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Review Article

The Role of Peripheral Cells in Neurocognitive Disorders Detection

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Abstract

Neurocognitive Disorders (NCDs) epidemiological data are distinctly alarming, testimony as they are to a marked increase in NCDs incidence, which will continue to be observed. In order to enable patients to benefit from possible therapies, it is vital to have the capacity for early disorders interception and for severity increase prediction. Accurate studies in this regard spotlight strategies' highly invasive nature and spiraling costs, which factors hinder their widespread employment. Consequently, there is increasing interest, in this connection, in easily accessible biological matrices. The aim of the present review is to analyze the possible role of these matrices' cellular, as opposed to fluid, component in clinical practice. We will therefore explore, in particular, the role played by various peripheral cells in screening, diagnosis, and follow-up. Reference will be made to a number of significant studies which highlight the importance of these cells as borne out by recent scientific literature. Peripheral Blood Mononuclear Cells (PBMNCs) and platelets, together with oral mucosa cells were at the centre of our focus.

Keywords: Neurocognitive disorders; Alzheimer's disease; Dementia; Peripheral cells; Peripheral blood mononuclear cells

Introduction

Neurocognitive Disorders (NCDs) represent one of the major public health issues, and, due the population growth, are destined to become even more prevalent [1]. The Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) [2] offers a comprehensive overview of these diseases, classifying them according to severity and etiology. Three disorders are identified: delirium, Major Cognitive Disorder (MaCD) and Mild Cognitive Disorder (MiCD), although it should be noted that the names "Mild Cognitive Impairment" and "Dementia" continue to be used in the literature and in clinical practice. As far as the disorders' causes are concerned, Alzheimer's disease (AD) is widely known to represent the etiology with the highest frequency. This is reflected in the vigorous level of scientific activity regarding Alzheimer's epidemiology, pathophysiology, clinical features, diagnosis, and therapy. But other causes should not be ignored, both degenerative-idiopathic ones and secondary causes, such as Human Immunodeficiency Virus (HIV) infection-related forms.

In order to prevent advanced disease progression, it is vitally important to develop and utilize screening methods to enable NCD investigation at an early stage [3] and, where appropriate, to follow up treatment program results over time. There is still no internationally recognized "gold standard" tool but for the time being physicians use various neuropsychological, neuroimaging and laboratory tests.

Pursuing this line of research, the present review's intention is to focus upon studies of the role of peripheral cells in NCDs pathophysiology and patients monitoring.

Pathophysiology Features

The physiology of the Central Nervous System (CNS) is very complex, and so is the pathology. In principle, the common process in neurodegenerative diseases is the accumulation of aggregate and misfolded proteins.

Various evidences reveal that the generation of Amyloid β (Aβ) is the key moment in AD development [4]. This protein derives from a gene, on the chromosome 21, called Amyloid Precursor Protein (APP): its product is processed by enzymes called secretases; in particular β-and γ-secretases are responsible for the anomalous processing of the peptide, giving Aβ40 and Aβ42 monomers, which will tend to aggregation and subsequent precipitation in the brain tissue. Here, Aβ activates microglia, which are CNS resident monocytes-derived-cells, and they can determine loss of synapse and neurotoxicity [5].

In addition to Aβ, which is a plainly manifest example, there are other molecules which, using similar mechanisms, contribute to the pathogenesis of various neurodegenerative diseases-not just those linked to NCDs. Among them should be mentioned:

1. Tau, in AD, Parkinson's Disease (PD), Frontotemporal Dementia (FTD), Progressive Supranuclear Paralysis (PSP) and Cortico-Basal Degeneration (CBD)
2. alpha-Synuclein, in PD and Multiple System Atrophy (MSA)
3. TAR DNA-binding Protein 43 (TDP-43), in FTD and Amyotrophic Lateral Sclerosis (ALS)
4. Prion Protein, in Transmissible Spongiform Encephalopathies (TSE)
5. Polyglutamine-Containing-Proteins, in Huntington's Disease (HD), some of the Spino- Cerebellar Ataxias (SCAs) and Bulbo-Spinal Muscular Atrophy (BSMA).

The microglia mentioned here also figure significantly in pathophysiology of secondary NCDs, such as HIV-1-Associated

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Neurocognitive Disease (HAND) [6]. These cells are not only considered to be long-life reservoirs of the virus, but they are directly involved in damage development. Though of much relevance, their activity is only one of several processes involved: HAND is known to be the product of DNA damage, chronic inflammation, accumulation of misfolded proteins and some other mechanisms, like the induction of cyclooxygenase 2 (COX-2) in brain microvascular endothelial cells, especially when interacting with HIV-infected monocytes [7].

