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Review Article

Effects of stress on HIV infection progression

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ABSTRACT

There is substantial body of evidence that psychosocial factors influence the disease progression in HIV infection. In particular, stress or stressful life events are considered important in terms of impacting the key biological markers of the disease – viral load and CD4 cell count. Both animal models and human research seem to prove that stance by examining various groups of patients (children and adults, males and females, MSM and heterosexual persons). There is no consensus as to the effects of stress-reducing interventions on improving the immune functioning of the patients, although there is research indicating that these techniques may be of benefit to the patients if used properly. There are two most often discussed biological models for explaining the mechanisms behind the mentioned effects – one relating to the actions of hypothalamus–pituitary–adrenal axis (HPA axis) and the second pointing to sympathetic nervous system (SNS) or sympathomedullary pathway (SAM). These two mechanisms should not be viewed as exclusive, but rather synergetic in action. Both of them, however, are not clearly understood and there are studies pointing to gaps in these theories. Further research is needed to examine the biological mechanisms and to distinguish the groups of patients that may benefit the most from psychological interventions.

1. Introduction

It is now a widely recognized fact that stress coupled with other psychological phenomena may explain some part of the variability of HIV infection progression [1]. On the other hand, in humans the social and psychological burden of the disease contributes to elevation of stress levels, which in turn may contribute to mental disorders more frequently observed in persons living with HIV (PLWH) [2]. Akin to other medical conditions this can result in poor health outcomes, via problems with medication adherence, lack of social support and unhealthy lifestyles. Nevertheless, the latter factors, however important, cannot sufficiently explain these connections [3]. Their nature is yet to be fully understood along with the role of various underlying mediatory mechanisms, however a complex and interactionist pattern of interrelations seems to be involved. The present article aims at discussing the results of research on the effects of stress on the disease progression and briefly summarizing the proposed explanatory mechanisms behind these connections.

2. The effects of stress on the disease progression in HIV infected patients

While there is much debate on what stress truly is, the American Psychological Association cites Zimbardo as the author of its accepted definition [4]. It states that stress is "the pattern of specific and nonspecific responses an organism makes to stimulus events that disturb its equilibrium and tax or exceed its ability to cope", while the "internal or external event[s] or stimul[i] that induce stress" are what Zimbardo calls stressors [5]. According to many authors stress has detrimental effects on number of HIV disease progression clinical outcomes, including AIDS stage, CD4 cell decline, increased viral load, AIDS diagnosis and AIDS mortality [6]. Effects of stress on immune functions are observed not only in case of HIV infection in adult patients, but in several other infections and medical conditions, in children as well [7]. The connections were also evaluated in animal models using simian immunodeficiency virus (SIV). In research conducted by Capitanio et al. [8], a group of 36 adult rhesus macaques were randomly assigned to stable or unstable social conditions, 18 of which were inoculated with SIV. Among those infected, the animals belonging to unstable conditions group not only had higher plasma concentrations of SIV RNA and lower levels of SIV IgG, measured respectably at week 10 and week 8 after inoculation, but also had

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significantly shorter survival rate. No animal died in the SIV-free controls in neither of the social conditions groups.

In humans the effects of stress on HIV progression are most clearly visible when stress is operationalized as being subject to traumatic life events or by using interview-based methods [3]. In a 1-year longitudinal study of a group of children and adolescents living with HIV ($n = 618$) CD4 percentage and number of negative stressful life events were measured. These events included (by order of frequency): family member hospitalized, family member sick, loss of or change in housing, family member left, death of a family member, parent lost job, death of a parent and death of a sibling. A threefold increase in risk of CD4 percentage decline was observed in a group that experienced two or more stressful life events compared to a group who did not [9]

A study on post-traumatic stress disorder (PTSD) in HIV+ survivors ($n = 145$) of the hurricane Katrina in New Orleans proved that risk of having detectable viral loads and CD4 cell counts <200 cells/mm^3 was elevated in patients who had symptoms of PTSD. Authors noted that although there were significant interruptions in medication use due to Katrina in the PTSD group, this effect may not be accounted for all the variance. By two years after the hurricane the differences in both viral loads CD4 and cell counts were significant, irrespective of patients' antiretroviral therapy status [10]. A well-established link exists between another highly stressful condition – bereavement – and HIV disease progression, even in the pre-HAART (highly active antiretroviral therapy) era, when it could not have been associated with poor medication adherence [3].

A 2008 study evaluated 200 HIV+ men and women whose levels of stress were measured using questionnaire-based methods along with various markers of immune functions and disease progression. Perceived stress correlated significantly with increased viral load, decreased CD4 cell count, but also diminished Natural Killer (NK) cell count and increased cytotoxic (CD8) T-cell activation. The latter two findings were interpreted by authors as mediatory between stress and disease progression markers [11].

