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Blood-Brain Barrier Disruption as a Key Role Problem in Multiple Sclerosis: A Novel Primary Prevention Strategy

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Abbreviations: MS: Multiple Sclerosis; CNS: Central Nervous System; BBB: Blood-Brain Barrier; CSF: Cerebrospinal Fluid; ER: Endoplasmic Reticulum; BBB: Blood-Brain Barrier; AD: Alzheimer Disease; CD: Cognitive Dysfunction; ROS: Reactive Oxygen Species; MSCs: Mesenchymal Stem Cells

ABSTRACT

Blood-barrier disruption is known to be a typical feature of Multiple Sclerosis. Such a vasal permeability let lymphocytes infiltration, with consequent central nervous system inflammation and demyelination. It has been demonstrated that blood-brain barrier disruption also occurs with aging and among pathology like Alzheimer's Disease and Cognitive Dysfunction. With this in mind, it is clear that such phenomenon is a common trait between vey important and severe neurodegenerative diseases, letting happen neurological damages such as harmful cytokine diffusion within central nervous system and inlet of autoreactive immune cells. Interestingly, research about primary prevention of blood-brain barrier disruption is still lacking, so that the aim of this work is to propose a novel strategy to forestall this important etiological event. As it has been discussed throughout the paper, many risk factors have been identified, i.e. smoking habits, juvenile obesity, low vitamin D and oxidative stress. Since the above cited disorders onsets occurs at least after 20 years of age, a preventive strategy has been designed to be employed since the early childhood. Such plan includes eliminating smoking habits, the employment of a Mediterranean diet supplemented with vitamin D rich foods, introducing physical activity and the consumption of food containing antioxidants.

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Multiple sclerosis (MS) is an idiopathic chronic inflammatory disease that affects the central nervous system (CNS) by demyelinating axonal processes; such pathology affects brain, spinal cord and optic nerves, sparing the peripheral nervous system. The sum of neurodegenerative and inflammatory processes generally results in discontinuous neurological disorders and progressive disability; such onset arises between 20 and 40 years of age. Since MS is known to be clinically heterogenous and displays different patterns, it could be safe to affirm the MS is a spectrum of diseases consisting by different pathological processes [1-5]. Such different forms are linked to virtually different pathophysiological pathways, though this a molecular demonstration is still lacking. Interestingly, within a single patient, the expressed pattern is homogenous even if the individual displays multiple lesions [6]. MS susceptibility can be conferred by different genes, such as those belonging to the major histocompatibility complex group, accountable for about 50% of genetic risk [7]. The current opinion recognizes MS as an immune-mediated process in which autoimmune T-cells enter the blood-brain barrier (BBB) acting by demyelinize axons, leading to various disabilities, and though research is untiringly going on, MS etiology is still largely unknown [8]. Histopathological evidences have been published, showing alterations of blood-brain barrier (BBB) in MS lesions matter [9-11]. Within this scenario it can be safely assumed that no definitive cure has been discovered, so it is reasonable to think that the best strategy is to identify risk factors, in order to try and prevent such disease. Since a primary prevention

strategy toward BBB disruption is still lacking, the aim of this work is to identify the critical risk factors and propose a prevention plan.

Blood-Brain Barrier Disruption

The most commonly investigated aspect of blood-brain barrier (BBB) dysfunction is disruption [12], which is typically considered to consist in a seeming loss of non-penetrant molecules. In addition to its above cited role in Multiple Sclerosis (MS), recent studies state that BBB disruption occurs in normal aging, worsening in individuals suffering from mild cognitive impairment, which is considered to be an early sign of Alzheimer's disease [13,14]. A simple method to indirectly estimate the magnitude of BBB disruption in patients is the measurement of BBB impermeant proteins such as immunoglobulin G (IgG) or albumin in cerebrospinal fluid (CSF). Anyhow, such measures can be mistaken by other central nervous system (CNS) deficits coming with aging, i.e. alterations in reabsorption and/or synthesis of cerebrospinal fluid (CSF) [15]. Furthermore, aging can coincide with a blood-CSF-barrier leakage, as well as with an altered protein synthesis [16,17]. In healthy mice (2 years old), it was observed a higher leakage of IgG within both cerebral cortex and hippocampus when compared with younger mice (3 months old); this finding suggests that BBB disruption occurred in this model. Such IgG increased leakage was linked with astrogliosis, endoplasmic reticulum (ER) stress, increased endothelial cell levels of TNF-α, circulating concentration of IL-6 and occludin expression in endothelial cells [18]. Molecular mechanisms of such phenomenon in aging have been found out and, surprisingly, comprehend under-expression of sirtuin-1 [19], a deacetylase related to senescence, lifespan and inflammatory responses [20].

