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Research Article

Brain and immune system: KURU disease a toxicological process?

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Abstract

Starting from observation of pathogenesis of KURU disease we try to investigate 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 molecule from gastro intestinal systems to the brain. (After cannibalistic behavior). The prions can be considered a sort of trace ant in KURU to monitoring this process and immune- brain relationship. Interesting information can be obtained useful to produce new pharmacological strategies in some other degenerative brain disease involving innate immune system activation.

Introduction

Observing the KURU disease we can have a model to better describe this process and its relationship. The aim of this review article is to show relationship between innate immune system in some brain neurodegenerative pathology useful to produce new therapeutic strategies that could be introduced. The rationale of this paper is that in KURU disease prions in CNS produce a degenerative response related also to innate immune system response.

The experimental hypothesis: the same activation of innate immune system could be the same role played in some central neurodegenerative disease. Observing that some cases of CJD are due by periferical 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. We consider KURU infectious disease an instrument to verify interconnection between immune cell out and in central nervous systems (a ERLIC magic bullet) Or an imaging treacer to follow the neuro immune process. Prions result neurotropic but other antigen are normally presented inside brain.

Other neurodegenerative brain disease present the similar pathogenetic movens INNATE immune system related whit few possibilities to be efficacy pharmacologically

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treated. Transgenic modified mouses study showed that immune system are involved in amplification and transmission of prions to central nervous system. (trought Limph. B and follicolar dendridic cell). (Other relevant fact is that in prions disease we see species barrer and is necessary a molecular similarity between prions and endogenous PRP-C.).

Relationship between some brain disease as amiloidosys and other degenerative disease like parkinson, dementia and prions disease and other must be deeply investigated especially by the innate immune system role played.

In SM (a neuro inflammatory disease) is involved adaptative immunity : Linphocite Tand 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 syntomatology after intake of Prions and (a slow process) related to the fast time in some cases involved in some neurotropic viruses we can think to a 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 (adapative 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 global efficacy of the actual pharmacological scenario.

This paper is produced 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 our opinion related to the KURU disease and other brain pathologies in order to verify the general immune status influences with some CNS local situations and its relationship in progression and evolution of this pathologies. The reported references was finded using biomedical databases. (Pub med and other resource). The keyword used was: KURU disease, prion disease pathogenesis, transmissible spongiform encephalopathy, innate immune system, neurodegenerative Brain disease and other topics related as fingolimod, SM therapy.

Results

From literature we have find

“Using fingolimod we have a reduction in linfocites 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 toxical doses, time of exposition, cumulative dosage, kinetics, dynamics, methabolism Iatrogenic ADME and other toxicological parameter can be usefully introduced also in neuro-immune toxicology to adeguately focus a physio-pathogenetic phenomena. The results related to the references citated 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 and solve the problems of its cause and transmission required the integration of knowledge from both anthropological and medical research. Anthropological studies elucidated the origin and spread of kuru, the local mortuary

practices of endocannibalism, the social effects of kuru, 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 phenomenon and way of explaining the causation of disease, and concepts of the 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 has also led to an understanding of the cultural achievements of the Palaeo-Melanesians, with deep roots in human history. Kuru presented itself to us in 1957 as a challenge to epidemiology and a clearly solvable problem, but it quickly led us to realize that its solution would contribute new vistas to clinical medicine, microbiology, immunology and neurology. It was fast in revealing that it would open new doors to virology, genetics, amyloidology and ageing.

Already in 1957, we were calling kuru galloping senescence of the juvenile and soon added to this the key to the ageing brain, amyloidosis, and the genetic control of ageing and the length of human life. It thus behoves me to trace some of the roads down which kuru research has taken us. Very early we recognized that it presented the problem of 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 transmission experiments (Gajdusek 1977). Clinical study of patients revealed quickly that it was non-inflammatory, and laboratory tests and neuropathology confirmed this. Its agent evoked no immune response. Igor Klatzo initially compared it in 1957 to Creutzfeldt-Jakob disease, which no one had seen in children and was unknown to most British and American physicians; only some 20 cases had been seen in the world.

