Brain and Immune System: KURU, a Strange Kind of Disease. An Endogenous Toxicological Process Like?

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Abstract

Starting from observation of pathogenesis of KURU disease we try to show the immunologic role played by central nervous systems. A deeply knowledge in the transmission model of this pathology can be an imaging/diagnostic tool to verify the progression of this prion disease from gastro intestinal systems to the brain. Can we consider a sort of trace ant the prions in KURU to monitoring this process? What information can we obtain in order to produce new pharmacological strategies in some other degenerative brain disease?

Keywords: Brain; Immune System; KURU

Introduction

Observing that some cases of CJD are due by peripheral exposition to prions and that KURU disease and BSE are transmitted by oral intake of infected food we try to produce new theories in immune systems and brain inter-connections. Can we consider KURU infectious disease an instrument to verify interconnection between immune cell out and in central nervous systems? Like a ERLIC magic bullet? Or an imaging tracer to follow the neuro immune process? Prions result neurotropic but other antigen are normally presented inside brain? And with what consequences? other brain disease present the similar pathogenetic move's immune system related? Transgenic modified mouses study showed that immune system are involved in amplification and transmission to central nervous system (Lymph. B and follicular dendritic cell). In prions disease we see species barrier and is necessary a molecular similarity between prions and endogenous PRP-C. Are present relationship between some brain disease as amyloidosis and other degenerative disease like parkinson, dementia and prions disease and other?

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In SM (a neuro inflammatory disease) is involved adaptative immunity: Lymphocyte T and B, While in other disease as Alzheimer (a neurodegenerative pathology) is involved the innate immunity (microglia- macrophage like activity, first immune control system in the central nervous systems). Observing the KURU disease, the time involved in presentation of symptomatology after intake of Prions and (a slow process) related to the fast time In soma cases involved in some neurotropic viruses

We can think to an passive vs active process by which immune systems transfer to the brain the toxic prions from GI system. In all this pathologies immune system play a relevant role (adaptive or innate) giving tissue damage and accumulation of bio products. Observing the global role played by immune system in some brain pathology under a specific toxicological aspect We can think to other therapeutic strategies to improve the actual pharmacological scenario. This paper is produces under a specific medicinal chemistry and pharmacological point of view.

Material and Methods

This review work has been implemented with an observational and review approach we have analyzed some relevant bibliography in order to verify the general immune status influences with some brain local situations and its relationship in some brain disease.

Results

From literature we have find: "Using fingolimod we have a reduction in lymphocytes activation and when discontinued this effect reduced (like a discontinue of a toxic substantia). Dose related and time related. FINGOLIMOD Significantly improved relapse rates and end points measured on magnetic resonance imaging (MRI) in objective way. Concepts as toxic doses, time of exposition, cumulative dosage, kinetics, dynamics, metabolism Iatrogenic ADME and other toxicological parameter can be usefully introduced also in neuro-immune toxicology to adequately focus a physio-pathogenetic phenomena. The results related to the references cited show a specific effect of a systemic drugs in a local place as brain. We think that observing a specific side effect of a drug can be a right method to clear some interference between immunologic status and some development disorder" [1].

Lindenbaum S writed that: "To understand kuru disease and solve the problems involved about of its cause and transmission process required the integration of different knowledge from both anthropological and medical research. Anthropological scientific studies elucidated the origin and spread of kuru disease, the ethnic local mortuary practices of endocannibalism, the social effects of kuru disease, the life of women and child-rearing practices, the kinship system of the Fore and their willingness to incorporate outsiders into it, the myths, folklore and history of the Fore and their neighbours, sorcery as a powerful social local phenomenon and way of explaining the causation of the pathology and concepts of the therapeutic treatment of disease" [2]. Haïk S., *et al*: "In contrast with other neurodegenerative disorders associated to protein misfolding, human prion diseases include infectious forms (also called transmitted forms) such as kuru, iatrogenic Creutzfeldt-Jakob disease and variant Creutzfeldt-Jakob disease. The transmissible agent is thought to be solely composed of the abnormal isoform (PrP(Sc)) of the host-encoded prion protein that accumulated in the central nervous system of affected individuals. Compared to its normal counterpart, PrP(Sc) is β-sheet enriched and aggregated and its propagation is based on an autocatalytic conversion process. Here, we review and discuss how genetic factors interplay with strain properties and route of transmission to influence disease susceptibility, incubation period and phenotypic expression in the light of the kuru epidemics due to ritual endocannibalism, the various series iatrogenic diseases secondary to extractive growth hormone treatment or dura mater graft and the epidemics of variant Creutzfeldt-Jakob disease linked to dietary exposure to the agent of bovine spongiform encephalopathy [3]. D. Carleton Gajdusek writed that: "The solution of kuru led us to the solution of Creutzfeldt–Jakob disease and to the elucidation, in humans and other species, of previously unknown mechanisms of infection. Kuru in its location in Papua New Guinea region has also led to an understanding of the cultural- social achievements of the Palaeo-Melanesians, with deep roots in the human history.