The Ideal Marker

Ideal markers have several essential features:

1. Obtainable with non-invasive techniques
2. Analyzable simply, quickly, following standardized methodology
3. Involving neither high costs nor the need for specialized operators
4. Marker concentration correlates with brain damage extent
5. MaCD, MiCD and non-impaired have different marker concentration/expression

Fluid Matrices

The main biomarkers in NCDs diagnosis are to be identified in the cerebrospinal fluid (CSF). In this biological matrix Aβ40, Aβ42 and total and phosphorylated Tau are commonly dosed for AD patients' stratification. But even the analysis of molecules accessible using a relatively invasive method, unfortunately, might not achieve early disease detection [3].

Other matrices (tears, saliva, urine) are mentioned in the literature in this regard. Though more easily accessed, analysis has been reported as subject to issues over low sample volume and regarding sample standardization [8].

Blood matrix analysis appears to be more advantageous. Several studies reported the importance of blood Aβ: in 2006 van Oijen et al. [9] indicated that high plasmatic Aβ40 levels together with low Aβ42 levels indicate risk of AD. In 2013 Zou et al. [10] underlined the role of Aβ43 in AD pathophysiology, suggesting that high plasmatic Aβ43 and Aβ43/Aβ42 ratio could be used as AD biomarkers.

In 2019, Pase et al. [11] concluded that plasmatic total-Tau (t-Tau) levels could be a useful marker to predict AD. In 2020 Karikari et al. [12] studied the concentration of plasmatic phosphorylated- Tau at Threonine 181 (p-Tau 181), comparing them with CSF and Positron Emission Tomography (PET) markers: they concluded that blood p-Tau 181 can predict AD and differentiate it from other disorders; incidentally, in one of the studied cohorts, it appeared unable to discriminate AD from MiCD. In 2019 Jia et al. [13], in a multicentric study, affirmed that blood levels of abovementioned exosomal biomarkers (Aβ42, t-Tau and p-Tau 181) are related to those in CSF – and they concluded that they have the same capacity for discrimination between AD, MiCD and controls.

As regards other markers, clusterin is associated with AD risk, and it was presumed to act as a diagnostic marker; its diagnostic usefulness, however, is currently under debate. Its prognostic value for MiCD to MaCD evolution, meanwhile, was highlighted by Jongbloed et al. in 2015 [14].

The Role of Lipids

Our group studied the role of cholesterol homeostasis in favouring neurodegeneration [15]: its modification creates a favorable environment in this sense, but it could also be a target for new therapies [15,16], as agreed by other authors (Zuroff et al. [17]).

In 2014 we made another review on the theme [18], underlining that alteration of this brain homeostasis is well reflected in cholesterol esters accumulation in Peripheral Blood Mononuclear Cells (PBMNCs). As will be discussed in the next section, this and other evidence supports the use of these cells as diagnostic and therapeutic NCDs markers. But how can lipids bring about neuronal damage?

Cholesterol is a ubiquitous molecule, due, for instance, to its important roles for example in biological membrane density modulation and electrical isolation, or its role in preventing oxidative damage. As is known, lipoproteins are unable to breach the blood-brain barrier, thus forcing the CNS to synthesize its own cholesterol, and, on the other hand, preventing it from eliminating excess cholesterol through the blood, which would be the usual way. Cholesterol synthetized by astrocytes is transported by ATP-binding cassette transporter 1 (ABCA-1) and ATP-binding cassette sub-family G 1 (ABCG-1) in CSF on ApoE molecules: the newly formed lipoproteins are internalized by neurons, due to their relatively poor synthesis capacity, and metabolized in 24S-OH-cholesterol, a polar molecule able to reach the liver [19,20].

CNS cholesterol accumulation appears to be related to AD [21]. Grimm et al. [22] affirmed that Aβ production could be related to cholesterol and, the other way around, that Aβ40 reduces cholesterol synthesis, inhibiting 3-OH-3-methylglutaryl-coenzymeA (HMG-CoAR), and that Aβ42 increases sphingolipid metabolism, activating sphingomyelinases.

Besides AD other diseases also appear to be related to these pathways, and, perhaps surprisingly, among them there are Autism Spectrum Disorders [23], whose epidemiological distribution diametrically opposed to that of the NCDs described above. Light has yet to be shed on cholesterol's role in the pathogenesis of these disorders [24].

Peripheral Cells

Peripheral blood mononuclear cells

Lymphocytes and monocytes make up the PBMNCs, representing 20-25% and 3-8% of blood leukocytes, respectively. The role microglia, which are monocyte-derived cells residing in the CNS, has already been explained in this review, but their peripheral-blood role in the NCDs context remains to be discussed. In this section some of the PBMNCs cellular physiology changes will be dealt with, followed by current prospects for the cells' role as NCDs markers.