Age-related BBB disruption could bring to a disease exacerbation through diffusion of potentially dangerous proteins into brain [14]. Anyway, it is not clear whether disruption will always lead to cerebral damage or not; for instance, some therapeutic strategies for bringing certain molecules to the brain have been carried out by temporarily disrupting BBB [21]. Latest study also reported that repeating transient disruption in human beings suffering from AD employing focused ultrasounds did not cause any severe adverse event [22]. Conversely, healthy rodents showed evidences of neurodegeneration when perfused with mannitol to disrupt BBB [23] and had an increasing in deposition of dangerous serum proteins in the CNS [24,25]. The seeming oxymoron, between attempting to use disruption as a therapeutic tool versus fearing it due to its bad effects on the CNS, underlines the complexities of BBB features as well as its role within brain pathophysiology.

Primary prevention: A Novel Proposal

According to literature, the main causes of blood-brain barrier (BBB) disruption are aging, inflammation and oxidative stress [26,27]. Although this phenomenon can be independent from pathogenetic processes associated to different diseases such as Multiple Sclerosis (MS), Alzheimer Disease (AD), Multiple Sclerosis (MS) and Cognitive Dysfunction (CD), it still remains an important risk factor linked to the above cited diseases [9-11,28-30]. Knowing that oxidative stress can lead to chronic inflammation by generating an imbalance between the synthesis of reactive oxygen species (ROS) and their elimination [31], and keeping in mind that aging causes neurodegeneration through oxidative stress [32], it is reasonable to infer that the most plausible molecular root of BBB disruption could be oxidative stress. Definitive cures and/or treatments to undo BBB disruption are still lacking and it is necessary to find a way to prevent this process, at least partially. Preliminary studies had been carried out in mice, employing mesenchymal stem cells (MSCs) in order to prevent BBB disruption after a transient ischemia [33] and administering topiramate to obtain the same result in a Type 2 Diabetes model [34].

With this in mind, it can be safely assumed that a primary prevention has still to be developed. Clearly, the only way is to eliminate all lifestyle-related risk factors, such as smoking and low vitamin D levels induced by both low dietary income and lack of sun exposure, as well as obesity during adolescence [35, 36]. Smoking habits can be stopped through various methods, including psychological therapy and nicotine-based drugs (e.g. nicotine patches, varenicline, bupropione) [37-39]; obviously, such methods depend on patient's will to actually quit smoking, and given that people freely choose start such habit, the only true primary prevention is to enhance public advertising against tobacco. Contrarily, low vitamin D levels can be both avoided by safely exposing individuals to sunlight, if possible since the early age [40], and by grating an appropriate dietary intake, supplementing meals with fish, mushrooms and sunflower oil [41]. Lastly, it is possible to hinder juvenile obesity by adopting healthy diets, such as Mediterranean one [42]. Adolescent overweight can be counteracted also by introducing an adequate physical activity, practiced on a regular basis [43,44]. The most innovative primary preventive strategy to lower both oxidative stress and inflammation is to consume antioxidant-rich food since childhood (e.g. tomato, carrots, cocoa, cranberries, grapefruit, pomegranate, etc.), since the early childhood [45,46].

Conclusion

To conclude, it can be said that blood-brain barrier (BBB) disruption risk could be reduced, on a scientific basis, with the following primary prevention strategy in both children and teenagers:

a. By preventing or eliminating smoking habit;

b. By giving them a healthy diet like the Mediterranean one, complete of vitamin D rich foods;

c. By accustoming them to habitual physical activity;

d. By consuming antioxidants rich foods since the early childhood.

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