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Kuru presented itself to us in 1957 year as a challenge to epidemiology science and a clearly solvable related problem, but it quickly led us to realize that its solution would contribute new vistas to clinical medicine disciplines, microbiology, immunology and neurology. It was fast in revealing that it would open new doors to virology fields, genetics, amyloidology, ageing and other already in 1957 year, we were calling kuru disease galloping senescence of the juvenile and soon added to this the key to the ageing CNS, amyloidosis, and the genetic control of ageing and the length of human life.

An infectious disease with a very long incubation period and its agent appeared to be very small compared with all other viruses, from the high titres it attained in the brain in our initial first transmission experiments (Gajdusek 77). Clinical study of patients revealed that it was non-inflammatory disease and lab tests and neuropathology confirmed this. Its agent evoked a no immune response. Klatzo initially compared it in 1957 to Creutzfeldt–Jakob pathology, which no one had seen in children and was unknown to most British and American physicians; only 20 cases had been seen in the world.

He emphasized the fact that the cerebral amyloid plaques seen in most cases had never before been seen in the CNS of children. When J. R. M. Innes and W Hadlow showed us the similarity of the disease to scrapie, we had the lead that led us to repeat our animal inoculations on a much wider basis and proceeded to show the process that it was transmissible to animals like chimpanzees and to monkeys, rodents and other animals, with long incubation periods time.

We have repeated the confirmation of resistance of a portion of infectivity of scrapie prions to temperature as high as 600°Centigrades. The great resistance to dry heat of a small fraction (one part in 106) of infectious nucleant activity can represent a molecular cast, or fingerprint, of the nucleant. Infectious nucleant or prion activity is the result of very close three dimensional matching behavior, fibrillate or form a two-dimensional molecular sheet that can trigger the process. The Amyloids enhancing factors are scrapie like infections-amyloid nucleants. Their discovery of amyloid-enhancing factors (Niewold., *et al.*), which were active in high dilutions situation and difficult to purify, reminded of our problems with the infectious agents of scrapie or kuru disease. I suggested that the amyloid enhancing factors were scrapie-like agents. Amyloid deposits (man or in animals) are always found to be contaminated with other proteins similarly polymerized into fibrils even co polymerized.

These are all the proteoglycans and glycosaminoglycans molecules, plasma P-protein, chymotrypsin, ubiquitin, light chains of gamma globulins and amyloidogenic proteins. The high-incidence foci of very different diseases, Guamanian amyotrophic lateral sclerosis and parkinsonism–dementia, occurred also in a few remote villages on Honshu Island in Japan and among the Auyu and Jakai people around Bade and Kepi places in southern West New Guinea.

It has disappeared with the introduction of civilization. These 3 foci were restricted to the remote communities in which there was a depletion of environmental calcium as to produce a chronic- severe deficiency of calcium diet, with calcium sparing led to soft tissue deposition of calcium aluminium silicate or montmorillonite clay deposits within brain cells, along with other heavy elements as diet provided.

These lay dormant status for decades until triggered later in life, to cause a specific neuronal damage leading to lytico or bodig. The Civilization process, with all its ills and consequences, has caused these two diseases in all the three locations to disappear. we discovered that kuru had no genetic boundaries" [4]. According Barry M Bradford., *et al.* Prion diseases or transmissible spongiform encephalopathies are a unique class of infectious protein-misfolding neurodegenerative pathologies. Cells of the innate immunologic system have been proven to be critical players in the initial pathogenesis process of prion disease, and a role in the progression of disease. Prion diseases or transmissible spongiform encephalopathies are infectious neurodegenerative conditions characterized by vacuolar degeneration of the CNS and deposition of an abnormal isoform of the host-encoded prion protein (PrP). These pathologies affect a wide variety of animal-species and with limited zoonotic potential. Often displaying a prolonged incubation periods, clinically recognized via progressive neurological deterioration resulting from synaptic and neuronal loss and associated activated glial responses to brain damage.

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Identification of the genetically inherited forms of these pathologies implicate further the critical role of the prions in pathogenesis and their classification as protein-misfolding disorders, with similarities to other progressive dementias such as Alzheimer's and Parkinson's diseases and amyotrophic lateral sclerosis. Sporadic prion pathologies, with no genetic risk factor or exposure to infection, have also been identified.

According the prion hypothesis the infectious agent may be solely composed of a proteinaceous molecule the disease-associated isoform of the prion protein (PrPSc), with the means to self-propagate via an auto-catalytic process of template-mediated refolding of the nascent cellular prion protein (PrPC). The peripheral pathogenesis of these diseases have been studied with animal models (mice) are naturally susceptible to sheep scrapie and bovine spongiform encephalopathy (BSE).

