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Review Article

Neurological Prion-Like Diseases. Is Its Cure Next?

Mariacruz López Díaz*

Instituto Nacional de Investigación y Tecnología Agraria y Alimentaria (INIA), Department of Animal Reproduction, 28040 Madrid, Spain

***Corresponding Author**: Mariacruz López Díaz, Instituto Nacional de Investigación y Tecnología Agraria y Alimentaria (INIA), Department of Animal Reproduction, 28040 Madrid, Spain. e-mail: lopez.maria@inia.es. Phone 34-913473757

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Abstract

Multiple System Atrophy (MSA) is the second human prion disease described by Prusiner fifty years after the discovery of the CJD´s transmission through prions. Meanwhile, the list of prion-like diseases is alarmingly enlarging as do concerns about a prion involvement in the etiology of numerous human diseases. If this were true, strategies to fight these diseases should be modified accordingly. We herein review some therapies which could reduce the circulating burden of infectious proteins. Detoxifying pathogenic proteins from the bloodstream by means of a "blood replacement" is discussed first. Secondly, the role of the microbiota, particularly that in the gut, which has been shown to play an indisputable role on the development of Parkinson's disease, is reviewed. Practices such as "fecal transplantation" for the restoration of the innate gut barrier are put forward as a tool to reset a healthy interconnection on the digestive-cerebral axis. In our opinion, there is no need to wait for new findings reinforcing the prion hypothesis; on the contrary, it is important to draw the attention of the scientific community to step forward novel therapeutic approaches assuming the existence of prion diseases instead of prion-like diseases.

Keywords: *Prion Diseases; Multiple System Atrophy (MSA); Blood replacement; Fecal transplantation*

In recent decades neurodegenerative diseases are insidiously affecting the population in developed countries. Although they are closely associated with an aging population, the increase in sporadic cases in younger and younger individuals has sparked health warnings and strengthened scientific interest. The results from meta-analysis, with high statistical power, support the implication of environmental contaminants and infectious agents as the primary risk factors [1-3]. These are diseases that, because of their symptoms and chronic nature, have a high emotional, social and economic cost in developed societies. The virtual absence of curative treatments is a fact, only palliative treatments are used depending on the disease and sometimes with very little success; they improve patients' quality of life. There are numerous diseases such as Creutzfeldt-Jacob's (CJD), Parkinson's (PD), Alzheimer's (AD) and ALS's, which present neurological symptoms. Although they have different nervous manifestations, in most of them the neurons degenerate irreversibly leading to progressive prostration of patients who often die with dementia. Amyotrophic Lateral Sclerosis (ALS), a devastating disease with an agonizing period of 2 and 5 years [1], would be the maximum exponent.

A growing evidence has made that a great part of the scientific community considers many of them as "prion-like" illnesses or similar to prion diseases. Prusiner [4] showed that sporadic cases of Creutzfeldt-Jacob were produced by a protein designed Pr^{Psc}. This protein had identical primary structure to PrP, an endogenous and nonpathogenic protein, but with different spatial structure that conferred a resistance to enzymatic digestion, which he called "prion", Going further, he showed that prions were able to multiply by contact "cell to cell transmission" and spread in the nervous system, which made he earned the highest scientific recognition with the awarding of the Nobel Prize in Physiology or Medicine in 1997.

There are up to 40 diseases that are included as "prion-like", including AD and PD with the highest incidence [5]. In the patients a common finding is the formation of protein aggregates in the nervous system, with an abnormal β -amyloid conformation; in the case of

Alzheimer's disease the protein is amyloid–β (A β) and in Parkinson's disease is the α -synuclein. The aggregated protein would injury different areas of the nervous system and cell types, which would lead to various diseases [1,5,6].

