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Research Article

Elevated Serum Levels of Interleukin-11 and Matrix Metalloproteinase-9 in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

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Abstract

Background/Aim: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a disease of unknown aetiology associated with chronic severe fatigue and neurological symptoms, including dizziness, sleep disturbances, cognitive impairment and pain. There are no reliable blood biomarkers available for ME/CFS.

Materials and Methods: We quantified the levels of interleukin-11 (IL-11) in the serum of female ME/CFS patients (n = 40; mean age 51 years) and age- and gender-matched healthy control subjects (n = 38; mean age 43), as well as matrix metalloproteinase-9 (MMP-9) in these patients (n = 18; mean age 57 years old) and healthy control subjects (n = 18; mean age 53 years old), using an enzyme-linked immunosorbent assay (ELISA). Mast cells (MCs) were grown from human umbilical cord blood CD34+ stem cells in vitro and incubated with recombinant Epstein-Barr Virus (rEBV) protein, following which the release of MMP-9 was assayed in the cell culture supernatant media by ELISA.

Results: There was a significant increase in serum levels of IL-11 and MMP-9 in ME/CFS patients compared to control subjects. rEBV protein stimulated MCs resulted significant release of MMP-9 compared to control cells.

Conclusions: IL-11 and MMP-9 are elevated in ME/CFS individuals.

Key Words: IL-11; matrix metalloproteinase-9; Myalgic encephalomyelitis/chronic fatigue syndrome; mast cells, serum biomarkers

Introduction

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a disabling complex chronic multisymptom disorder associated with severe fatigue and neurological symptoms, including sleep disturbance, cognitive impairment and dysautonomias [1-4]. It is estimated that about 3.3 million people in the United States of America (U.S.A) suffer from ME/CFS (Centers for Disease Control and Prevention-CDC) [5]. Its prevalence is about 0.42% among adults, and the females are affected three times more than males [6]. The ME/CFS is most common in people between the ages of 40-60 years [5]. ME/CFS patients show subtle brain changes in vivo [7]. There are no effective treatments for ME/CFS because the causes and disease mechanisms are not clearly understood yet [8]. ME/CFS often develops after an infection or other triggers [9]. Some patients with post-COVID sequelae (Long COVID) also suffer from ME/CFS (CDC) [10,11].

Lack of biomarkers makes it difficult to develop reliable objective diagnosis and effective therapeutic agents for ME/CFS. Despite many efforts in identifying useful biomarkers, except for some proinflammatory cytokines being elevated early in the course of the disease [12], no blood biomarker has been found to be significantly associated with ME/CFS [13]. A recent systematic review concluded that all potential ME/CFS biomarkers differed in efficiency, quality, and translatability, with poor

reproducibility of findings between studies [1]. We recently reported stress-induced immune signature changes in ME/CFS patients [14].

Interleukin-11 (IL-11) is a proinflammatory, profibrotic IL-6 family member expressed by many cell types, including astrocytes, monocytes, macrophages, endothelial cells, dendritic cells, neutrophils, and damaged cells [15-19]. IL-11 has been implicated in several inflammatory and autoimmune diseases [19]. Increased levels of IL-11 were found in patient serum, plasma, and lesions of patients with Multiple Sclerosis (MS) [15,20], and have also been associated with other diseases of the nervous system [15]. IL-11 is implicated in senescence and aging pathologies, and inhibition of IL-11 can extend mammalian health span and lifespan [21]. IL-11 expression could affect central nervous system (CNS) pathologies [22].

Matrix metalloproteinases (MMPs) are enzymes that degrade the components of the extracellular matrix (ECM) in tissues. This tissue reorganization is essential for embryonic development, angiogenesis, and the wound healing process in the body [23]. Abnormal expression of MMPs leads to loss of normal degradation of ECM, which causes many pathological conditions, including chronic degenerative diseases [23]. MMP-9 is a macromolecular zinc-dependent endopeptidase involved in the pathogenesis of CNS disorders through altering ECM reorganization, and disrupting neuronal connectivity; thus contributing to cognitive impairment and neuropsychiatric disorders [24-26]. MMP-9 could be released from microglia [27], but also from mast cells (MC) [28]. Interestingly, MC activation disorders have often been seen as a comorbidity in patients with ME/CFS [29]. We recently reported elevated levels of MMP-9 in the serum of Long COVID patients compared to healthy control subjects [30]. In fact, ME/CFS and Long COVID share several similar symptoms and pathological characteristics, including immune and inflammatory abnormalities and gene expression signatures [31,32]. Disrupted ECM homeostasis and reduced cell-cell adhesion have been reported in ME/CFS [33].