Using biological methods to quantify the load of stress on the organism provides insight into the nature of this relation. A study of 100 mothers living with HIV involved measuring a composite biomarker index (CBI), including levels of cortisol and catecholamines and other stress-influenced health indicators such as blood pressure, BMI and wait-to-hip ratio. CBI turned out to be a good predictor of CD4 cell count after controlling for age, years since diagnosis, prior CD4 cell counts and medication adherence. Authors, however, failed to provide detailed analysis of the correlations between individual elements of the provided CBI, which limits the field of interpretation. Using indices based on stress-related (or stress-influenced) biomarkers shows promise in research, as it aims at objectifying stress as a physiological response or, perhaps more accurately, a cumulative load of stress during prolonged periods of time. However, their relationship to stress, understood as a set of psychological and physiological responses may pose a conceptual and methodological challenge [12].

If there is a causal relationship between stress and poor disease prognosis, then perhaps by reducing stress the progression of the disease could be decelerated. Therefore, present research is focused on examining the role of stress-reducing interventions in improving the immune functions in PLWH. However, some authors conclude that the evidence for such effects are unconvincing. Scott-Scheldon et al. [13] claim in a meta-analysis (ranging in years 1989–2006) that although stress-reducing interventions have beneficial effects on anxiety, depression, psychological distress, fatigue, quality of life and possibly medication adherence in PLWH, they do not improve the immune functioning or hormonal mechanism that could influence immunity. The authors, nevertheless, note that these – unexpected to them – results could be attributed to the methodological flaws in the analyzed research that would not enable to detect less pronounced effects. In particular, most of the research was based on samples of patients already quite advanced in their disease, when the 'devastating' effects of HIV on the immune system could not be efficiently reversed [13].

In the last few years, however, a growing body of evidence has suggested that stress-reducing interventions may be beneficial to PLWH in terms of immune functioning, for example by using techniques involving mindfulness-based stress reduction (MBSR) [14]. MBSR is a popular approach to stress reduction evaluated extensively in literature in various clinical settings [15]. A study of 173 HIV+ Iranian patients who participated in 8-week MBSR reported that they experienced increases in CD4 cell count, although these effects were modest and transient. The patients also reported significant improvements in self-reported symptomatology compared to controls, which may suggest that the immune functioning may have improved in other ways [16]. Another, however smaller ($n = 21$), study indicated possible immune activation stabilization in PLWH who participated in Transcendental Meditation stress-reduction. However the positive effects on immune functioning seemed controversial this method clearly improved the quality of life of PLWH in the intervention group and improved their perceived symptomatology and vitality [17]. The problem with evaluating such research is that it is often lacking the description of various domains of patients' functioning that may be improved by stress reduction. For example, among stress-reducing methods, or perhaps – more accurately speaking – stress-reducing phenomena the researchers list: positive affect, finding meaning, positive coping, spirituality, emotional expressions, beneficial personality traits, self-efficacy, social support and altruism. All of these factors, clearly associated with improved stress-coping mechanisms, are cited as having positive effects on the quality of life and, probably, on the disease outcomes via various mechanisms [18].

Many authors claim that it is coping with stress instead of stress itself that is modulating the impact of potentially stressful life events on the disease progression. Such claims were made also based on animal models. In the continuation of his team's previous research [8], Capitanio aimed at observing the mediatory effect of personality traits on stress and SIV progression in macaques [19]. The researchers evaluated Sociability and proved that also in animal models personality traits may indeed modulate the effects of stress on disease progression by influencing stress-coping behaviors in a complex manner. The Sociability trait from the aforementioned research may be parallel to Extraversion [20] in the Five-Factor Model (FFM) of Personality developed by Costa and McCrae which is commonly used in psychological research on human personality [21]. Capitanio et al. concluded with a plausible explanation that most probably interaction between stressful events and personality lead to different coping mechanism that along with various other physiological factors may affect disease progression in animal models, which perhaps may be extrapolated to human research.

In psychology, it is widely accepted that personality traits influence both stress responses and coping strategies, making some people more prone to detrimental effects of stressful life events on health-related functioning and their own perception of well-being [22]. One such example is alexithymia, which may be defined as a stable personality trait associated with poor assimilation or recognition of own thoughts, feelings and emotions. Although in most cases researchers and clinicians view it as a disadvantage, alexithymia is not considered a psychopathology or psychiatric disease per se – more likely it is a trait which gives way to the development of other clinical conditions [23]. Research indicates