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IP Indian Journal of Neurosciences

Journal homepage: www.ipinnovative.com

Review Article

CSF biomarkers as potential screen of HIV-1 subtype C in post-HAART era

Mamata Mishra[1],*, Prasanna Kumar Dixit[2]

[1]*National Burns Centre, Airoli, Navi Mumbai, Maharashtra, India*
[2]*PG Dept. of Zoology, Berhampur University, Ganjam, Odisha, India*

ARTICLE INFO

Article history:
Received 25-04-2020
Accepted 28-05-2020
Available online 20-07-2020

Keywords:
Biomarkers
Cerebrospinal fluid (CSF)
Central nervous system (CNS)
HIV associated dementia (HAD)

ABSTRACT

Since past 10 years, biomarkers for neurodegenerative diseases are becoming advantageous and have great impact on clinical trial. Neuropsychopathological changes in the central nervous system (CNS) and progressive neuronal dysfunction leading to cognitive and behavioural changes, is a common phenomenon in almost all the neuro-degenerative disorders. The deadly virus HIV-1 causes HIV associated dementia. Although disease severity has been reduced by the successful introduction of combined antiretroviral therapy (CART), complete eradication of HIV-1 has not been possible, especially from the central nervous system (CNS). Despite this success in post highly active anti-retroviral therapy (HAART) era, milder forms of neurological diseases remain common in HIV infection. Cerebrospinal fluid (CSF) is the connective source of information for HIV infection and disease severity between systemic and CNS infection. CSF biomarkers represent as valuable objective approach to understand the evolving patho-biology of HIV associated neurocognitive disorders.

Clinical implications : 1. Biomarkers in cerebrospinal fluid (CSF) act as an indicator in the neurological disease progression in CNS and correlate with disease status, 2. Novel CSF biomarkers help in distinguishing drug naïve HIV positive subjects with various type of opportunistic infections (OIs) such as toxoplasmosis, cryptococcus meningitis and tuberculosis meningitis, 3. It compares the minimal neurological scores (less diseases condition) with that of HIV uninfected individuals.

1. Introduction

Identification of reliable molecular markers is a critical gap in the field of Neuro-AIDS, which disclose the mechanism of neuropathogenesis. Over 20 years of surveillance HAART failed to provide the complete protection and eradication of HIV-1 from its reservoir central nervous system (CNS) and also seems to be an impossible tax. In post HAART-era immune reconstitution is one of the additional problems where HIV making the patient more complicated for diagnosis and treatment. The striking question next to this is how much we understand the effect of CART. Fortunately the more severe form of HIV-1 associated dementia (HAD) has been disappeared and antiretroviral therapy can arrest the progress of neurological dysfunction. Despite this success in post HAART era, milder forms of neurological diseases remain common in HIV infection.Price[1] HIV associated dementia turned out to be subtype dependent and neuronal injury depends upon the subtype specific HIV proteins.[2] The connective source of infection is the cerebrospinal fluid (CSF) and it represents the status of HIV infection and disease severity between systemic and central nervous system infection. CSF biomarkers represent as valuable objective approach to understand the evolving pathophysiology of HIV associated neuro-cognitive disorder.[3] neuroneuro-cognitive reportsfrom the developing country like India and it is kind of under explored area where we findmore than 95 % of HIV infection is due to subtype C and opportunistic infection is verycommon too.[4,5]Remarkably, 50% of global HIV-1 infection is due subtype C.Cneurocongnitive impairment is being done are

* *Corresponding author*.
E-mail address: mmnbrc@yahoo.com (M. Mishra).

https://doi.org/10.18231/j.ijn.2020.016

generally descriptive and lacks sensitivity and specificity. Recently, thbiomarkers, especially CSF biomarker which can establish laboratory based parameters to estimate the neurocognitive impairment status.[Neurologicalassociated with soluble factors secreted bymacrophages and microglia and soluble toxins of cerebrospinal fluid. In particular theneuro-protective or anti-inflammatory factors correlate with neurologicaldiseases. The pathobiology of the HIV associated neurological complications are more accurately diagnosed by patients' cerebrospinal fluid biomarkers which gives valuable approach to understand the interaction of HIV and central nervous system (CNS).[6]

In this article, role of CSF biomarker has been reviewed. CSF biomarkers analysed in two way approach, (i) Targeted hypothesis driven methods in which samples from cross sectional subject groups with and without opportunistic infections of defined patients across the spectrum of systemic and CNS disease progression and (ii) Non-targeted exploratory methods where longitudinal study of the CSF proteome in subjects initiating the antiretroviral treatment. The known biomarkers as well as recently identified novel biomarkers are useful and represent "guide biomarker". These valuable approaches may help the neuropatho-biologists to understand the HIV infection and other neurological disease activity in CNS in a better way.

