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Review Article

Inflammation of the Central Nervous System and Disease in Children

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Abstract

An impressive development and broadening of our knowledge has happened the previous years due to the application of technologically advanced imaging methods and the investigation of the function and immunity of the Central Nervous System (CNS). Consequently, an innovative approach to diseases of CNS and in addition to new treatments has been established. Acute and chronic inflammation of the CNS as well as autoimmune phenomena has been considered the etiologic basis of post infectious encephalitis syndromes such as PANDAS disease as well as psychiatric diseases either of adulthood such as Alzheimer disease or childhood such as autism.

Keywords: *Neuroinflammation; Central Nervous System; Alzheimer Disease; Autism*

Introduction

Neuroinflammation is a complex inflammatory process of the Central Nervous System (CNS) against pathogens, toxins and substances that cause neurodegeneration. A new discipline namely psychoneuroimmunology has emerged that concentrates to the immune processes in the brain. The new scientific field was established by Aderand Cohen in 1970 who discovered T lymphocytes within the parenchyma showing no specific differentiation. Moreover, subsequent investigation showed that CNS accommodates these cells in order to maintain its function and development. Thus, the dogma that the brain is a 'protected' area from the immune system was debated and assumptions of the significant role of undifferentiated T lymphocytes and microglia emerged [1].

Immunity of the central nervous system

There are a lot of differences regarding the immunity of CNS compared to other tissues. Two basic cell populations displaying an important defensive role against infectious pathogens but also towards the removal of toxic agents. In addition, those populations control the integrity of the blood-brain barrier but also the maintenance of the so called 'plasticity' of the brain. The last denomination is given to the appropriate electric function of the CNS, the construction of synapses and the development of the brain [1].

The cells of the immune system performing these functions are T lymphocytes and microglia. In the brain the inflammatory process is triggered not only by chemokines and cytokines as in the rest of the body, but mainly by oxidative stress [2]. T lymphocytes of the brain are undifferentiated and there do not exist memory lymphocytes. However, under certain pathological conditions differentiated T cells enter into the parenchyma through the choroid plexus and meningeal veins. The brain accommodates myeloid cells, astrocytes and microglia during fetal development that dynamically contributes to its construction, function and homeostasis [2].

On the other hand, microglia is also conducive to the plasticity of the brain. It can actually obtain different phenotypes generating from molecular and functional alterations relative to the stimuli. Thus, 'the classic phenotype' is responsible for inflammation and neurotoxicity whereas the 'alternative phenotype' generates less inflammation and is protective and repairing. In other words, there are 'on' signals activating microglia in response to chemotactic factors, pro-inflammatory cytokines, in particular tumour necrosis factor-α (TNF-α) and interleukin-1β (IL-1β), and with an increased level of inducible nitric oxide synthase expression and 'off' signals generated from structural substances, that when absent microglia is activated (Figure 1). The 'alternative activation' of microglia is associated with secretion of high levels of anti-inflammatory cytokines and neurotrophic factors leading to inhibition of pro-inflammatory responses, neuroprotection and wound. The procedure is not an 'on-off' process, but rather a combination of signals leading to intermediate phenotypes [3].