In the present study, we report elevated levels of both IL-11 and MMP-9 in serum from patients with ME/CFS compared to healthy controls, as well as release of MMP-9 from cultured human MCs stimulated by recombinant Epstein-Barr Virus (rEBV) protein.

Materials and Methods

ME/CFS patients for this study were selected as described previously [34]. These patients met the 1996 CDC/Fukuda and 2003 Canadian Case definitions for ME/CFS, and were recruited (2007-2012) at the Department of Medicine, University of Miami Miller School of Medicine. Inclusion criteria were post-exertional malaise, prolonged fatigue and tiredness, pain, immunological abnormalities, sleep disturbances and cognitive disorder. Exclusion criteria were the presence of any other active medical conditions, such as diabetes, neuropsychiatric disorders, substance abuse or use of immunotherapeutic agents. This study was conducted in accordance with the University of Miami/Nova Southeastern University (NSU) Institutional Review Board (IRB) approved guidelines (# 20060815).

Serum samples from age-matched healthy female control subjects were obtained frozen and stored at -80°C until used for assays. These samples were collected under informed consent and other appropriate regulatory and ethical approvals. The blood samples were collected in serum separation tubes, allowed for 1 hour at room temperature, centrifuged for 10 min at 2000xg in a refrigerated centrifuge and serum was collected, aliquoted and stored at -80 °C until analysis using enzyme-linked immunosorbent assay (ELISA) was performed.

We measured the levels of IL-11 (Catalog # DMP900, BioTechne R&D System, Minneapolis, MN, USA) in the serum of female ME/CFS patients (n=40; mean age 51 years old) and age and gender-matched healthy control subjects (n=38; mean age 43 years old) by (ELISA using commercial Kits and microplate reader, as we have reported previously [30]. We also measured serum MMP-9 (Catalog # DY911, BioTechne R&D System, Minneapolis, MN, USA) levels in female ME/CFS patients (n=18; mean age 57 years old) and age and gender-matched healthy control subjects (n=18; mean age 53 years old). The number of samples in ME/CFS patients used to measure IL-11 and MMP-9 is different due to the limited quantities of serum samples available for this study.

MC culture, stimulation and MMP-9 ELISA

MCs were grown from human umbilical cord blood-derived CD34+ cells by incubating with stem cell factor (SCF, 100 ng/ml) and IL-6 (50 ng/ml) in Iscove's Modified Dulbecco's Medium (IMDM) for 14-16 weeks, as we have previously reported [35]. These MCs were incubated with recombinant EBV protein (rEBV, Abcam, Waltham, MA, USA) at 100 ng/ml or lipopolysaccharide (LPS; Thermo Fisher Scientific/Invitrogen, Miami, FL, USA) at 10 ng/ml in 24-well tissue culture plates ($1x10^5$ cells/ml media/well) in serum-free media. Then the supernatant media was collected after centrifugation and stored at -80ºC freezer until ELISA for MMP-9 (Catalog # DY911, BioTechne R&D System, Minneapolis, MN, USA) using a commercial ELISA kit.

Statistical Analysis

The results are presented as mean ± SEM. Statistical analysis of the data was performed using an Unpaired t-test or one-way analysis of variance (ANOVA) followed by Tukey's post hoc analysis to determine statistically significant differences between the healthy controls and ME/CFS patients by using GraphPad Prism (Version 10.6.0, GraphPad Software). Scatter graphs represent individual data for both ME/CFS and healthy control subjects with mean bars. A p-value of less than 0.05 was considered statistically significant.

Results

There was a significant increase in serum levels of IL-11 in ME/CFS patients (mean 127 pg/ml; n=40) compared to healthy control subjects (mean 67 pg/ml), as shown in Fig. 1A (n=38, *$p<0.001$). Further, our results showed significantly increased levels of serum MMP-9 in ME/CFS patients (126 ng/ml; n=18) compared to healthy control subjects (17 ng), as shown in Fig. 1B (n=18, *$p<0.0001$). Scatter graphs show individual data of IL-11 and MMP-9 in patients and control subjects. Horizontal bars in the scatter graphs are the means of the data. Different patient cohorts for IL-11 and MMP-9 were used due to lack of the same samples and limited numbers for this study.