Regarding the causative agents, they act with very long prodromal phases, even 50 years of silent incubation period has been reported [7]. It has been proposed that the causative agent will act by altering the natural mucous barriers of the innate immune system; digestive, respiratory and skin. The abnormal proteins once reached a concentration threshold in the organism would spread exponentially and would progress retrogradely through the nervous system causing extensive injuries. One of the most enlightening experiments has been conducted by Pan-Montojo., *et al* [8]. They reproduced in mice the symptoms of PD after administration of rotenone and he also stopped the disease after vagotomy. In this work it follows that the action of a toxic would be sufficient cause to trigger neurodegenerative pathology and also shows that the propagation can occur through the nervous system that connects the axis gut-nervous. Supporting a vagal progression of the pathogenic proteins, patients who had have vagotomy had lower risk to suffer PD [9]. Additionally, in recent studies it has been found that the innate immune gut barrier is injured, and in fact the intestinal microbial alteration has already been demonstrated in murine models for both diseases, PD as well as ALS [10,11]. Going further, Sampson., *et al*. [12] have reproduced parkinsonian symptoms in mice transplanted with cecal contents from human patients. In this extraordinary work, they propose that maybe the etiology of α -synucleopathies and other neurodegenerative diseases is at the gut level.

The prion-like etiopathogenesis hypothesis has prompted the interest on several "classical" therapies never used in Alzheimer's patients before. Preliminary results claim a stop in the disease progression and even a partial recovery of lost memory after plasmapheresis in combination with specific antibody treatment [13]. For this end, blood albumin carrying pathogenic Aβ is renewed by plasmapheresis with clean/new albumin. The free pathogenic forms $A\beta_{40}$ and $A\beta_{42}$ bind to exogenous albumin displacing the equilibrium reaction "$free\ A\beta_{pathogenic} + albumine \leftrightarrow albumine\text{-}A\beta_{pathogenic}$" to the right. The result is that there is a reduction of the free pathogenic forms ($A\beta_{pathogenic}$), in a compartmentalized and successive manner, first clearance from blood and then from the cerebrospinal fluid.

In any case, and regardless of what the cause is, there are 35.6 million people affected worldwide with dementia (Dementia: a public health priority, WHO 2015 source) that require immediate treatment and above all, a common strategy in prevention of the progression of whatever the neurological disease may be.

Therefore, based on the conceptual change on the pathogenesis of neurological diseases prion-like, we propose a global strategy that we consider necessary to detoxify the body from abnormal proteins and to restore the innate immune system barriers. We believe that experimental curative treatments have to take a new direction in order to pursue the following objectives:

Detoxication of pathogenic proteins from bloodstream: Many scientists have claimed as a therapeutic approach that it would be important to download the organism from the toxic prion/s or protein/s. To this end, plasma or blood exchange should be indicated [13].

Plasma exchange is been used in renal and autoimmune diseases in order to decrease toxic metabolites and autoimmune or inflammatory mediators. Therefore, these routine procedures well known in the clinical praxis could be practicable immediately. Regarding to neurodegenerative diseases, it is not new the use of plasma exchange with results very variable from little success in ALS to moderated good results in peripheral neuropathies associated with plasma cell dyscrasia [14]. In general, the plasma exchanges (complete or partial) are well tolerated by patients and in some instances can be practiced for life. We must emphasize that in spite of an explicit recommendation made in 1996 by the American Academy of Neurology; still very few controlled clinical trials have been done in neurodegenerative diseases [15].

The autoimmune origin of many of these diseases has been explored over the years with great uncertainty about the results of the diagnosis, for instance in the case of ALS no supporting evidences have been obtained. The immunoglobulins from the acquired immune system cannot distingue PrP from PrP^{Sc}. Perhaps, the difficulty to confirm with reliable diagnosis arises from the fact that many aspects of the mechanisms of innate immune system are still unknown. We must bear in mind that PrP and α -synuclein are endogenous pro-

teins with innate immunological roles. In fact, Leis., *et al*. [16] have suggested a profound immunosuppression followed by an autologous hematopoietic stem cell transplantation in ALS, as it has been done with success in other autoimmune diseases reluctant to standard treatments [17]. In multiple sclerosis (MS) other possible combinations are being testing, for instance plasmapheresis with adjunctive therapies as specific antibody (Natalizumab) and transplantation of stem cell [18].