1.1. Biomarkers in NeuropathogenicHIV-1 Subtypes

Neither it is possible to hit the HIV where it hides, nor to prevent the CNS infection and related CNS injury. In pre-HAART era HIV-associated dementia (HAD) was the most common (20-30%) worldwide among HIV infected AIDS people, especially subtype B predominant infections. However, in post-HAART era the less severe form of neurological disorders consists of a spectrum of neurological complications ranges from mild cognitive motor disorder (MCMD), HIV-1 associated neuro-cognitive disorder (HAND) and asymptomatic neurocognitive impairment (ANI) which are more or less equal among different subtypes.[1] Anti-retroviral therapy can detain the nature of HIV associated CNS disease severity, however milder forms of neurological dysfunction remain common.[1,7]

1.2. Inflammatory molecules as Biomarkers

Previously, in patients without antiretroviral therapy, strong correlations were reported between CSF HIV RNA level and HAD.[8] In contrast, by the use of CART, association between viral load, immune markers and neurological status are relatively weak.[9] In the post-HAART era, the point of difficulties in the neurological disorder underlying the nature of impairment rely chiefly on neuropsychological test performances.[10] The indistinguishable problem is to find the particular CNS damage or ongoing injury before and after CART, where laboratory based biomarkers stand with certain potential for HIV related CNS injury.[6] Although neurological damages occur by HIV were incompletely understood, many studies suggested that development of dementia correlated with the elevation level of MCP1 and RANTES,[11] interferon-gamma inducible protein IP10 or CXCL10 in CSF.[12] Large amount of immune activation marker such as neopterin, released by macrophages is negatively correlated with CD4+ T-cell concentration[13] and level of CD38 increases in CSF.[14] In the absence oftherapy, inflammatory cytokines in serum and CSF such as TNF alpha, IFN gamma getmost of the HIV infection and indicates the systemic as well as CNS diseaseprogression.[15]However, in subjects with anti-retroviraltherapy, the CSF may not contain the associative quantity of inflammatory cytokines, whichis why to correlate the CNS disease condition, several CSF biomarkers molecules haveCathepsin B and cystatin B are lysosomal proteinssecreted by macrophages and microglia and the increased level in CSF indicatesusceptibility for neurotoxicity.Deficits in monocyteantioxidants may contribute to identify developed and progression of cognitiveimpairment.neurovirulence in post-HAARTera, mononuclear phagocyte secreted neurotoxic proteins that affect neurocognitiveimpairment have been used in several studies such as N-acetyl aspartate (NAA),arachidonic acid, PAF. The HIV RNA level in CSF toplasma seen in pre-HAART era correlates with neurocognitive status, moreover in post-HAART era the correlation is no longer seen. It is not clear as there are multiple factorsmicroglobulinquinolinicacid, matrix metalloproteinasegangiosides.[16] The progression of mildneurologic disorder is variable, sometimes patient suffers from mild dysfunction for a longerperiod of time and sometimes sever impairment occurs due to rapid progression ofneuronal dysfunction.Spatients[17]

1.3. Abnormally expressed protein as Biomarkers

The brain being the sanctuary of HIV, maintain a balanced immune privilege environment with neurotoxins as well as neuroprotective factors. Neopterin, neuro-metabolites such as glutamate, glutamine and glial metabolites like myo-inocytol and choline compounds were suggested to be CSF biomarker for neurological dysfunction.[15] More importantly, neuroprotective factors such as BDNF, NT-3 used to get declined during neurocognitive impairment.[18] Glycogen synthase kinase 3 beta level increases by any neurotoxins. GSK-3 beta inhibitors, phosphorylated form of GSK3 beta and 14-3-3 family of protein are used as neurological signature during CNS disease progression. Neuron specific enolase (NSE) and S100 beta, MBP and glial fibrillary acidic protein (GFAP) in CSF consider as putative marker of CNS disease progression in HIV patients.[19]

Active HIV-related neurodegeneration can be correlated with neurofilament light chain (NFL) present in CSF.