Gu et al. [25], in 2016, studied the innate phagocytic function in various monocytes-"non classic" ($CD14^{dim}/CD16^{+}$), intermediate ($CD14^{+}/CD16^{+}$) and "classic" ($CD14^{+}/CD16^{-}$)-at basal levels and pre-treating the cells with both a phagocytosis stimulator and an inhibitor: basal phagocytosis did not present relevant differences between AD patients and controls, while it increased in patients with high Aβ burden (assessed by PET). On the other hand, pre-treatment revealed a differential performance in different clinical statuses as well.

In a 2019 study carried out on a population in India, Jairani et al. [26] demonstrated the role of oxidative stress in decreasing Aβ macrophage phagocytosis, which was correlated with the presence of ApoEε4 allele-known to be a high genetic risk factor for AD and other neurological diseases [27].

Another interesting contribution on the role of phagocytosis is given by Prokop et al. [28], who in 2015 presented an animal model (mice) to assess the capacity of peripheral macrophages to reduce Aβ plaques. An experiment involving in microglia-ablated mice gave results showing that, although the microglial cells were rapidly repopulated by peripheral cells, they were unable to significantly effect Aβ burden reduction.

To further support the assumption of phagocytosis' occupying a central position in AD pathophysiology, many authors emphasized PBMNCs' role in Aβ clearance, as Schulz et al. [29] did in 2007, writing that, in vitro, Aβ is capable of enhancing cholesterol accumulation in monocytes/macrophages.

In 2020, Chen et al. [30] showed that Aβ monocyte uptake tends to decrease with ageing and AD – but not PD. It was also shown that peripheral expression of Toll-like Receptor 2 decreases in AD patient monocytes.

The role of PBMNCs is not limited, as reported, to AD alone. It is clearly present also clear in HIV-1 infection. As Ryan et al. [31] demonstrated, the TNF-related apoptosis-inducing-ligand, known as TRAIL, is present in greater quantities in HIV-1-infected PBMNC membranes, and these amounts are related to neuronal expression of caspase-3, which plays a key role in inducing neuronal apoptosis.

Another interesting correlation with neuronal damage is shown by Veenstra et al. [32], in 2019: intermediate monocytes, in HAND patients' blood, express C-C chemokine receptor 2 (CCR-2) more than HIV-infected-patients without cognitive symptoms, and also more than patients with other NCDs. Moreover, the expression of CCR-2 is also related to HIV-DNA copies in the cells.

In HIV-infections, a great deal of attention is often paid to viral RNA, whereas, in HAND, it appears that DNA, the product of reverse transcription, plays a leading role [33,34]. It actually seems that, although HIV RNA levels might be undetectable, a patient may have HAND by reason of a high HIV DNA copies in his peripheral monocytes. This question should also be considered from the therapeutic point of view, because even if we manage to remove the viral load, HIV can continue to harm the CNS through these reservoirs.

One of the reasons for the role of PBMNCs in HAND was given in 2008 by Ancuta et al. [35]. The study begins with signs of HIV-infection - blood lipopolysaccharide levels as a sign of microbial translocation-and chance of immunodeficiency. This molecule levels are higher in HAND patients than in controls, regardless of viral load or $CD4^+$ T-lymphocytes and it is not surprising, given what has been described earlier. This study assumes that LPS will, by activating monocytes, be able to promote their migration to the CNS, where they will be active. The activation of them is confirmed by the up regulation of markers like HLA-DR and CD69 in lymphocytes.

CD69 expression was also studied in 2001 by Stieler et al. [36], this time not in HAND, but in AD. It was noted that molecule overexpression in T- and B-lymphocytes was higher in AD patients than in controls.

In past years, our research group has produced evidence of neutral lipid accumulation in PBMNCs as marker of various subtypes of NCD [37-40].

We used freshly isolated (ex vivo) PBMNCs, analyzing neutral lipids with the Oil Red O (ORO) staining method [41]. Cholesterol esters appeared as red spots, while nuclei were blue, due to the use of hematoxylin. The intensity of the red color, proportional to cytoplasmatic lipid accumulation, was measured on a semi-quantitative scale from 0 - "no staining" - to 4 - "intense diffuse staining".

Our first studies [37,38] reported significantly higher neutral lipid levels in PBMNCs from AD patients compared to controls, demonstrating that PBMNC cholesterol metabolism assessment is not only useful for diagnosing AD, but also for identifying subjects that may have an increased risk of developing the disease. We were also able to demonstrate that neutral lipid level and the lipids' cluster-forming tendency are linked to the disease from an early stage.