After natural peripheral exposure to prions, infection is usually sequestered to the lymphatic organs prior to invasion of the brain and nervous system.

In absence of local draining lymphatic tissue, circulation to other lymphoid organs and neuroinvasion are ultimately blocked disease-associated PrP is deposited in lymphatic follicles and replicates upon the follicular dendritic cells As such a positive relationship has been firmly established between the immune-competence of the host and ability to support prion pathogenesis. The innate immune system is considered to be a protective system that is older in evolutionary terms than the adaptive immune system. A great systemic pool of cellular (inflammatory) and proteinaceous components of the innate immunologic system also exists, to be mobilized rapidly (in response to signals from epithelia or resident innate immune cells).

Below we consider the various components of the innate immunologic system, cellular and proteinaceous, and their roles in prion pathogenesis. The epithelial cell layers constitute one of the first physical- barrier to infection progression prion infection via skin is experimentally (facilitated by scarification or breaking of the keratinized epidermal barrier layers to) allow the access to the epithelial layer beneath. The Prion infection process via the oral or nasal route appears as to be naturally more efficient. Prion pathogenesis can be high enhanced by disruption of the epithelial layers (involved in these routes) Under a steady stat oral uptake of prion infection occurs via specialized microfold cells localized to the follicle-associated epithelium of intestinal Peyer's patches. The de-differentiation of the M-cells prior to oral scrapie infection was sufficient condition to block pathogenesis completely. Innervation of the lymphatic organs show to be critical for prion neuro-invasion. These experimental data provide a hard argument against hematogenous spread of prion agent directly to the brain. Following aerosol exposure, prion pathogenesis occurs independently of the immune system, FDC, B cells, T cells, NK cells, lymphotoxin β receptor or CD40 ligand signaling complement has been shown to be activated early during prion pathogenesis by as yet undetermined mechanisms and may constitute the first active response to infection.

Prion or TSE agents are opsonized by complement components, via the classical complement activation pathway, which may aid in their targeting of the agent to lymphatic follicles. Mice lacking in complement components revealed deficient peripheral prion pathogenesis under specific conditions. THE cleavage of the cellular prion protein has been shown to protect against the infection and cleavage of PrPSc has been shown to modulate the prion propagation in a similar way.

There is a little evidence supporting a the role for complement in prion pathogenesis within the CNS. Mice lacking C1qa, C2 or C3 revealed no deficit to prion pathogenesis following intracerebral inoculation and mice lacking both complement components C3 and C4 revealed unaltered pathogenesis following aerosol exposure to prions mast cells have been implicated in prion pathogenesis due to their high expression levels of cellular prion protein (PrP or PrPC) and their ability to traffic to the brain. The role of mast cells within the brain is thought to be neuro-modulatory and mast cell trafficking to the brain is linked to steroidal hormones and sexual activity or anxiety behaviors.

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The presence of mast cells within the brain and their ability to shed expressed PrP upon activation can have implications for prion pathogenesis in CNS. Shedding of PrPC by mast cells likely occurs via proteolytic or lipolytic cleavage mechanisms removing the. The activation of the mast cells within the brain and CNS may provide copious extracellular PrPC substrate for conversion to the pathology-associated isoform late in the disease process, when significant damage has occurred to the CNS already, adding to the exponential accumulation of misfolded protein within the clinical stage of the pathology. (Mononuclear Phagocytes cells *et al*: Microglia, Macrophages, Monocytes, Dendritic Cells and Langerhans Cells) the uptake and spread of prions to lymphoid organs occurs using MNP as a 'Trojan horse' vhit a similar like mechanism.

This fact reflects a wide diversity of MNP and its roles in innate immunity. (1) resident cells with degradative functions; (2) resident cells with APC antigen presenting functions and (3) systemic circulating cells responsive to THE inflammatory stimuli. MNP-mediated uptake of prion agent is enhanced by complement opsonization (The uptake of prions likely involves complement, lectin or scavenger receptors while there is evidence that Fc.