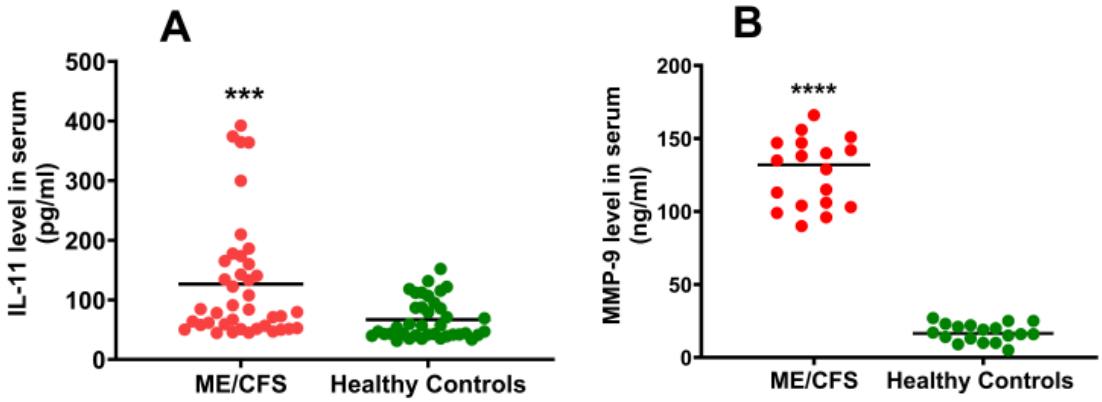

Figure 1: Elevated levels of serum IL-11 and MMP-9 in patients with ME/CFS. IL-11 and MMP-9 levels in the serum of ME/CFS patients and healthy control subjects were quantified using commercial ELISA kits. The scatter plots represent serum (A) IL-11 levels in individual female patients (n=40; mean age 51 years) and age-matched control subjects (n=38; mean age 43 years) measured (*p<0.001). (B) the scatter plots represent serum MMP-9 levels in individual female patients (n=18; mean age 57 years) and age-matched control subjects (n=18; mean age 53 years; (*p<0.0001). Horizontal bars indicate the means of the data. Different patient cohorts for the IL-11 and MMP-9 were used due to the limited availability of samples for this pilot study