In HIV-1 subtype B infected patients, elevated level of neurofilament light chain in CSF have been reported by several investigators.[20] Neopterin, the inflammatory biomarker of CNS immune activation have been reported in pre and post antiretroviral therapy by many groups.[13,18,21] Unlike Alzheimer's patients, the elevated level of t-tau protein in CSF of HAD patient is one of the defined pathways to neurological injury in brain.[22] CSFMMP9 level increases in patients with opportunistic infections which indicate that the increase in MMP9 may degrade the extracellular matrix of blood brain barrier and trans-endothelial migration of virus may increase. In a collective study from four different broad groups (Milano, Sweden, California and Australia) before and after CART,[13] it has been reported that CSF neopterin is not simply a reflection of CNS inflammation; it may provide the degree of vulnerability of neural cells in brain.

Healthy individual contains 3- 5nmol/L neopterin in CSF, where as in HIV infected CART treated patients the level estimated to be 16-20nmol/L which indicates intrathecal immune activation.[23] Often there is a good correlation between blood and CSF neopterin and study from a computed tomography demonstrated that significant correlation between blood neopterin concentration and loss of brain tissues. As many cytokines including IFN-γ have short half-lives, they might not be well reflected in CSF. In contrast, neopterin has long half-life and stability in biological fluid due to its non-polar chemical character; it appears to provide a stable indicator among HIV infected patients with progressive neurological diseases.

In a developing country like India, late diagnosis of HIV, due to irregular immuno-virological monitoring, the effect of opportunistic infections in patients with antiretroviral therapy has not been well defined. In addition, very few studies have been carried out in patients with opportunistic infections (OI). In the post HAART era, the neurological complications due to subtype B or C do not show much difference and report from clade B predominant countries follow the similar kind of observations. From the CNS HIV antiretroviral therapy effects research (CHARTER) studies, several reports suggested that although sever form of HAD drop down by antiretroviral therapy, milder form of cognitive impairment remain to be continued and prevalence of mild neurocognitive impairment increased in India[7,15]. Most of the cognitive performances measured by international dementia scale is partly depends upon the educational status of HIV patients and it was found lower level of education has significant effect on the text performances. Neurocognitive impact of HIV-1 subtype C has been studied by various independent groups of south India and almost similar observation were found in the neuropsychological performances. Mild neurocognitive impairment is of 35.3 %, mild moderate impairment is 21.9% and moderate-sever impairment is 3.3% in the study sample[24]. In developed country, the milder forms are found as ANI 32.7%, MND 11.7% and HAD 2.4% and association of neuropsychological impairment correlate with sustained elevation of macrophage/microglia activation marker sCD163 in CSF and plasma.[25]

1.4. Biomarkers of Subtype C intimately related to OI

In post-HAART era, apart from CD4 T-cell count, HIV viral load, quantization of immune activation marker in plasma, enormous amount of studies have been carried out in developed country to understand the neuropathological mechanism which may not be directly relevant to Indian scenario, because co-infections are intimately related to the immunological parameters of HIV patients in India and secondly opportunistic infections in CNS predominantly affect the subtype C associated neuropathogenesis.[5,26] From a recent study of asymptomatic and symptomatic group of neurocognitive patients of subtype C HIV infected subjects from India, CSF biomarkers have been analyzed. As expected IL6, TNF alpha, beta-2 microglobulin and neopterin level are significantly higher in neurocognitive symptomatic groups in comparison to that of asymptomatic groups.[12] However, the specific parameter in asymptomatic groups which may contain the information about local pathogenic progression in CNS is lacking. Increased NFL in CNS has been predicted as vulnerability of CNS injury.[22] Unfortunately, there is unavailability of this kind of study from Indian patients. Decline in certain neuro-protective factors like BDNF, NT-3 may explain the level of ongoing neurodegeneration in those asymptomatic groups which are worthwhile to predict the future neurological impairment. It is important to note that in addition to soluble CD14,CCl2, IL6 and general growth factors level may increase in CSF along with many other monocytic activation markers,[12] but the decline in essential neurotrophic growth factors would make a special attention to identify a trend that give a signature molecule to predict the neuropathological status. Including viral and host response tissue regulatory CSF markers, many other CSF biomarkers have been reported in subtype B infected patients, but none of them systematically studied in drug naïve versus cART treated patient in India. Moreover, it is essential to consider the other associated neurological diseases in the patients as well as the immunological status if patient has more than one systemic opportunistic infection. Hence more CSF biomarkers need to assessed using new advanced techniques and these efforts are essential to understand the interaction of HIV-1 in brain for the longer period of stay. More importantly CSF NFL, neopterin, BDNF, NT-3 are the factors to examine as these CSF biomarkers might help to understand and monitor the immune reconstitution inflammatory syndrome (IRIS) and ongoing disease progression in brain.