Degradative MNP

The expression of cellular prion protein in MNP has been associated with the phagocytic ability - modulation of inflammatory responses. Evidence suggests that macrophages degrade the prion agent. The degradative and prion clearance abilities of macrophages appear to be down-regulated when macrophage (Mϕ) activation is stimulated by other danger signal molecules prion infection. Antigen Presenting Cells APC have long been identified as being critical to prion pathogenesis. respectively. These findings strongly link these cell to the retention of intact prion and, in the case of classical DC, traffic of the agent in the pre-neuroinvasive stage of infection. MNP in the CNS Within the CNS the innate immune response is mediated by specialized MNP CELL known as microglia. 2.5. Granulocytes: Neutrophils, Basophils and Eosinophils gene expression data reveal that PrP expression is generally down-regulated during granulocyte differentiation phenomena though some expression is still detectable. Neutrophil functions have been shown to be inhibited by both native and scrapie associated prion protein, resulting in failure of neutrophil aggregation and deficits in superoxide radical and beta-glucuronidase export A 20 amino acid fragment of the prion protein sequence (termed PrP106-126) has been shown to be directly neurotoxic, activate MNPs and act as a chemotactic agonist for the FPRL1 receptor. NK and γδ T cells are thought to play little role in the pathogenesis of the prion diseases.

Both this cell types require triggering or activation by a danger signals, for NK cell this is usually via cytokines and for γδ T cells little is known about their activating signals. NK cells first respond to virally-infected cells and function to destroy these cells via expression of perforin and granzyme. Perforin-knockout mice revealed an unaltered prion pathogenesis. A lack of reported NK cell response to prion pathogenesis suggests that prion agents uptake by monocytes may fail to activate the NK cells. In Recent time NK/T cells (a subset of T-cells that express both the NK1.1 marker and αβ T cell receptor) in the spleen have been associated with prion infectivity. Investigating the role of NK/T cells in prion disease progression is hampered by the fact that though Rag2−/− mice are deficient in NK/T cells they are unsusceptible to prion infection- disease due to their B-cell deficiency and failure to generate mature FDC. An increase in γδ T cells in peripheral blood mononuclear cells has been reported following scrapie infection in sheep. The megakaryocyte lineage and platelets have been associated with the expression of prion protein. The routing of prion pathogenesis has been characterized in precise immune histological detail and describes neuroinvasion from lymphoid organs via the peripheral nervous system expression of the cellular prion protein by the hematopoietic compartment is not required for prion pathogenesis, confirm that the innate immune system role in disease pathogenesis operates via non-PrPC dependent mechanisms. Little is known related the uptake mechanisms of prions and the factors that lead to cell clearance, infection or passivity that may facilitate transport. PrPC is not required for uptake of prions *in vitro*, even by non-phagocytic cell types such as neurons. Maturation of cells in response to all-trans retinoic acid is one mechanism known to down-regulate PrP expression. The most common mechanism for determining or proving a correlation between components of the innate immune system (be they cells or proteins) and prion pathogenesis is via transgenic mouse models. These kind of models have been used to determine

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the effect of knockout or overexpression of a particular protein or cell type on prion pathogenesis. The experiment revealed that knockout of Prnp resulted in complete resistance to prion infection Various of immunity-associated candidate genes have been identified by observational techniques e.g. following gene expression profiling and numerous genes have been screened for a role in prion pathogenesis via knockout transgenic mouse models.

The majority of such experimental studies have determined that knockout of an individual component does not prevent prion pathogenesis. From these candidates molecule all have previously been implicated with prion pathogenesis, Il-4, Il-6 and Il-12 have been shown not to be required. Il-10 knockout-mice revealed major alterations to, but not prevention of, the prion pathogenesis. These experimental data reveal the cytokine milieu occurring during prion pathogenesis and may underlie the basis of alternative activation of MNP and lack of inflammatory, or tolerization of, responses during prion infection. prion pathogenesis is influenced by the steady-state, activation and response of the innate immune system. The innate immune system has many and varied roles in the response to prion pathogenesis, The activation of mononuclear phagocyte -cells appears critical to both peripheral and central prion pathogenesis through as unidentified receptors and signaling pathways [5]. "The word prion was established in 1982 by Stanley B Prusiner. It is derived from protein and infection and is short for "proteinaceous infectious particle". Prions can self transform their shape and propagate. Thus they can be transmitted from cell to cell, between individuals, and even between animals of different species. For his discovery of prions, Prusiner was awarded the Nobel Prize in 1997. The neuropathology of Parkinson's disease (PD) is characterized, in part, by severe loss of dopaminergic neurons

Due to the shared pathological feature of α-synuclein aggregates, PD, DLB and MSA are known as α-synucleinopathies. Recently, several proteins that are prone to misfold, form aggregates in the brain and that each define specific neurodegenerative disorders have been shown to transmit from one cell to another in in experimental disease models. This applies to α-synuclein in models of PD, DLB and MSA, as well as Tau in models of Alzheimer's disease; mutant huntingtin in Huntington's disease models, and mutant SOD in amyotrophic lateral sclerosis (ALS) models [2,3]. The behavior of these disease-related proteins has been called "prion-like". In this minireview, we briefly describe 1) evidence that α-synucleinopathies are prion-like disorders; 2) mechanisms that underlie intercellular transfer of misfolded α-synuclein; and 3) the relevance to future therapies and diagnostics. We also discuss where the first misfolding events might occur, and controversies regarding the possibility that α-synucleinopathies might be communicable. What triggered the idea that α-synuclein might be a prion-like protein?