Many antibodies around the world are being proven for the treatment of AD like Solanezumab (Lilly), Bapinezumab (Pfizer, Johnson and Johnson), Gantenerumab (Roche) and Aducanumad (Biogen). Unfortunately, most of them have failed in the pre-clinical phase III. In our opinion, if we want to get rid of a toxic protein the sensitivity of the antibody has to be one order of magnitude higher than the concentration at which the endogenous proteins reach the equilibrium, that is, at least in the order of pg/ml [19-21]. There are very encouraging results from the use of antibodies with good sensitivity and specificity against $A\beta_{40}$ (ABvac40) and $A\beta_{42}$ (ABvac42), they have passed the pre-clinical phases I and II, and get into the phase III in 2017 and 2019, respectively (Araclon Biotech, Grifols).

The possibility of pathological proteins being carried by blood cells has been proven in AD and PD and it cannot be overruled in other prion-like diseases. If this is the case, without any doubt, not only plasma but also blood cells should be replaced. In fact, nowadays the scientific studies involved in the mechanism of age-related diseases are going back to old experiments of "parabiosis" in which blood exchange between young and old animals induced rejuvenation of the latter by unknown mechanisms. The most prominent research centers and institutions in the world have renewed their interest on this phenomenon. Some of the works have revealed that blood exchange would rescue adult stem cells from different organs among other beneficial effects [22].

Ideally, this phase should be endorsed with kinetic studies (competitive studies, Kds) of abnormal proteins for specific antibodies (if available). Selected antibodies with high sensitivity have a double utility; they can be used to study the clearance of pathogenic proteins from the blood stream and later on, as passive immunizing agents. Furthermore, in those diseases from which no specific antibodies are available, blood replacement could also be done as preventive "blind" treatment.

Restoration of the endogenous microbiota of innate immunological barriers by probiotics ad hoc and/or antibiotics.

Endogenous intestinal microflora of patients with neurodegenerative diseases is altered. Eighty percentage of patients with Parkinson have constipation, however there are very few studies where the microbial flora had been characterized. Only in recent studies a decrease in *Prevotellaceaes* (77.6%) has been observed compared to a predominance of *Enterobacteriaceas* [23-25]. It has also been shown that bactericidal proteins that recognize gram-positive peptidoglycans are altered in Parkinson's patients (increased PGLYRP 4) [26].

Lack of treatments with emphasis on bacterial involvement may be due to the complexity of the mechanisms that establish the connection between the brain and innate immune barriers, through the so-called digestive-cerebral axis. This axis is being deeply studied, especially associated with the most frequent neurodegenerative diseases and others such as autism, depression and anxiety with great advances [27,28]. In the intestinal epithelium has been described the disappearance of cellular desmosomes, which produces intestinal leaking or intestinal drip leakage in murine models, in both PD and ALS. There are already some papers claiming to have solved leaking in Parkinson's model mice by a mixture of Lactobacillus helveticus R0052 and *Bifidobacterium Longum* R0175 [29]. In other study made with old rats, the administration of a probiotic mixture (VSL # 3) of 8 Gram positive bacteria, as well as the administration of antibiotics (neomycin, bacitracin and piramicin) improve many indicators of nervous function such as exploratory behavior, neuronal plasticity and increased brain-derived neurotrophic factor in the hippocampus (BDNF Brain-derived neurotrophic factor) [30].

Although these results are very revealing, we cannot ignore that many previous studies have pointed to microbial agents as causative agents. Therefore, it is essential to advance in the knowledge of the patients´ microbiota. One reason why clinical research has neglected to investigate which pathogens could be implicated might arise from the fact that microbiological diagnosis is extremely difficult, since the infectious agent could have acted many years before symptoms appear. In this sense, for instance PD has been associated with infections

of *Nocardia asteroides, Helicobacter pylori* and *Mycobacterium paratuberculosis*, but serological diagnosis lacks specificity and give poor results [31-34].

Therefore, we must emphasize again that it is determinant to use antibodies with sufficient specificity and sensitivity to identify both the infectious agent and pathogenic protein. Recently, Nature echoed of this serious problem in biomedical research, the authors stressed that from 53 emblematic preclinical works; only 6 could be replicated when other antibodies were used [35].

In the event that the triggering cause was an infectious agent, this phase is extremely important, because if the infectious agent is still present, it would have to be identified and treated.

