oxidative processes are indispensable for muscle's production of energy [51], needed for catch-up growth.

Therefore, it is conceivable to speculate that increased LDL-cholesterol blood levels obtained from enriched fat diets, when available (breast-milk), and enhanced intestinal cholesterol absorption [80] likely seen in APOE4 carriers [81,82], and more underweight children [83], would support a rapid catch-up required for optimal development and survival.

The transitional weaning time from breastfeeding, which occurs unusually early in Brazilian shantytown children [84,85], opens the door to enteric diseases and diarrhea during those vulnerable first two years of life.

Despite the increasing risk of developing Alzheimer's disease in APOE4 subjects, in children with history of heavy diarrhea burdens, APOE4 appears to endow survival advantages by protecting against the cognitive impairment in developing countries. Although APOE4 is known to increase risk for cardiovascular and neurodegenerative diseases, it may well have evolved because it benefits the development of children under the stresses of repeated diarrheal diseases in impoverished areas. However, potential mechanisms of APOE4 protection on enteric infections remain to be elucidated. One may involve the oxidative stress balance during parasitic infection, possibly involving arginine transport. Since the arginine selective cationic transporter is upregulated in APOE4 knock-in mice in neuroglia, increased arginine uptake by enterocytes could provide critical generation of NO during enteric infection caused by *Giardia lamblia* [86,50], which we and others have found to be correlated with cognitive deficits following diarrhea [49,87], thus enhancing host defenses against enteric infections and diarrhea. Those potential mechanisms are topics of our ongoing studies.

Conclusions

In summary, we have reviewed critical gene–environment interactions which play a role in protecting children in impoverished areas from major stressful challenges early in life, however, they may impose a risk thereafter to prematurely acquiring degenerative diseases with aging. This concept is now being revisited and has been applied to address paradigms regarding human ontogeny [88–90,54]. We have focused on triggered early adaptations in children afflicted by bouts of heavy diarrhea burdens and enteric infections, which pose a risk to fulfillment of the genetic program of normal physical and cognitive development. Indeed, it might highlight a feature of evolutionary adaptations to survival amidst an impoverished environment, where heavy burdens of diarrhea and enteric infections are a

threat to full potential development. As a result, a compensatory feedback of a complex gene and signaling pathway machinery is upregulated in response to the life-threatening situations in order to assure a basic level of protection against severe diarrhea burdens and to preserve the development of fundamental cognitive, immune and physical capacities.

Indeed, the required adaptation to deal with prolonged and recurrent infections early in development may take priority for to optimal coping with repeated, malnourishing infections. In this regard, others' and our recent findings have highlighted a set of “obesity genes” which is critical to regulate energy storage, usage and expenditure [49,91,92]. These genes might play a “two edged-sword” role depending on changes in diet and life style during lifespan and therefore are the focus of our current functional genomic studies in poor shantytown Brazilian settings, where diarrhea and enteric infections are ubiquitous in early childhood. In another words, the trigger of an evolutionary genetic alarm is required to adjust homeostasis against severe infection rates during early childhood, to shield the body index and brain development and to recover growth following malnourishment, stunting and weight loss. According to this theory, this set of inner adjustments is only necessary as long as the life-threatening situation prevails and thereafter is shutoff. However in some extreme conditions, it might set a long-lasting “default” program, which might predispose to obesity and neurodegenerative diseases later in life, especially when the lean life-style is changed and more fat-caloric diet is abundant during adulthood and aging. Parallels between evolutionary genetics and societal evolution arose as we struggled to understand the potential significance of our recent findings of a detrimental gene providing an advantage for impoverished children.

Although it is difficult to associate complex multiple interactions during early development of one single gene where dynamic gene-to-gene interplay prevails, APOE4 appears to provide adaptations against such stresses as heavy burdens of diarrhea and enteric infections. These findings should enhance our understanding of the threat that early enteric infections still pose for children, and should focus attention on the need and means to prevent or reduce these effects in impoverished settings.

In this review, we highlight some of the complex relationships between genetic and environmental risks that influence child development. Hence, the biological and environmental sciences must be coupled to address these important issues in children's health. The specific APOE alleles may be either helpful or harmful, depending on age and stress. Understanding host genetics thus can elucidate long-term health consequences of infectious diseases of poverty. The effects of APOE4 on developmental neurobiology and cognitive outcomes following enteric infections and diarrhea that ubiquitously afflict children in the poorest areas of the developing world thus require further attention to clarify and ameliorate these potentially major effects.

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Box 1 Model for survival/adaptation against diarrhea/malnutrition endowed by the apoE-cholesterol phenotype

Subject	Hypotheses
Intestinal maturation	(a) APOE4 by increasing cholesterol absorption may improve intestinal cell maturation and polarity and adhesiveness by maintaining the integrity of tight junctions [93,94,48]
	(b) ApoE-cholesterol may influence cholesterol:phospholipid molar ratios in the enterocyte brush border [95–97]
	(c) APOE4 may enhance the corticosterone-IGF-1 system during weaning, thus improving intestinal maturation and responsiveness to infection [98,99]
Brain plasticity	(a) Increasing arginine transport to the brain and increasing NO traffic to neurons during development. NO is critical for synapses [100–103]
	(b) Increasing cholesterol availability to the developing brain, cholesterol as a glial synaptogenic factor and indirect trigger for myelination in the brain [34,104,28,105,27]
Infection	(a) ApoE4 by downregulating LDL receptors may starve enteric pathogens from cholesterol and block proliferation. The LDL-receptor pathway is also highly conserved across the animal kingdom [106–110]
	(b) ApoE is secreted in a polarized manner by enterocytes, increased by 25-OH-cholesterol and decreased by LPS through an LXR_{α}/*RXR independent signaling pathway* [47].