In 2005 John Hardy speculated that "permissive templating" could play a key role in the pathogenesis α-synucleinopathies [4]. A. The final take home message, however, should be that the most important issue is not classification or not of α-synucleinopathies as prion diseases, but the realization that prion properties of α-synuclein contribute to the pathogenic process and further understanding of mechanistic underpinnings can lead to new therapeutic strategies" [6].

Thomas Korn., *et al*: "T cells are required for immune surveillance of the central nervous system (CNS); however, they can also induce severe immunopathology in the context of both viral infections and autoimmunity. The mechanisms that are involved in the priming and recruitment of T cells to the CNS are only partially understood, but there has been renewed interest in this topic since the 'rediscovery' of lymphatic drainage from the CNS. Moreover, tissue-resident memory T cells have been detected in the CNS and are increasingly recognized as an autonomous line of host defence. In this Review, we highlight the main mechanisms that are involved in the priming and CNS recruitment of CD4+ T cells, CD8+ T cells and regulatory T cells. We also consider the plasticity of T cell responses in the CNS, with a focus on viral infection and autoimmunity [7].

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Iannacone M., *et al*: "Lymph nodes (LNs) capture microorganisms that breach the body's external barriers and enter draining lymphatics, limiting the systemic spread of pathogens. Recent work has shown that CD11b(+)CD169(+) macrophages, which populate the subcapsular sinus of LNs, are critical for clearance of viruses from the lymph and for initiating antiviral humoral immune responses.. These results identify SCS macrophages cells as crucial gatekeepers to the CNS- brain that prevent fatal viral invasion of the nervous system on peripheral infection" [8]. Ironside Jw., *et al*. "The human prion pathology comprise Creutzfeldt-Jakob disease, variably protease-sensitive prionopathy, Gerstmann-Sträussler-Scheinker disease, fatal familial insomnia, and kuru. Each is a uniformly fatal- rare neurodegenerative pathology in which conformational changes in the prion protein are thought to be the central pathophysiologic event. The intensive study of these diseases continues to inform on neurodegenerative mechanisms and the role of protein misfolding in more common neurodegenerative diseases such as Parkinson disease PD and Alzheimer path" [9]. Iwasaki Y., *et al*: "MV2-type sporadic Creutzfeldt-Jakob disease (sCJD), which was previously called "Kuru-plaque variant", was gradually revealed to have a wide spectrum and has been classified into three pathological subtypes: MV2K, MV2C and MV2K + C. We herein describe the detailed clinical findings and neuropathologic observations from an autopsied MV2K + C-type Japanese sCJD case with widespread cerebral cortical pathology and Kuru plaques. In the early stages of the disease, the patient exhibited gait disturbance with ataxia and dysarthria as well as gradual appearance of cognitive dysfunction. Diffusion-weighted images (DWI) on MRI revealed extensive cerebral cortical hyperintensity. Pathologic investigation revealed extensive spongiform change in the cerebral cortex, particularly in the deeper layers. Vacuole size varied, and some were confluent. Prion protein (PrP) immunostaining revealed extensive PrP deposition in the cerebral cortex, basal ganglia, thalamus, cerebellum, brainstem and spinal cord. In the cerebral cortex, synaptic-type, Kuru plaque-like, and coarse plaque-type PrP depositions were mainly observed, along with some perivacuolar-type PrP depositions. Kuru plaques and coarse plaque-type PrP depositions also were observed in the cerebellar cortex. PrP gene analysis revealed no mutations, and polymorphic codon 129 exhibited Met/Val heterozygosity. Western blot analysis revealed a mixture of intermediate-type PrPSc and type 2 PrPSc. Based on previous reports regarding MV2-type sCJD and the clinicopathologic findings of the present case, we speculated that it may be possible to clinically distinguish each MV2 subtype. Clinical presentation of the MV2K + C subtype includes predominant cerebral cortical involvement signs with ataxia and DWI hyperintensity of the cerebral cortex on MRI" [10]. Rayman JB., *et al*: "Prions are proteins that can adopt self-perpetuating conformations and are regarded as the etiological agents of infectious neuro- degenerative diseases in humans, such as Creutzfeldt-Jakob disease, kuru, and transmissible encephalopathies in recent time a great consensus has emerged that prion-like, self-templating mechanisms also underlie a variety of neuro- degenerative disorders, like amyotrophic lateral sclerosis, Alzheimer's disease, and Huntington's disease. Perhaps most surprising, not all prion-like aggregates are related with pathological changes.