He emphasized that the cerebral amyloid plaques seen in most cases had never before been seen in the brains of children. When J. R. M. Innes and William Hadlow showed us the similarity of the disease to scrapie (Hadlow 1959; Innes & Saunders 1962), we had the lead that led us to repeat our animal inoculations on a much wider basis and proceeded to show that it was transmissible to chimpanzees and to monkeys, rodents and other animals, with long incubation periods. Molecular casting: nucleants at nanoscale. We have repeated confirmation of resistance of a portion of infectivity of scrapie to temperature as high as 600°C (Brown et al. 2000). The enormous resistance to dry heat of a small fraction (approx. one part in 106) of infectious nucleant activity may represent a molecular cast, or fingerprint, of the nucleant. Infectious nucleant or prion activity is the result of very close three-dimensional matching. Any particle that can sufficiently mimic the molecule to be nucleated to crystallize, fibrillize or form a two-dimensional molecular sheet can trigger the process. Amyloid-enhancing factors are scrapie-like infections/amyloid nucleants.

Their discovery of amyloid-enhancing factors (Niewold et al. 1987), which were active in high dilutions and difficult to purify, reminded me of our problems with the infectious agents of scrapie or kuru. I suggested that amyloid-enhancing factors were scrapie-like agents. Amyloid deposits in man or animals are always found to be contaminated with other proteins similarly polymerized into fibrils-even co-polymerized. These are all the proteoglycans and glycosaminoglycans as well as plasma P-protein, chymotrypsin, ubiquitin, light chains of gamma globulins and other amyloidogenic proteins. The high-incidence foci of two very different diseases, Guamanian amyotrophic lateral sclerosis (lytico) and parkinsonism-dementia (bodig), occurred also in a few remote inland villages on Honshu Island in Japan and among the Auyu and Jakai people around Bade and Kepi in southern West New Guinea (Gajdusek & Salazar 1982). It has virtually disappeared from all of these places with the introduction of civilization. These three foci were restricted to remote communities in which there was such a depletion of environmental calcium as to produce a chronic severe deficiency of calcium in the diet, with the result that calcium sparing led to soft tissue deposition of calcium aluminium silicate or montmorillonite clay deposits within brain cells, along with other heavy elements as the diet provided. These lay dormant for decades until triggered later in life to cause specific neuronal damage leading to lytico or bodig. Civilization, with all its ills, has caused these two diseases in all the three locations to disappear. In pursuing the establishment of the boundary of kuru through many different cultures and linguistic groups, we discovered that kuru had no genetic boundaries [4]."

According Barry M. Bradford et al., Prion diseases or transmissible spongiform encephalopathies are a unique category of infectious protein-misfolding neurodegenerative disorders. The main focus of pathological damage in these diseases occurs within the central nervous system. Cells of the innate immune system have been proven to be critical players in the initial pathogenesis of prion disease, and may have a role in the pathological progression of disease. Prion diseases or transmissible spongiform encephalopathies (TSEs) are infectious neurodegenerative conditions characterized by vacuolar degeneration of the central nervous system (CNS) and deposition of an abnormal isoform of the host-encoded prion protein (PrP). These diseases affect a wide variety of animal species and display limited zoonotic potential. Usually displaying prolonged incubation periods, they are clinically recognized via progressive neurological deterioration resulting from synaptic and neuronal loss and associated activated glial responses to CNS damage. Identification of genetically inherited forms of these diseases implicate further the critical role of the prion protein in disease 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 diseases, with no known genetic risk factor or exposure to infection, have also been identified. The disease-associated isoform of the prion protein gains several properties including ability to transmit infection, limited protease resistance, and increased ability to fibrillize and form amyloid, these observations on both etiology and biochemical nature of the agent resulted in the prion hypothesis.

The prion hypothesis proposed that the infectious agent may be solely composed of a proteinaceous particle, i.e., 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 pathway and mechanisms from refolding of the prion protein to neurodegeneration are still unknown. The peripheral pathogenesis of these diseases have been extensively studied using animal models, as mice are naturally susceptible to both sheep scrapie and bovine spongiform encephalopathy (BSE). Following natural peripheral exposure to prion agents, infection is usually sequestered to lymphoid organs prior to invasion of the nervous system (termed neuroinvasion) (2,3). In the absence of local draining lymphoid tissue, subsequent circulation to other lymphoid organs and neuroinvasion are ultimately blocked (4,5).

Using transgenic mouse models or bone marrow chimeric mouse models various hypotheses regarding the genes and cells involved in the prion infectious pathway have been proven or refuted. Though often contradictory, results from these studies have revealed that disease-associated PrP is deposited in lymphoid follicles and replicates upon follicular dendritic cells (FDCs). As such a positive relationship has been firmly established between the immune-competence of the host and ability to support prion pathogenesisThe innate immune system is considered to be a protective system that is older in evolutionary terms than the adaptive immune system. This tissue-resident, or homeostatically maintained, population primarily assesses and responds to insults accordingly, and likely deals effectively with acute insults. A large systemic pool of both cellular (inflammatory) and proteinaceous components of the innate immune system also exists, to be mobilized rapidly in response to signals from epithelia or resident innate immune cells. Below we consider various components of the innate immune system, both cellular and proteinaceous, and their possible roles in prion pathogenesis.