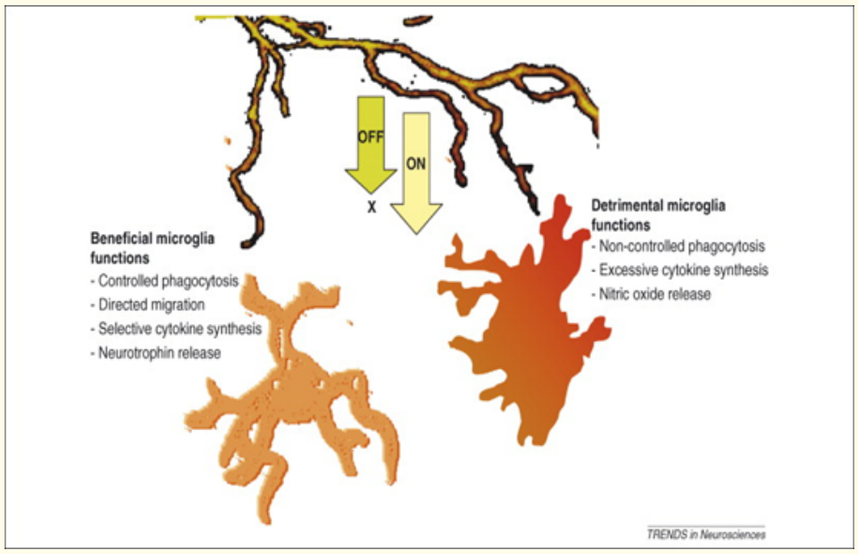

Figure 1: *Neuroglia differentiation under appropriate stimuli [3].*

Under normal healthy conditions microglia acquires the 'resting phenotype' with a typical ramified morphology maintaining minimal functions and reduced expression of receptors on the surface of the cell. It contacts synapses, 'stripping' dysfunctional ones, removing cell debris, and sensing and modulating neuronal activity and supervising the function of neurons contributing to the homeostasis of the CNS and to the plasticity in a variety of reactions. The balance is dynamic and microglia cells are quite sensitive in the detection of harmful stimuli of the milieu. When danger signals are detected related to infection or tissue damage, microglia alters its phenotype either causing damage or providing protection. Thus, microglia cells can shift from a functional state, mainly associated with the maintenance of CNS homeostasis and plasticity characterized by neuroprotective features, to a pro-inflammatory state often related to defense functions that may occur upon infections, or acute and chronic CNS injuries [3]. Microglia are also rapidly gaining attention because of their possible role in the development of psychopathology [2].

Cytoskeletal rearrangement of activated microglia results in the modification of receptor patterns on their surface, which assists their migration to the source of inflammation and to a transformation of the cell to a phagocyte. Alternatively, some cells migrate near neurons and they contribute to their dysfunction or destruction (Figure 2) [2]. Microglia activation has been demonstrated in most neurological diseases of diverse etiology and has been implicated as a contributor to neurodegeneration. The possibility to promote microglia's neuro-protective phenotype has therefore become a therapeutic goal [4].

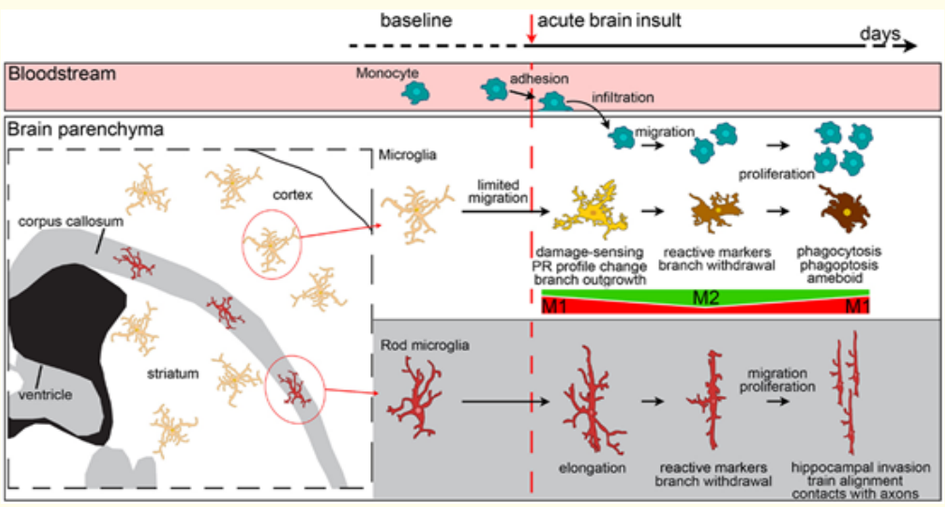

Figure 2: *The phenotypes of microglia during brain injury [4].*

As far as T lymphocyte is concerned, the undifferentiated phenotype generates under different stimuli either a TH1 (T helper 1) phenotype which promotes antigen presentation through CD40-CD40 ligand interaction and the production of interferon-γ or a TH2 (T Helper 2) phenotype that leads to the production of interleukin 4 and neurotrophic factors [2].

Research is currently focusing to demonstrate how chronic stress contributes to immune dysfunction meaning how the neuroendocrine system influences immunity. Decreased receptor sensitivity to glucocorticoids namely glucocorticoid resistance combined with increased production of IL-6 may reduce the anti-inflammatory effect of glucocorticoids and the production of proinflammatory cytokines; consequently, stressed individuals exhibit persistent inflammation leading to a variety of disease states. In adults chronic stress leads to the well-known state of immunosenescence characterized by declining adaptive responses, expanded late effector CD8+ T cell pools and decreased naïve T cell numbers [5].