There are now many examples of prion-like proteins in mammals that serve positive biological functions in their aggregated status. In this review paper, we discuss the functional prions in the nervous system, with particular emphasis on the cytoplasmic polyadenylation element-binding protein (CPEB) and the role of its prion-like aggregates in synaptic plasticity and memory. We mention a recent example of a functional prion-like protein in the brain, TIA-1, and its role during stress. These studies of functional prion-like proteins have provided a number of generalizable insights on how prion-based like protein switches may operate to serve physiological functions in higher eukaryotes" [11].

The adaptive immune system in diseases of the central nervous system David C Wraith., *et al*: " Tissues of the CNS, such as the brain, optic nerves, and spinal cord, may be affected by a range of insults including genetic, autoimmune, infectious, or neurodegenerative diseases and cancer.

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The immune system is involved in the pathogenesis of many of these, either by causing tissue damage or alternatively by responding to disease and contributing to process of repair. It is clearly vital that cells of the immune system patrol the CNS and protect against infection. in contrast to other tissues, damage caused by immune pathology- disease in the CNS can be irreparable. The nervous and immune systems have, coevolved to permit effective immune surveillance while limiting immune pathology we will consider aspects of adaptive immunity in the CNS- brain and the retina, both in the context of protection from infection as well as cancer and autoimmunity, while focusing on immune responses that compromise health and lead to significant morbidity" [12].

According to Ann-Christin Wendeln., *et al*. "Innate immune memory is a vital mechanism of myeloid cell plasticity that occurs in response to environmental stimuli and alters subsequent immune responses. 2 types of immunological imprinting can be distinguished training/tolerance. These are epigenetically mediated and enhance or suppress subsequent inflammation, respectively. we demonstrate that peripherally applied inflammatory stimuli induce acute- immune training and tolerance situation in the brain and lead to differential epigenetic reprogramming of brain-resident macrophages (microglia) that persists for at least 6 months. Strikingly, in a mouse model of A.D pathology, immune training exacerbates cerebral β-amyloidosis and immune tolerance alleviates it; similarly, peripheral immune stimulation modifies pathological features after stroke. Our results finded identify immune memory in the brain as an important modifier of neuropathology [13]. 13)

Robert Dantzer writed that: "Because of the compartmentalization of disciplines that shaped the academic landscape of biology and biomedical sciences in the past, physiological systems have long been studied in isolation from each other. This has particularly been the case for the immune system.

Accordingly, it has taken a long time for immunologists to accept the concept that the immune system is not self-regulated but functions in close association with the nervous system. These associations are present at different levels of organization. At the local level, there is clear evidence for the production and use of immune factors by the central nervous system and for the production and use of neuroendocrine mediators by the immune system. Short-range interactions between immune cells and peripheral nerve endings innervating immune organs allow the immune system to recruit local neuronal elements for fine tuning of the immune response. Reciprocally, immune cells and mediators play a regulatory role in the nervous system and participate in the elimination and plasticity of synapses during development as well as in synaptic plasticity at adulthood. At the whole organism level, long-range interactions between immune cells and the central nervous system allow the immune system to engage the rest of the body in the fight against infection from pathogenic microorganisms and permit the nervous system to regulate immune functioning. Alterations in communication pathways between the immune system and the nervous system can account for many pathological conditions that were initially attributed to strict organ dysfunction. This applies in particular to psychiatric disorders and several immune-mediated diseases. This review will show how our understanding of this balance between long-range and short-range interactions between the immune system and the central nervous system has evolved over time, since the first demonstrations of immune influences on brain functions. Finally, a few examples will illustrate how dysfunction in these communication pathways results in what was formerly considered in psychiatry and immunology to be strict organ pathologies" [14].

Rimona S Weil., *et al*: "Parkinson's disease dementia (PDD) and dementia with Lewy bodies are relentlessly progressive neurodegenerative disorders that are likely to represent two ends of a disease spectrum.

It is well established that are characterised pathologically by widespread cortical Lewy body deposition.

It was also not understood why some cells are particularly vulnerable in PDD/DLB, nor why some individuals- patients show more aggressive and rapid dementia than others.

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Recent experimental studies using animal and cell models as well as human post mortem analyses have provided important insights into these questions. Here, we review recent experimental developments in the pathophysiology in PDD/DLB.

We examine the role of this pathological proteins other than α-synuclein, consider particular morphological and physiological features that confer vulnerabilities on some neurons, finally examine genetic factors that may explain some of the heterogeneity between individuals with PDD/DLB [15].

Gail Chan., *et al.* showed a link between CD33 protein of immune systems and other protein linked to AD: "We used a protein quantitative trait analysis in monocytes from 226 individuals to evaluate cross-talk between AD loci. The NME8 locus influenced the PTK2B and the CD33 risk allele led to a greater TREM2 expression. There was a decreased TREM1/TREM2 ratio with a TREM1 risk allele, decreased TREM2 expression with CD33 suppression and elevated cortical TREM2 mRNA expression with the amyloid pathology [16]. The Immunology origin and functional properties of catalytic autoantibodies to amyloid beta peptide.