The epithelial cell layers constitute the first physical barrier to infection. Prion infection via the skin is experimentally facilitated by scarification or breaking of the keratinized epidermal barrier layers to allow access to the epithelial layer beneath (25). Prion infection via the oral or nasal route appears to be naturally more efficient. Prion pathogenesis can be greatly enhanced by disruption of the epithelial layers involved in these routes (26,27). Under steady state conditions oral uptake of prion infection occurs via specialized microfold cells (M-cells) localized to the follicle-associated epithelium (FAE) of intestinal Peyer's patches The de-differentiation of M-cells prior to oral scrapie infection was sufficient to block pathogenesis completely.

Innervation of the lymphoid organs has been shown to be critical for prion neuroinvasion (20). Manipulation to shorten the distance between FDC and peripheral nerves has shown to increase the rate of neuroinvasion (37). These data provide a strong argument against hematogenous spread of prion agent directly to the CNS. 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 protein has been shown to be directly bound by C1q and Factor H (41) and this binding occurs specifically when prion protein is conformationally modified to represent the conversion to the disease-associated isoform (42). The role of complement in prion pathogenesis has recently been subject to review (43). In brief prion or TSE agents are opsonized by complement components including C1q and C3, most likely via the classical complement activation pathway, which may aid in their targeting of the agent to lymphoid follicles. Mice lacking in complement components C1qa, C2 or C3 revealed deficient peripheral prion pathogenesis under specific conditions

Cleavage of the cellular prion protein has been shown to protect against infection (49), whilst cleavage of PrPSc has been shown to modulate prion propagation in a similar fashion there is currently little evidence supporting a role for complement in prion pathogenesis within the CNS. Mice lacking C1qa, C2 or C3 revealed no deficit to prion pathogenesis following intracerebral inoculation (44) 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 (59) 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 (62). The presence of mast cells within the brain and their ability to shed expressed PrP upon activation (59) may have implications for prion pathogenesis

within the CNS. Shedding of PrPC by mast cells likely occurs via proteolytic or lipolytic cleavage mechanisms removing the glycosylphosphatidylinisotol (GPI) anchor from the protein (59,63). Activation of mast cells within the CNS may provide copious extracellular PrPC substrate for conversion to the disease-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 disease.

Mononuclear Phagocytes: Microglia, Macrophages, Monocytes, Dendritic Cells and Langerhans Cells.

It is most likely that the uptake and spread of prions to lymphoid organs occurs using MNP as a 'Trojan horse' via a similar mechanism. This reflects the wide diversity of MNP and their roles in innate immunity (1), resident cells with degradative functions; (2) resident cells with antigen presenting functions and (3) systemic circulating cells responsive to inflammatory stimuli. At present there is little evidence implicating circulating 'inflammatory monocyte' populations in prion pathogenesis due to the non-inflammatory nature of infection. 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 (44).

Degradative MNP. The expression of cellular prion protein in MNP has been associated with phagocytic ability and modulation of inflammatory responses (70-72). Evidence suggests that macrophages (generally identifiable by the markers integrin alpha M, Macrosialin or the F4/80 antigen) degrade the prion agent (73). The degradative and prion clearance abilities of macrophages appear to be down-regulated when macrophage (Mϕ) activation is stimulated by other danger signal molecules (74). Prion infection. The degradation of agent is countered by the relative replicative ability of the prion agent and its spread through the host. While much has been postulated regarding the prion protein sequence, protein folded conformation and glycosylation Antigen Presenting Cells.

APC have long been identified as being critical to prion pathogenesis. Respectively. These findings strongly link these cell types to the retention of intact prion agent and, in the case of classical DC, traffic of the agent in the pre-neuroinvasive stage of prion infection. MNP in the CNS With in the CNS the innate immune response is mediated by specialized MNP known as microglia. Microglial 2.5. Granulocytes: Neutrophils, Basophils and Eosinophils Gene expression data reveal that PrP expression is generally down-regulated during granulocyte differentiation (151) though some expression is still detectable (152). 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 [153]. 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 (121).