Dysfunction of the immune system and autoimmunity

The representative example of autoimmunity in the CNS is the neuropsychiatric disease following a streptococcal infection namely Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections or PANDAS syndrome. The disease is characterized by aggressive-compulsive behavior and tics. The etiology is oxidative stress following the infection with streptococcus and the deregulation of the endocrine and immune system [6].

Multiple sclerosis is considered a prototype of inflammatory, demyelinating, neurodegenerative disease and current investigation has confirmed that treatment with anti-inflammatory medication mediates neuroprotection by switching the phenotype of microglia from a detrimental to a 'calming' and protective one [2].

A number of autoimmune antibodies are combined with neurodegenerative diseases such as the so called anti- MOG against myelin in multiple sclerosis and acute disseminated encephalomyelitis (ADEM) as well as anti-NR1 increased in psychiatric Systematic Lupus Erythomatosous (17-57%) and Rasmussen's encephalitis [7].

Neuropsychiatric Diseases

Alzheimer disease is a chronic inflammation of the CNS combined with activation of the microglia and intrusion of immune cells in the parenchyma leading to the destruction of neurons and death. The characteristic accumulation of β-amyloid substance and phosphorylated protein Tau leads to the destruction of the blood- brain barrier and the increase of vascularization.

The etiology is not yet known, but increased release of cytokine 1 (IL-1) and other proinflammatory cytokines probably leads to the overproduction of amyloid and the development of plaques on the parenchyma of the brain. Protein S100B is produced by the transcription of genes in chromosome 21, which is the prodromal protein of the amyloid of the plaques. In addition, activation of MAPK-p38 leads to hyperphosphorylation of Tau and the generation of fibrous. A vicious cycle starts with more inflammation promoting the destruction of neurons. The same findings have been discovered in Down syndrome preceding neurodegeneration [8].

Autism was described by Leo Kanner in 1943 and it was considered a dysfunction of the relation of the child with his mother. Until now, it is regarded a psychiatric disease and thus treated with behavioral therapies and antipsychotic drugs. 'Autism spectrum' is a neurodevelopmental disorder accompanied by behavioral dysfunction related to the interaction and communication with the environment and stereotypes. The soaring trend of autism after 1990 standing at 289% in percentage terms has found the medical society unprepared [9].

Although around 100 genes have been implicated in the appearance of autism, none has proved to be implicated in more than 10% of the cases. However, the most important genes are PTEN (phosphatase and tensin homolog) and TSC1/2 (tuberous sclerosis protein 1 and 2). The relative proteins inhibit the function of the mTOR (mammalian target of rapamycin) gene which is responsible for the expansion of mastocytes and microglia [10].

Recently, there are a lot of publications illustrating that children within the spectrum of autism develop inflammation or encephalitis in different parts of the brain. A conservative estimation of the inflammation is that 69% of children have increased biomarkers of inflammation. Postmortem biopsies confirm the existence of inflammation and the increased density of microglia. Acute reaction proteins such as TNF, IL-6 and monocyte chemotactic protein 1 (MCP-1) are found elevated in spinal fluid. The increase in arginine-vasopressin is used as a biomarker to detect inflammation in children with autism in research. In addition, the increase of the NF-κB factor in the frontal cortex as well as the increased density of the region in Positron Emission Tomography (PET) is features questioning the etiology of autism [11].

Advances in research in monkeys have revealed that activation of the immune system during intrauterine and early life determines the size and the development of the brain, thus it could be responsible for psychological and behavioral discrepancies [12]. Environmental factors have been implicated for the toxic destruction of neurons such as air pollution, pesticides and fertilizers, metals and hydrocarbons through the generation of oxidative stress and epigenetic modifications of the genome. The immune deregulation during early life alters brain connectivity and function and plays a role in autism phenotypes. The recent demonstration that microglia, the resident immune cells of the CNS, contribute not only to inflammatory events but also to neural development, has raised new hypotheses regarding their role in the etiology of autism [13].

New therapeutic treatments that reduce inflammation have shown promising results. InhibitorsofmTORsuchasrapamycinandluteolinhavebeenusedwithfavoriteresults.Treatment of children with autism with corticosteroids or biologic therapies have positive results. However, research is ongoing on the field with revolutionary results due to the advances of our knowledge of the function of the immune system of the brain [14].

Conclusion

Basic immunology knowledge regarding CNS has provided new insights regarding diseases of childhood. Apart from explaining the nature of autoimmune diseases, it has posed new data regarding neurogenerative diseases such as autism. Although physicians treating autistic children would be skeptical, they should take into consideration these revolutionary data.

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