In 2015 we studied another cohort of subjects, one made up of patients who had been infected with HIV. Results using the same technique were quite similar [40]. We found ORO scores and cluster-forming tendency to be closely related to lower cognitive performances, as assessed with Repeatable Battery for the Assessment of the Neuropsychological Status (RBANS) [42].

Going on to then, in 2017, study Mixed Dementia (MD) and Vascular Dementia (VD) [39], we found ORO score was not significantly different between AD, MD and VD. But in all three cases scores were significantly higher than in MiCD, with this last being significantly higher than controls.

In spite of the technique's demonstrable simplicity and usefulness, interest, as revealed in literature, unfortunately does not appear very great. However, as will be reported, several authors have focused their research-owing to the ease of simple taking-on abnormal lipid accumulation and/or of peripheral cells-monocytes, lymphocytes, platelets, and, amongst others, mucosal cells, as cognitive deficit markers.

A different but interesting contribute on PBMNC use in clinical practice was made in 2015 by Di Francesco et al. [43]. Epigenetics was the subject of their research - in particular, DNA methylation. An increase in methylation was observed in late-onset AD patients, compared to controls. It was shown to be related to worse cognitive performances and higher DNA- methyltransferase 1 expression. Here, the methylation of CCGG restriction sites was ascertained by Luminescent Methylation Analysis (LUMA).

Oral epithelial cells

Speaking of easy obtainable cells, in 2002 an experiment on oral epithelial cells was carried out by Hattori et al. [44]. Finding higher intracellular Tau levels in AD than in controls, they concluded that Tau could be helpful in AD diagnosis. Incidentally, no correlation was established between Tau levels and NCD severity.

By 2007, Thomas et al. [45-47] had made three studies on oral cells. Compared to controls, lower basal cells, condensed chromatin cells and karyorrhectic cells, increased 17 and 21 trisomy, and shorter telomeres were found in AD.

By 2014 François et al. [48,49] had performed experiments on cytological alteration in oral mucosa cells too. Starting out, the authors noticed that neutral lipid content was significantly lower in their

MiCD group than in controls. They also studied DNA content and abnormal nuclear shape: DNA content and DNA content/ORO ratio were higher in MiCD (2.8-fold) and MaCD (2.3- fold) than in controls, as was the degree of abnormal nuclear shape. Later on some results were contradictory: in 2016 they found similar DNA and neutral lipid contents, as well as similar aneuploidy and Tau content, in all groups, while finding higher intracellular Aβ levels in AD than in controls.

The same cells were studied in 2016 by Garcia et al. [50] using super-resolution microscopy. An AD interchromatin compartment increase, as compared to controls, was noted.

Platelets

Finally, we consider it important to mention the possible utility as a biomarker of another corpuscular blood-matrix component: platelets. In 2018 Akingbade et al. [51] published a review describing the state of the art regarding the role of platelet proteins and mean platelet volume, displaying cautious optimism on the matter, but also speaking of the need of further consideration with a view to ascertaining whether or not platelets could be effectively clinically employed.

Platelets were also studied one year later by van der Willik et al. [52], who concluded that a higher number of platelets, together with a higher granulocyte/lymphocyte ratio and platelet/lymphocyte ratio, is associated with increased risk of dementia.

Conclusion

It would seem the more sensitive cognitive deficit markers are, the more invasive they are. Several studies have been done on plasmatic markers, which appear to play a growing role in NCD diagnosis, while a smaller number of articles focused on the cells' importance.

With this backdrop, the present review aims to spotlight scientific progress made on the subject, focusing attention on the role of easily accessible cells.

Various authors have focused on oral cells. Contradictory results, moreover conducted on small samples, leads us to believe that, in order to fully and accurately assess the role of these cells in NCDs, samples should be enlarged, and AD diagnosis backed up both clinically and with non- clinical support. In this way, interesting results might follow concerning other NCDs as well.

Regarding platelets, other authors have already highlighted the need for further studies, in order to clarify their role in pathophysiology and diagnostics.

We, for our part, were able to produce evidence of how a cheap, easy and non-invasive technique, requiring only 500µl of blood, can be used to detect AD and other NCDs, readily distinguishing MiCD, MaCD and healthy control subjects. However, though of much interest and potential utility in clinical practice, study results were of limited significance owing to the research having taken place in our centre only. It would be useful-and necessary for validation purposes to examine a larger number of subjects in a multicentric study.

Consequently, we are of the opinion further lipid homeostasis and cellular pathology studies, regarding various NCDs etiologies, could help not only in diagnosis and cognitive impairment level discrimination, but also in developing targeted and effective therapies for these widespread disorders.

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