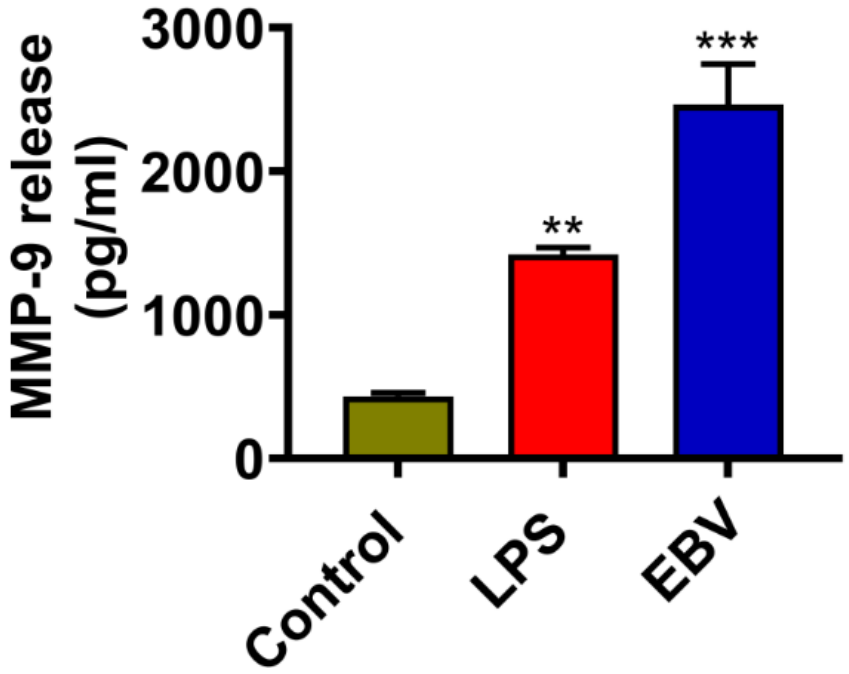

Figure 2: rEBV protein activates human MC and releases MMP-9 in vitro. MC (1x10^5 cells/ml) were incubated with rEBV (100 ng/ml) protein for 24 hr in tissue culture plates at 37°C. After the incubation was over, the culture supernatant media were collected by centrifugation and quantified the levels of MMP-9 by ELISA (n=3). LPS (10 ng/ml) was used as a positive stimulant for MC. Both rEBV and LPS significantly released high levels of MMP-9 compared to untreated control cells (**p<0.01, ***p<0.001, one-way ANOVA and Tukey's multiple comparisons test).

Next, we investigated if rEBV can activate MC to release MMP-9 in vitro. Incubation of human MC with rEBV (100 ng/ml) protein for 24 hr significantly released MMP-9 (mean 2464 pg/ml) compared untreated control cells (433 pg/ml). LPS used as a positive stimulant also significantly increased MMP-9 release (1422 pg/ml) compared to untreated control cells (Fig. 2, n=3, one-way ANOVA and Tukey's multiple comparisons test **p<0.01, ***p<0.001).

Discussion

In this pilot study, we found significantly elevated levels of IL-11 and MMP-9 in the serum of ME/CFS patients compared to age and gender-matched healthy control subjects. We also found that incubation of MCs with rEBV protein significantly increased the release of MMP-9 compared to untreated control cells in vitro, indicating a new source of MMP-9 from MC. Studies have shown that viral and other infections may be involved in the pathogenesis of ME/CFS [36,37]. High levels of IL-11 were reported in the respiratory tract of virally induced asthma [38], indicating an IL-11 response with viral infections. A recent review article hypothesized that immunosenescence-associated age-dependent immunity decline could contribute initiate and maintain fatigue in ME/CFS [39]. Increased levels of IL-11 may contribute to the neurosenescence, inflammaging and immunosenescence, as recent reports demonstrated that IL-11 as the master regulator of aging in mice [40,41]. IL-11 could contribute to inflammaging, and that pharmacologic

inhibition of the IL-11 signaling pathway increases the lifespan and health span in mice [41]. Similarly, another study also showed that blocking the age-related increase in IL-11 restores immune-metabolic homeostasis and extends health span and lifespan in mice [18,42]. It has been shown that IL-11 activates nuclear factor-κB (NF-κB) and janus kinase/signal transducers and activators of transcription (JAK/STAT) signaling pathway and mediates proinflammatory cytokine expression [19], which could contribute to the chronic inflammation in ME/CFS. Additional studies are needed to determine if inhibiting IL-11 would be useful to treat diseases or if it interferes with any physiological processes [41].

MMP-9 plays an important role in many pathophysiological conditions, including immune-associated CNS diseases MMP-9. [43]. is crucial for synaptic plasticity, learning and memory, axonal regeneration and brain development [44]. MMP-9 mediated blood-brain barrier (BBB) disruption is a hallmark of bacterial, viral, fungal, and parasitic CNS infections, facilitating immune cell infiltration and pathogen entry and exacerbating neuroinflammation and tissue damage [45,46]. Increased MMP-9 could contribute to the disturbed ECM homeostasis in ME/CFS patients. High levels of plasma MMP-9 have been reported in mild cognitive impairment (MCI) and Alzheimer's disease (AD) and may be involved in neuroinflammation and neurodegeneration [47]. Another recent study reported that high levels of MMP-9 in cerebrospinal fluid (CSF) are correlated with CNS infections [45]. We analyzed MMP-9 in the serum of ME/CFS patients and found a similar increase. A recent study using a multiplexing custom assay for MMPs, MMP-1, MMP-2, MMP-7 and MMP-10 showed one patient cluster with higher levels of MMP-1, MMP-2, and MMP-10 profiles than in another cluster of patients with ME/CFS [48], implicating MMPs in ME/CFS disease pathogenesis. The above study suggested investigating MMP-9 in these patients would be very important since MMP-9 is known to be involved in neuroinflammation [48]. Our present study fills this gap and reported elevated levels of MMP-9 in ME/CFS patients.

