Low Cerebrospinal Fluid Beta Amyloid1-42 in Patients with Tuberculous Meningitis

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Abstract

Introduction Tuberculous meningitis (TBM) is an important disease leading to morbidity, disability and mortality that primarily affects children and immune-depressed patients. Specific neuromarkers predicting outcomes, severity and inflammatory response are still lacking. In recent years an increasing number of evidences show a possible role for infective agents in developing neurodegenerative diseases.

Methods We retrospectively included 13 HIV-negative patients presenting with meningeal tuberculosis. Lumbar punctures were performed for clinical reasons and CSF biomarkers were routinely available: we analyzed blood brain barrier permeability (CSF to serum albumin ratio, "CSAR"), intrathecal IgG synthesis, (CSF to serum IgG ratio), inflammation (neopterin), amyloid deposition (1-42 β -amyloid), neuronal damage (T-tau, P-tau, 14.3.3) and astrocytosis (S-100 β).

Results Patients were 83% male and 67 % Caucasian with a median age of 51 years(24.5-63.5 IQR). Apart from altered CSAR (median value 18.4, 17.1-30.9 IQR), neopterin (14.3 ng/ml, 9.7-18.8) and IgG ratios (15.4, 7.9-24.9) patients showed very low levels of 1-42 β -amyloid in their CSF (348.5 pg/mL, 125-532.2). Protein 14.3.3. tested altered in 38.5% cases. T-tau, ptau and S100Beta were in the range of normality. Altered low level of beta amyloid correlated over time with classical TBm findings and altered neuromarkers.

Conclusion CSF Biomarkers from patients with TBM were compatible with inflammation, blood brain barrier damage and impairment in beta amyloid metabolism. A β 1-42 could be tested as a prognostic markers, backing the routine use of available neuromarkers. To our knowledge this is the first case showing such low levels of A β 1-42 in TBM; its accumulation, drove by neuroinflammation related to infections, can be central in understanding neurodegenerative diseases.

Introduction

Central nervous system (CNS) infections are uncommon diseases characterized by significant morbidity, disability and mortality. Tuberculous meningitis (TBM) is the most severe manifestation of extrapulmonary infection by *Mycobacterium tuberculosis*. It is characterized by a slowly progressing granulomatous inflammation of the basal meninges, an inflammatory reaction that can lead to complications such as hydrocephalus, cerebral vascular infarction, cranial nerve palsy and, if untreated, death. Vulnerable populations are at higher risk of infection and complications. Rapid diagnosis and initiation of treatment is therefore necessary to reduce the high mortality and severe sequelae associated with the disease. Diagnosing TBM can be difficult as the symptoms are non-specific and they mimic other infections or vascular disorders. The identification of specific plasma or cerebrospinal fluid (CSF) biomarkers may be relevant for an early diagnosis and for prognosis. TBM is traditionally characterized by CSF pleocytosis, increased proteins, decrease of glucose concentration. Although other CSF biomarkers have been investigated none has reached clinical practice. S100b, NSE (neuron-specific enolase) and Interleukines have been advocated to be predictive of disease's severity and outcome [1-

3,29,30] Recently, several infectious agents have been called out to be possible triggers in causing neurodegenerative diseases, especially Alzheimer Disease (AD). The total burden of infectious agents have been linked to the development of AD in sporadic cases [16]; this appears to be substantially due to microglia activation [24], long acting inflammation neuronal alteration, oxidative stress and beta amyloid accumulation but also to a direct effect by infectious agents. Specifically viruses from the Herpesviridae family have since long been called out to play a decisive role (together with APOE phenotype) [9,15,33] in affecting disease onset and clinical progression. Other bacteria have also been suggested to have a causative role including *Spirochetaceae*, *Chlamydia* and Gram negative bacteria [26,31]. Recent reports suggest also a role for Parasites in stimulating different pattern of inflammation [27] and no data have been outlined for Fungi. Beside this, beta amyloid has also been identified as a protein acting as an anti-infective peptide playing a direct role in the clearance of different infections in various animal models. HHV6 appears to be capable of directly enhance the seeding and acceleration of amyloid deposition despite a debated pathogenic potential [10]. Following an important review [26], this suggestive hypothesis could link the accumulation of Beta amyloid during infection and the subsequent development of neurodegenerative disease. Aim of this analysis was to study the CSF concentrations of several biomarkers in patients with TBM

Materials And Methods

We collected cerebrospinal fluid samples from patients among hospitals of Turin between 2001 and 2018, undergoing lumbar puncture (LP) for clinical reasons. All of them were morning LP. Patients signed a written informed consent for CSF withdrawal, storage and analysis. The retrospective analysis of the collected data was approved by the Ethics Committee (Città della Salute e della Scienza, Ospedale Molinette, RetroNEG Protocol, n 0094995, October 4th 2017).