Natural Killer Cells and γδ T Cells

Natural killer (NK) and γδ T cells are thought to play little role in the pathogenesis of prion diseases. Both cell types require triggering or activation by danger signals, for NK cell this is usually via cytokines and for γδ T cells little is known about their activating signals. NK cells primarily respond to virally-infected cells and function to destroy these cells via expression of perforin and granzyme. Perforin-knockout mice revealed unaltered prion pathogenesis. The lack of reported NK cell response to prion pathogenesis suggests that prion agent uptake by monocytes may fail to activate NK cells. There are numerous viral mechanisms used to evade NK cell activation including regulating apoptosis, modulating cytokines and chemokines, and compromising DC functions for review see.

Little evidence has been discovered for any of these functions following prion infection apart from the possible induction of apoptotic cell death mechanisms (in neurons). Recently 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 [91]. Investigating the role of NK/T cells in prion pathogenesis is hampered by the fact that though Rag2−/− mice are deficient in NK/T cells they are unsusceptible to prion infection due to their B-cell deficiency and failure to generate mature FDC. An increase in γδ T cells in the peripheral blood mononuclear cells (PBMCs) has been reported following scrapie infection in sheep (116). 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 (167,168).

Prion Protein Expression of the cellular prion protein (PrPC) by the hematopoietic compartment is not required for prion pathogenesis (170), confirming that the innate immune system function in disease pathogenesis operates via non-PrPC dependent mechanisms. Little is known about 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 (171). Maturation of cells in response to all-trans retinoic acid is one mechanism known to down-regulate PrP expression (151) 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 models have been used to determine the effect of knockout or overexpression of a particular protein or cell type on prion pathogenesis. The classic experiment revealed that knockout of Prnp resulted in complete resistance to prion infection (140,141). A plethora 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, e.g., (130). The majority of such studies have determined that knockout of an individual component does not prevent prion pathogenesis, for some a slight alteration in pathogenesis was observed and for relatively few a block of pathogenesis was observed and then often only under certain specific conditions.

From these candidates 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, prion pathogenesis.

These 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.

Many of these genes and their regulators effect MNP differentiation, maturation and homeostasis as well as modulating MNP responses during infection. These findings indicate that prion pathogenesis is influenced by the steady-state, activation and response of the innate immune system.

In summary the innate immune system has many and varied roles in the response to prion pathogenesis, The activation (or alternative activation) of mononuclear phagocyte cells appears critical to both peripheral and central prion pathogenesis through as yet 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 in the substantia nigra

and the development of intraneuronal α-synuclein aggregates called Lewy bodies and Lewy neurites (collectively Lewy pathology) in widespread brain regions [1]. Patients with Dementia with Lewy bodies (DLB) also develop intraneuronal α-synuclein aggregates, while in Multiple System Atrophy (MSA) the majority of the α-synuclein aggregates are located in oligodendrocytes.

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 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 the rapeutic 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].

Iannacone M1 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 (SCS) of LNs, are critical for the clearance of viruses from the lymph and for initiating antiviral humoral immune responses.. These results identify SCS macrophages as crucial gatekeepers to the CNS that prevent fatal viral invasion of the nervous system on peripheral infection [8]."

Ironside Jw et al., "The human prion diseases comprise Creutzfeldt-Jakob disease, variably protease-sensitive prionopathy, Gerstmann-Sträussler-Scheinker disease, fatal familial insomnia, and kuru. Each is a uniformly fatal rare neurodegenerative disease 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 and Alzheimer disease [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 JB1 et al., "Prions are proteins that can adopt self-perpetuating conformations and are traditionally regarded as etiological agents of infectious neurodegenerative diseases in humans, such as Creutzfeldt-Jakob disease, kuru and transmissible encephalopathies. More 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. Perhaps most surprising, not all prion-like aggregates are associated with pathological changes. There are now several examples of prion-like proteins in mammals that serve positive biological functions in their aggregated state.

In this review, we discuss 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 also mention a more 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 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. Wraith1 and Lindsay B. Nicholson 1,2. "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. 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 repair. It is clearly vital that cells of the immune system patrol the CNS and protect against infection. However, in contrast to other tissues, damage caused by immune pathology in the CNS can be irreparable. The nervous and immune systems have, therefore, coevolved to permit effective immune surveillance while limiting immune pathology. Here we will consider aspects of adaptive immunity in the CNS 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 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. Two types of immunological imprinting can be distinguished—training and tolerance. These are epigenetically mediated and enhance or suppress subsequent inflammation, respectively. Whether immune memory occurs in tissue-resident macrophages in vivo and how it may affect pathology remains largely unknown. Here we demonstrate that peripherally applied inflammatory stimuli induce acute immune training and tolerance in the brain and lead to differential epigenetic reprogramming of brain-resident macrophages (microglia) that persists for at least six months. Strikingly, in a mouse model of Alzheimer's pathology, immune training exacerbates cerebral β-amyloidosis and immune tolerance alleviates it; similarly, peripheral immune stimulation modifies pathological features after stroke. Our results identify immune memory in the brain as an important modifier of neuropathology [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 (DLB) are relentlessly progressive neurodegenerative disorders that are likely to represent two ends of a disease spectrum. It is well established that both are characterized 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 show more aggressive and rapid dementia than others.