The source of either IL-11 or MMP-9 in the serum of patients with ME/CFS is not presently known [15]. IL-11 production in macrophages is regulated by several cytokines [17]. Intracerebral hemorrhage was associated with elevated levels of IL-11 in peripheral blood [49]. Astrocytes may be the main sources of MMPs, but may also derive from fibroblasts, endothelial cells and MC. Additionally, MMP-9 could be released from microglia [27]. One study reported that the transformed human MC line secreted MMP-9 in response to phorbol 12-miristate 13-acetate (PMA) [28]. Also, MC activation disorders have been frequently observed as a comorbid condition in patients with ME/CFS [29]. EBV infection may be associated with the development of ME/CFS in some individuals [50]. We found that rEBV protein activated MCs released significantly high levels of MMP-9. We recently reported increased levels of MMP-9 in Long COVID patients, who share some similar symptoms with ME/CFS [31,32]. including infection-associated chronic immune exhaustion [51]. We used n=3 in this pilot in vitro experiment with MC, since mature MC generation from CD34+ cells takes over 12 weeks in culture that are ready to use for stimulation experiments. We will test more MC cultures in the future studies with rEBV protein to validate the present findngs.

There is no single fluid biomarker available for ME/CFS currently; a combination of markers may be useful for ME/CFS or a select category of patients [52-55]. Moreover, all ME/CFS patients may have different underlying pathogenetic mechanisms that could differently affect the various biomarker profiles [48]. Therefore, no clear ME/CFS subtypes are established yet [48]. There are no effective U.S. Food and Drug Administration (FDA)-approved treatment options for either ME/CFS or Long COVID [56]. Though there are no effective therapeutic options for ME/CFS, some treatments reduce select symptoms. Interestingly, dietary supplementation appears to show some potential in reducing fatigue in ME/CFS patients, but the results are inconsistent [57]. In particular, the flavonoid luteolin, especially formulated in aliposomal form using olive pomace oil (PureLut) may be useful as it was shown to be a more potent inhibitor of human MCs than the "MC stabilizer" drug cromolyn [58].

The anti-aging gene is important in inflammatory, autoimmune and neurodegenerative disorders [59,60], and may also be involved in the ME/CFS. Sirtuin 1 (SIRT1), an NAD+-dependent deacetylase, has been explored for therapeutic potential in aging and neurodegenerative diseases. It plays an essential role in various signaling pathways in regulating cellular metabolism, energy homeostasis, gene expression, cellular longevity, autophagy, oxidative stress, and cellular differentiation [59,61]. SIRT 1 activators could provide benefit to these patients by preventing cellular death and improving mitochondrial functions [60,62-64]. Therefore, future studies may include measurement of Sirtuin level in the serum of patients with ME/CFS before and after treatment with possible subset analysis. We did not measure Sirtuin in this pilot study due to the limited availability of samples.

Many limitations exist, mainly methodological biases, number of subjects analyzed, the paucity of individual characteristics other than age and sex, as well as the lack of an exercise stress component. The total number of samples analyzed was not large enough for both MMP-9 and IL-11 to make any subgroup analysis in ME/CFS.

Increased IL-11 level in this study could also be a compensatory protective mechanism in the ME/CFS patients and thus needs longitudinal analysis of these serum markers. Also, the elevation of certain fluid biomarkers may vary depending on the disease status and the causes of the disease. This pilot study findings could be expanded and validated in the future by analyzing IL-11, MMP-9, and other parameters using more cohort samples that enable the analysis of subgroups of ME/CFS and comorbid conditions.

Conclusions

IL-11 and MMP-9 may be elevated in a subset of ME/CFS individuals, and this should be investigated in a larger group of ME/CFS patients.

Acknowledgment

Conflicts of interest: There are no competing interests.

Authors' contributions: TCT, NK and DK conceived the project. KA, AM, and KSD prepared serum samples from ME/CFS patients. KD, BC, SPK, RSJ performed all assays. KD and TCT reviewed the results and their significance, reviewed the literature and wrote the manuscript.

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Informed consent: Informed consent has been obtained from all individuals included in this study.

Institutional Review Board Statement: This study was conducted in accordance with the University of Miami/Nova Southeastern University (NSU) Institutional Review Board (IRB) approved guidelines (20060815).

Data Availability Statement: The data that support the findings of this study are available on reasonable request from the corresponding author.

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