We included patients with confirmed *Mycobacterium tuberculosis* meningitis (positive *Mycobacterium tuberculosis* DNA or culture on CAF). We studied biomarkers of blood-brain-barrier (BBB) permeability (CSF to serum albumin ratio, "CSAR"), inflammation (CSF to serum IgG ratio, neopterin), amyloid deposition (1-42 β -amyloid), neuronal damage [Total tau (T-tau), Phosphorylated tau (P-tau), 14-3-3 protein) and astrocyte damage (S-100 β) [1-3, 28]. Quantitative determination of albumin in serum and CSF was measured by Immunoturbidimetric methods (AU 5800. Beckman Coulter, Brea, CA. USA), 14-3-3 protein was measured by immunoenzymatic methods (ELISA) (Santa Cruz Biotechnology); CSF tau, P-tau and 1-42 β -amyloid were measured by immunoenzymatic methods (Fujirebio diagnostics, Malvern. U.S.A.). Neopterin and S-100 β were measured through validated ELISA methods [DRG Diagnostics (Marburg, Germany) and DIAMETRA S.r.l. (Spello, Italy), respectively]. Reference values were as follows: CSAR [<6.5 (up to 35 years) and <8.0 if aged above 35 years], IgG ratio (<0.7), 14.3.3 protein (normally absent), T-tau [<300 pg/mL (patients aged 21 – 50), <450 pg/mL (patients aged 51 – 70) or <500 pg/mL in older patients], P-tau (<61 pg/mL), 1 – 42 beta amyloid (>770 pg/mL), neopterin (<1.5 ng/mL) and S-100 β (<380 pg/mL)[1-3, 28]. Imaging (either MRI or CT) and electrophysiological studies (EEG) were performed for all patients. Data were analyzed using standard statistical methods: variables were

described as number (percentage) with medians [interquartile ranges (IQR) or ranges (minimum-maximum)]. Additionally, correlations were analyzed through Spearman test for bivariate analysis. Data analysis was performed using SPSS software for Mac (version 26.0. IBM Corp). Graphs were created with both SPSS and PRISMA.

Results

Thirteen patients were included: 10 (83%) were male and 8 (67%) Caucasian, median age was 51 [24.5–63.5]. All tested negative for HIV, viral hepatitis, renal impairment and no other reasons for immunosuppression were found. Two participants (15%) showed hypertension as comorbidity, 2 (15%) diabetes and 1 (7%) hypothyroidism; 7 (58.3%) showed focal or diffuse imaging abnormalities at CT/MRI scans and 2/13 (15%) had EEG alterations. Baseline CSF parameters showed typical TBM findings: 150 CSF cells/mm³ [50-245], 129 mg/dL of proteins [5-109] and 32 mg/dL of glucose [25.5-45.5]. CSF biomarkers are described in Tables 1 and 2. Values outside ranges observed in healthy volunteers were observed for CSAR [13.8 (17.1-30.9)], neopterin [14.3 ng/ml (9.8-18.8)], IgG ratios [15.4 (7.9-24.9)] and 14.3.3 (positive, 5/13, 38.5%) ; very low levels of CSF 1-42 β -amyloid were observed [348.5 pg/mL (125-532.2)].