Finally, based on the good results obtained in patients with intestinal infections produced by *Clostridium difficile*, we strongly recommend "feces transplantation" approaches [36]. Obviously, the donors have to be healthy young individuals, with the same blood group, sex, etc., because the compatibility of the immune system must be seen as a whole. If the etiology of numerous neurological disorders is in the gut, as Sampson., et al. have suggested [12], the fecal transplant should be applied as soon as possible. Additionally, last Prusiner's results have demonstrated that Multiple System Atrophy (MSA) is the second "prion disease" after CJD. The MSA is an α– asynucleopathy frequently misdiagnosed as PD and only confirmed postmortem. Therefore, without any doubt our proposed strategy is especially important for MSA and misdiagnosed PD patients.

Once the body has been detoxified and sealed the entrance gates, depending on the recovery obtained with the above treatments and disease stage, it could proceed with different treatments: vaccination, transplantation of neural progenitor cells NPC, and stimulation of the affected area in Parkinson patients by ultrasonic plate, etc.

Regenerative therapy: At the moment, the best clinical results are obtained with embryonic and human fetal cells. Nowadays, there are available different cell lines for research purposes (line H9 and RC17), remaining only ethical objections for their use. We could say that is only indicated in certain circumstances as in young patients or in lesions quite extensive.

Although pluripotent cell therapy is making strides, three significant drawbacks still remain a concern: a tendency to form tumors, a lack of functional maturation of the grafted cells and immune rejection. The latter might be a minor problem in the CNS because of the relative "isolation" from the immune system provided by the blood-brain barrier [37,38].

In patients with PD, it should be stressed that the replacement of nervous tissue using human neural stem cells (NSCs) derived from fetuses, have been more than encouraging. Implantation of fetal ventral cells from Mesencephalon, in the Putamen of Parkinson´s patients, resulted in a complete recovery of the innervations in this structure. Beneficial effects after the transplantation included; motor symptoms recovery and even withdrawal of the treatment with LDOPA [39]. In fact, the deaths of some patients had nothing to do with the disease [40]. After twenty four years post-implantation functional dopaminergic neurons still remained in the Putamen. Thanks to a recent published and splendid work made by Kirkeby., *et al*. [41], we could say, without being extraordinary optimistic, that transplantation of human embryonic stem cells (hESC) is ready for clinical use in patients with PD. First the authors decipher specific markers for functional DOPArgic neurons in relationship with the results obtained after transplantation. Secondly, taking into account those markers, they stablish a robust good manufacturing practice (GMP) for differentiation of hESC into DOPAergic neurons.

Remarkable Conclusions

The controversy has accompanied the "prion hypothesis" since Prusiner discovered the prion entity and unfortunately we must say that it is still alive. The titanic efforts of diverse groups of scientists around the world have tried to explain all aspects of prion and prion-like diseases in a unified hypothesis. As a result of this, other explanations have been enunciated such as the "Amyloid hypothesis" [42], "Conformational selection model" [7], "Dynamic equilibrium oligomers" [43], "Proteome equilibrium" [44,45] and "prion hypothesis" [12,46]. Perhaps, these discrepancies arise from the difficulty to differentiate between endogenous from infectious proteins. Also, from

the fact that many transgenic proteins used in the experiments have been developed in systems lacking the proper glycosylation machinery (*E. coli*), and therefore with inappropriate tertiary/quaternary structure. In our opinion, unfortunately basic research still has two bottlenecks ahead: to decipher the structure of pathogenic prions and to develop antibodies with proper specificity and sensitivity.

Meanwhile, regardless of the pathogenesis of the different neurodegenerative diseases, from a clinical point of view it is important to step forward and find out useful therapies. Herein we propose a conventional therapy very well-known with minimal side effects, "blood replacement". Also we propose an unorthodox treatment, "fecal transplantation" with extraordinary good results in intestinal infections and unexplored applications in other illnesses [36]. As far as we know, there is an absence of clinical studies in which blood replacement and fecal transplantation from healthy young donors to adult patients had been undertaken. In any case, both therapies should be done previously if we want to obtain success with other sophisticated treatments (f. i. deep brain stimulation, stem cells transplant and antibody treatment).

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