Paul S., *et al*: Objectives The objectives of this study are to (1) evaluate the ability of the immune system to synthesize specific antibodies that catalyze the degradation of amyloid beta peptide (Abeta) and to (2) evaluate the prospect of developing a catalytic IVIG (CIVIG) formulation for therapy of Alzheimer's disease (AD).

"Polyclonal autoantibodies from humans without dementia hydrolyzed Abeta specifically. The catalytic activity improved as a function of age. Patients with AD produced catalytic antibodies at increased levels. IgM-class antibodies expressed the activity at levels superior to IgGs. Production of catalytic autoantibodies appears to be an innate immunity function with adaptive improvements occurring upon Abeta overexpression, which suggests a beneficial function of the catalytic activity. The catalytic autoantibodies impeded Abeta aggregation, dissolved preformed Abeta aggregates, and inhibited Abeta cytotoxicity in tissue culture. Recombinant catalytic antibodies from a human library have been identified, validating the phenomenon of antibody-catalyzed Abeta cleavage. As a single catalyst molecule inactivates multiple Abeta molecules, catalytic antibodies may clear Abeta efficiently. IVIG did not cleave Abeta, indicating the importance of purification procedures that maintain catalytic site integrity. Traditional Abeta-binding antibodies form immune complexes that can induce inflammatory reaction and vascular dysfunction. Catalysts do not form stable immune complexes, minimizing these risks. Criteria appropriate for developing a CIVIG formulation with potential therapeutic utility are discussed, including isolation of the Abeta-specific catalytic subsets present in IgM and IgG from human blood [17]. In article Prion-like properties of Tau protein: the importance of extracellular Tau as a therapeutic target.

Holmes BB., *et al*. writed that: And related to: Immune system linked with accumulation of toxic tau protein: "Work over the past 4 years indicates that multiple proteins associated with neurodegenerative diseases, especially Tau and α-synuclein, can propagate aggregates between cells in a prion-like manner.

The prion model predicts a crucial role for extracellular protein aggregates in mediating progression of disease.

This suggests new kind of therapeutics approaches based on blocking the neuronal uptake of protein/aggregates and promoting their clearance. This will likely incl This suggests new kind of therapeutics approaches based on blocking the neuronal uptake of protein/aggregates and promoting their clearance. This will likely include therapeutic antibodies or small molecules, both of which can be developed and optimized in vitro prior to preclinical studies [18]. This suggests new kind of therapeutics approaches based on blocking the neuronal uptake of protein/aggregates and promoting their clearance. This will likely include therapeutic antibodies or small molecules, both of which can be developed and optimized in vitro prior to preclinical studies [18]. ude therapeutic antibodies or small molecules, both of which can be developed and optimized *in vitro* prior to preclinical studies [18].

A New research paper, published by Cell Press in the October 7th issue of the journal Neuron, provides mechanistic insight into a link between the immune system and neurodegenerative disorders like Alzheimer's disease that are associated with abnormal accumulation of tau protein: "In conclusion, this study demonstrates that altered microglia activation plays a direct role in modulating the hyperphosphorylation and aggregation of MAPT within neurons and suggests potential strategies for therapeutic intervention in tauopathies" [19].

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According to Heppner FL., *et al*: "The past two decades of research into the pathogenesis of Alzheimer disease (AD) have been driven largely by the amyloid hypothesis; the neuroinflammation that is associated with AD has been assumed to be merely a response to patho-physiological events. However, new data from preclinical and clinical studies have established that immune system-mediated actions in fact contribute to and drive AD pathogenesis. These insights have suggested both novel and well-defined potential therapeutic targets for AD, including microglia and several cytokines. In addition, as inflammation in AD primarily concerns the innate immune system - unlike in 'typical' neuroinflammatory diseases such as multiple sclerosis and encephalitides - the concept of neuroinflammation in AD may need refinement" [20].

Heneka MT., *et al*: "Classically AD has been viewed as a neurodegenerative disease of elderly, by the extracellular deposition of mis-folded amyloid-β (Aβ) peptide and the intracellular formation of neurofibrillary tangles.

Only in recent time has neuroinflammation emerged as an important component of AD pathology.

Experimental, genetic, epidemiological data indicate a crucial role for activation of the innate immune system as a disease-promoting factor.

The sustained formation - deposition of the Aβ aggregates causes a chronic process activation of the immune system and disturbance of microglial clearance functions" [21].

"In toxicology field usually are high considered the external-environmental factors but is important to observe under toxicological approach also the inside intra/extra cellular local micro-environment (paraphysiologic-pathologic conditions).