We analyzed all available CSF biomarkers per patient and calculated the correlation among them (at the same time point for a total of 66 pairs): CSF Amyloid Beta₄₂ was associated with CSF cells (ρ = -0.777, p =0.009), CSF glucose [ρ 0.568, p =0.009], CSAR [ρ -0.690 p =0.004], FTau [ρ 0.717, p =0.04] [Fig. 3]. Seven days [1-7.5] lasted from symptoms' onset to first LP, 13 days [4-32] to second LP and 7.5 days [1-14] to treatment. 10 patients received more than one LP with a median of 3 (2-4): time course of CSF proteins and Beta₄₂ is shown in Figures 1 and 2. All patients were treated with standard TBM regimens; 5 (38%) and 2 (15%) received additional fluoroquinolones or linezolid. All patients received high dose steroid as an adjunctive therapy. One patient had disseminated tuberculosis. No concomitant infections were recorded. No patient died; 7 subjects (54%) survived but suffer long-term disability and 6 (46%) survived with no consequences [data updated at the end of 2019]. We exploratory observed a non-statistically significant difference between CSF amyloid Beta₄₂ (at admission in our ward, second LP received by patients) in those who suffered sequelae versus those who did not [142 vs. 568 pg/mL, p =0.095) (Suppl. Fig1).

Discussion

In this small case series we measured several cerebrospinal fluid biomarkers in meningeal tuberculosis. We confirmed the presence of classical TBM CSF findings such as BBB impairment, inflammation and report here, for the first time, very low level of 1-42 Beta amyloid [1,2,3,21,28] Neuronal damage is a classical feature of TBM due to its devastating inflammation and disruptive process. 14.3.3 positivity was found in 5/13 (38.5%) of TBM; this cellular-cycle protein, previously associated with prionic disease, accumulates in the CSF after neuronal damage especially during bacterial involvement of CNS and it is cleared from the CFS after successful treatment [4]. BBB impairment and IgG synthesis were observed;

CSAR and IgG ratios were high in TBM, confirming results in literature where a significant impairment in BBB due to TBM is described [3, 21]. A raised level of neopterin can be found in TBM, denoting intrathecal production by macrophage-derived cells and, as the BBB has a low permeability for peripheral neopterin, it represents a relevant index of local inflammation. [4,8,9]

Moreover, we found out that classical markers of TBM disease activity had a good correlation with 42 Beta Amyloid: low glucose and higher cells correlates with lower amyloid, BBB damage expressed by CSAR, as well as FTau, resulted higher in lower amyloid [5,21]. These findings outlines the possibility for Beta Amyloid of being a good proxy of precocious disease activity and a potential marker to follow over time. Also, lower amyloid level was associated with worse outcomes, thus suggesting a possible prognostic of this marker in clinical practice. Additionally, the observation of low levels of A β 1-42 in patients with TBM is of potential interest and should be interpreted in the context of the recent discovery of a possible antimicrobial role of β -amyloid [7,12] and of a hypothetical infectious “trigger” for Alzheimer Disease [6]. Amyloid protein seems to be shedded and playing an anti-infective role in response of several infections in a murine model [14]. In vivo low levels of CSF A β 1-42 have been observed in patients with pneumococcal meningitis and other bacterial meningitis [28, 11]

That is critical because observing amyloid metabolic alterations during TBM is perhaps the key passage for understanding amyloid’s antimicrobial role. This may show how amyloid metabolism is potentially altered by several infections, as seen for HSV6 and 7 that have been recently associated with development of Alzheimer Disease, probably playing an important role in driving alterations such oxidative damage and progression to accumulation of neurofibrillary tangles.

Several mechanisms regarding that finding, besides amyloid deposition in the brain parenchyma, can be hypothesized. Amyloid levels could be reduced because of the interaction of amyloid fragments with albumin, usually elevated in CSF TBM, thus lowering levels of the free peptide. Additionally A β 1-42 can cross the BBB by leaking in CNS and then accumulating (even if it is known that in peripheral tissues A β 1-40 is prevalent), in the context of increased permeability, thus being lower in the CSF/CNS. Data on the potential measurement of serum amyloid peptides in the setting of Alzheimer’s dementia may confirm this hypothesis.[8,21,22] Another mechanism could be an impaired and reduced amyloid clearance from the CNS [11]: the ISF/CSF flow is believed now to be partially convective and through perivascular spaces that can be harmed during tubercular infections of the CNS and systemic inflammation [24]. That could be particularly relevant following the recent discovery of the so called Glymphatic Central Nervous System [19,23]. TBM it is known to affect the basal anatomic section of the brain with a reduced CSF recirculation, a fibrosant effect and a possible central hypertensive syndrome. In view of these observations it is possible that even the glymphatic recirculation is altered; unfortunately data are scarce and there are no reliable markers up to date.