Recent studies using animal and cell models as well as human post-mortem analyses have provided important insights into these questions. Here, we review recent developments in the pathophysiology in PDD/DLB. Specifically, we examine the role of pathological proteins other than α-synuclein, consider particular morphological and physiological features that confer vulnerabilities on some neurons rather than others, and 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 immunes systems and other protein linked to AD. "We used a protein quantitative trait analysis in monocytes from 226 individuals to evaluate cross-talk between Alzheimer loci. The NME8 locus influenced PTK2B and the CD33 risk allele led to greater TREM2 expression. There was also a decreased TREM1/TREM2 ratio with a TREM1 risk allele, decreased TREM2 expression with CD33 suppression and elevated cortical TREM2 mRNA expression with amyloid pathology [16].

Immunological 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. This means that once an aggregate is formed it can escape the cell of origin, contact a connected cell, enter the cell, and induce further aggregation via templated conformational change. The prion model predicts a key role for extracellular protein aggregates in mediating progression of disease. This suggests new therapeutic approaches based on blocking 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].

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]."

According: 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 neuro inflammation that is associated with AD has been assumed to be merely a response to pathophysiological 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' neuro inflammatory diseases such as multiple sclerosis and encephalitides - the concept of neuro inflammation in AD may need refinement. [20]."

Heneka MT et al., "Classically AD has been viewed as a neurodegenerative disease of the elderly, characterized by the extracellular deposition of misfolded amyloid-β (Aβ) peptide and the intracellular formation of neurofibrillary tangles. Only recently has neuro inflammation emerged as an important component of AD pathology. Experimental, genetic and epidemiological data now 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 local micro environment and inters cellular communication situations. In some 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 much rapid evolution or too slow reduction in balancing equilibrates physiologic systems. We need to introduce more 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 memantine, 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]."

Discussion

In this review paper we have seen the role of immune system in some brain disease and transmission way (in example KURU).Some molecule like prions are

currently sended to central neurvous system by immune system cells.(form gastro-intestinal apparatus to SNC).Not only prions are neutropic, also some bacteria and viruses of meningitis in example. Interesting the delay observed in KURU to see the symptoms that show a slow process not active but passive it seems. We have also see the pharmacological activities of Fingolimod, A SYSTEMIC drug, towards central nervous systems linphocye , this effect gives information related immune system pharmacological systemic control and the effect in local place (brain). So From literature observed immune system and some brain disease are strictly interconnected. And related some neurodegenerative disease: "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].

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) NEURODEGENEREATIVE PROTEIN RELATED DISEASE (taupatie), with brain accumulation and interference with many cognitive functions. Are there similarity in some neurodegenerative pathology like Tuapatie, alfa – sincucleinopaty and CJD, prions diseae? And related to other progressive dementias such as Alzheimer's and Parkinson's diseases, amyotrophic lateral sclerosis? (catabolic- cumulated immune toxic mediated process ?) Is universally know that in example some plants produces alckaloids as bioproducts in their methabolism not having excretor apparatus as other animal organism. Can we consider waste of immune systems some accumulation substatnties' in some brain disease? (Materials that cannot leave from central nervous system: a global catabolic- afinalistic process?) Observing this literature we can say that some neurologic disease can present common aspect: Accumulation of some metabolic- catabolic toxic substantia and related to the progression of disease and involved with immune system activation.

Chronic inflammatory process could be responsible for AD progression related to related immunitary 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 as well as fingolimod spectrum of activity. A method useful for better clear some etio-pahtological aspec in some neurodegenerative brain disease involving immune system activation (adaptative or innate). The KURU disease and other neruotropic viruses kinetics (active or passive transport) show that the immunes systems is currently involved in some brain pathology (neurodegenerative or neruoflogotic). An iper activation of this system that can be associated to some brain disease. (Adaptative immune cell limph. T and B coming from blood and innate systems microglia in the brain tissue). Observing the global low efficacy of current therapy actually used in some neurodegenerative disease a new approach, under a specific immune - toxicological aspect, Could be a useful tool.

In example in Taupatie the amyloid palques [23].

Clarifications

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

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