In some pathology the time is relevant added to endogenous local micro environment and inters cellular communication situations.

In some situation: time related local metabolic-catabolic-toxic status we can observe some cellular effect resulting in some organ failure. The time involved in resolve some temporary gradients or the process velocity in this process can be fundamental.

The same effect related to too a much rapid evolution or a too slow reduction in balancing equilibrates physiologic systems. We need to introduce more metabolic- toxicological methods in some pathologies in order to clear some relevant aspect in etiology, diagnosis and therapy" [22].

Götz J., *et al*: "With populations ageing worldwide, the need for treating and preventing diseases associated with high age is pertinent. Alzheimer's disease (AD) is reaching epidemic proportions, yet the currently available therapies are limited to a symptomatic relief, without halting the degenerative process that characterizes the AD brain. As in AD cholinergic neurons are lost at high numbers, the initial strategies were limited to the development of acetylcholinesterase inhibitors, and more recently the NMDA receptor antagonist meman-tine, in counteracting excitotoxicity. With the identification of the protein tau in intracellular neurofibrillary tangles and of the peptide amyloid-β (Aβ) in extracellular amyloid plaques in the AD brain, and a better understanding of their role in disease, newer strategies are emerging, which aim at either preventing their formation and deposition or at accelerating their clearance. Interestingly, what is well established to combat viral diseases in peripheral organs - vaccination - seems to work for the brain as well. Accordingly, immunization strategies targeting Aβ show efficacy in mice and to some degree also in humans. Even more surprising is the finding in mice that immunization strategies targeting tau, a protein that forms aggregates in nerve cells, ameliorates the tau-associated pathology. We are reviewing the literature and discuss what can be expected regarding the translation into clinical practice and how the findings can be extended to other neurodegenerative diseases with protein aggregation in brain" [23]

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Discussion

We have seen the role of immune system in some brain disease and transmission way (in example KURU).

From this last example we can say that some antigen are currently sended to central nervous system?

Why PRIONS arrive form gastro- intestinal apparatus to SNC trough immune systems cells?

Only prions are neurotropic? And the delay observed in KURU to see symptoms?

We have also see the pharmacological activities of Fingolimod, A SYSTEMIC drug, towards central nervous systems lymphocyte.

From literature observed immune system and some brain disease are strictly interconnected.

"The intensive study of these diseases continues to inform on neurodegenerative mechanisms and the role of protein misfolding in more common neurodegenerative diseases such as Parkinson disease and Alzheimer disease" [9].

Recently, a growing consensus has emerged that prion-like, self-templating mechanisms also underlie a variety of neurodegenerative disorders, including amyotrophic lateral sclerosis, Alzheimer's disease, and Huntington's disease [11]

The same is clear the fingolimod brain effect (a systemic drugs).

Other example can be therapeutic strategies in SM with immuno modulant agents and observing also the different degenerative brain disease, with accumulation we can verify if exist an immune systems role (AD, Parkinson, Lewy Body Dementia, pick disease and other brain amyloidosis) neurodegenerative protein related disease (taupatie), with brain accumulation and interference with many cognitive functions.

Are there similarity in some neurodegenerative pathology like Tuapatie, alpha – synucleinopathy, CJD, prions disease?

There are similarities to other progressive dementias such as Alzheimer's and Parkinson's diseases and amyotrophic lateral sclerosis? (catabolic- cumulated process?).

Is universally know that in example some plants produces alkaloids as bioproducts in their metabolism. Not having excretory apparatus as other animal organism.

Can we consider waste of immune systems some accumulation substanties' in some brain disease?

Can be consider waste materials that cannot leave from central nervous system?

Can be considered as a same global catabolic (afinalistic?) process?

Observing this literature we can say that some neurologic disease can present common aspect:

- Accumulation of some metabolic- catabolic substantia and related to the progression of disease
- And in some cases involved with immune system.
- Chronic inflammatory process could be responsible for AD progression related to related immunity Response [16].

Conclusion

Related to the result of this review Kuru disease transmission can be a interesting model to investigate brain and immune system relationships. A method useful for better clear some etiopathological aspect in some neurodegenerative brain disease. The KURU disease and other neurotropic viruses kinetics (active or passive transport) and the immunes systems involved (innate or specific adaptative) show an activation of this system that can be associated to neuro inflammatory or neurodegenerative brain disease. Adaptative immune cell lymph. T and B coming from blood or by innate systems (microglia in the brain tissue)

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Can we consider a sort of endogenous toxicology phenomena? Observing the global efficacy in this kind of pathology using a new approach, under a toxicological aspect. Could be an useful tools to be added to the actual therapeutic scheme. Clarifications.

This work has no any diagnostic or therapeutic intent, only to produce research hypothesis.

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