To conclude, the analysis regarding the time to normalization for A β 1-42 in our population deserves an additional remark: relying on our data only three patients normalized Amyloid during follow-up. Patient 4 at day 22, patient 1 at day 190, patient 3 at day 267 [fig.3]. Acknowledging that data are limited and we

were not able to measure these equally for all patients, it is still of great interest that the vast majority of patients did not normalize amyloid while hospitalized nor under treatment; moreover, the time to normalization was not homogenous between patients suggesting a persistent and unpredictable ongoing accumulation and probable undergoing slight but constant and enduring inflammation, which is coherent with TBM physiopathology and such a life-threatening condition. Following a recent article and debate [29,30] A β 1-42 could be tested as a prognostic markers in both pediatric and adult population, backing the routine use of available neuromarkers for both a better tailored approach to patients and in research. An adjunctive information may come from retesting A β 1-42 levels at the end of therapy (one year follow-up retesting). To our knowledge this is the first case showing such low levels of A β 1-42 in TBM; its accumulation, drove by neuroinflammation related to infections, can be central in understanding neurodegenerative diseases. This study has several limitations: study design, number of patients enrolled, impossibility to perform homogenous number of lumbar puncture at follow-up for all patients and incomplete data on Neurofilaments (NFL). Nevertheless the finding of low A β 1-42 concentrations warrant further analysis in controlled settings.

Conclusions

CSF Biomarkers from patients with TBM were compatible with inflammation, blood brain barrier damage and impairment in beta amyloid metabolism. A β 1-42 could be tested as a prognostic markers, backing the routine use of available neuromarkers for both a better tailored approach to patients and in research. To our knowledge this is the first case showing such low levels of A β 1-42 in TBM; its accumulation, drove by neuroinflammation related to infections, can be central in understanding neurodegenerative diseases. Further studies are needed in order to understand the relevance of these observations

List Of Abbreviations

TBM Tuberculous meningitis; NSE neuron-specific enolase; AD Alzheimer Disease; CNS Central nervous system; LP lumbar puncture; BBB Blood-brain barrier; CSF cerebrospinal fluid

Declarations

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Competing interests: The authors declare no competing interests

Availability of data and material

The data that support the findings of this study are available from "Città della Salute e della Scienza, Ospedale Molinette, RetroNEG Protocol, n 0094995, October 4th 2017". Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the authors with the permission of third party.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to participate: Informed consent was obtained from all individual participants included in the study.

Consent for publication: consent was obtained from all individual participants included in the study

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Tables

	Median	Percentile 25	Percentile 50	Percentile 75
42BetaAmyloid (pg/ml)	348.6	125	348.6	532.2
Ftau (pg/ml)	18.1	16.7	18.1	20.5
Tau (pg/ml)	85.1	61	85.1	333.9
IgG ratio	15.4	7.9	15.4	24.9
CSAR	18.4	17.1	18.4	30.9
CSF glucose (mg/dl)	32	25.5	32	42.5
CSF proteins (mg/dl)	129	106.5	129	216
CSF Cells (n/mm3)	150	84.5	150	330
Delta symptoms (Days)	7	1	7	7.5

Tab 1. Neuromarkers, median values

Percentage of values outside reference range (Baseline)	
14.3.3.	
Neopterin	38.5 %
Tau	15.5 %
FTau	0 %
42 BetaAmyloid	15.5 %
CSAR	100 %
IgG Ratio	100 %
CSF Proteines	100 %
CSF Glucose	93 %
S100Beta	93 %
	0 %
Days from symptoms to treatment	7.5 (1-14)
Abnormal brain MRI	53 (%)
Diffused	38.5 (%)
Focal	61.5 (%)
Abnormal EEG	15 (%)

Tab 2. Population features

Figures

Figure 1

Time trend values for CSF protein. The red line indicates Normal values. Data in mg/dl.

Figure 1

Time trend values for CSF protein. The red line indicates Normal values. Data in mg/dl.

Figure 2

Time trend values for beta amyloid. The red line indicates Normal Values (>770) Data in pg/mL.

Figure 2

Time trend values for beta amyloid. The red line indicates Normal Values (>770) Data in pg/ml.

Figure 3

Grouped biomarkers analyzed through spearman test for bivariate. Beta amyloid (x) correlates with classical tb findings and altered neuromarkers

Figure 3

Grouped biomarkers analyzed through spearman test for bivariate. Beta amyloid (x) correlates with classical tb findings and altered neuromarkers

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