1.5. Great potential of Biomarker for Neurodegenerative diseases

Biomarkers are believed to have great potential in early diagnosis of diseases, setting standard for developing new remedies to treat disease. To identify the biomarkers of several different neurodegenerative diseases, new advanced technology enabled the modern scientists. The biomarkers that have been recently recognised are phosphorylated tau protein and aggregated beta-amyloid peptide for Alzheimer's Diseases, alpha-synuclein contained Lewy bodies and altered dopamine transporters. The light subunit of the neurofilament protein (NFL) is a major structural component of myelinated axons is essential to maintain axonal calibre and to facilitate effective nerve conduction, CSF concentrations of NFL provide a sensitive marker of CNS injury in a number of neurological diseases. In CSF, the light subunit of the neurofilament protein (NFL) concentrations across the spectrum of HIV-infection has been developed.[1,7,27]

1.6. Future prediction

CSF explores the possible global scenario of neuropsychological change. Novel biomarkers have been identified in CSF of the HIV infected patient with different opportunistic infection, prior to anti-retroviral and after anti-retroviral therapy. The significant differences in neurologically normal and declined patients are able to distinguish by biomarkers. The efforts of the critical evaluation of biomarkers lead to the identification of biomarkers of CART drug suppressive asymptomatic subjects, to delineate the neurological impairment mechanism from the various biochemical parameters. Also biomarkers are able to determine the increase in Blood brain barrier (BBB) permeability due to OIs and the impaired function of HBMECs, tight junction proteins and increase of matrix metalloproteinase altogether may allow the infiltration of activated monocytes to perform the oxidative damage to neuron as well as hamper the supportive activity of glial micro environment inside the CNS. Further, early CSF biomarkers are desperately needed to interpret CNS disease progression and for therapeutic intervention. The wide range CSF samples analysis may provide a trend to associate the disease progression at CNS level.

2. Summary

To monitor the alteration in CNS environment, cerebrospinal fluid is the optimal medium. In the pre-cART era viral RNA was used as an indicator. However after use of HAART or combined ART, the viral RNA no longer be detectable in most of the cases. Hence in recent day's immune-related (inflammatory molecules) or infected CNS secreted abnormal proteins are used as biomarkers to treat and save the HIV associated neurocognitive disorder patients.

3. Abbreviations

ANI-asymptomatic neurocognitive impairment, BBB-blood brain barrier,

BDNF- brain derived neurotrophic factor, CART-combined anti-retroviral therapy,

CNS- Central nervous system, CSF- cerebrospinal fluid,

CHARTER- CNS HIV Antiretroviral Therapy Effects Research,

HIV- human immunodeficiency virus, HAD- HIV associated dementia,

HAND- HIV associated neurocognitive disorder,

HBMECs- human brain micro-vascular endothelial cells,

IRIS- immune reconstitution inflammatory syndrome, OI- opportunistic infection,

MCMD-mild cognitive motor disorder, NFL- Neurofilament light chain

4. Source of Funding

None.

5. Conflict of Interest

None.

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Author biography

Mamata Mishra Senior Research Scientist

Prasanna Kumar Dixit Reader and Head

Cite this article: Mishra M, Dixit PK. **CSF biomarkers as potential screen of HIV-1 subtype C in post-HAART era**. *IP Indian J Neurosci* 2020;6(2):78-82.