

Chapter 10

The Physical Burden of Immunoperception



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Abstract The previous chapter introduced the ImmunoEmotional Regulatory System (IMMERS). Also, there was a brief discussion about psychological states/psychiatric disorders that so far have been linked to the IMMERS. The present chapter considers another aspect of the IMMERS in which physiological states/physical diseases can be fit to the IMMERS.

Keywords Allergic rhinitis · Asthma · Autoimmune diseases · Cancer · Cardiovascular diseases · Emotion regulation · Emotion dysregulation · Hemodialysis · Human immunodeficiency virus · Immunoemotional regulatory system · Infection · Inflammatory bowel disease · metabolic syndrome · Neurological diseases · Physical diseases · Physiological states · Skin diseases · Sleep disorders · Stroke · Trauma · Vaccination

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The Physiological States/Physical Diseases Associated with the IMMERS

Allergic Rhinitis and Asthma

Evidence emerged supporting the notion that asthma-related characteristics are linked to various emotions [1]. This link is thought to be mediated by stress-induced corticotropin-releasing hormone (CRH) or related peptides followed by activation of mast cells and an inflammatory process in the airway [2, 3]. Interestingly, forced expiratory volume in 1 s (FEV1), which is an indicator of pulmonary function, was negatively correlated with emotional/mood states induced by videos, particularly negative ones, in asthmatic patients, but not in control subjects without asthma [4, 5]. Moreover, stress-induced situations led to reducing emotional expression in asthmatic children, but not in nonasthmatic ones [4, 5]. The regulation of both emotional and cognitive processing involves anterior cingulate cortex (ACC) (for review, see reference [6]). To investigate the influence of ER on the inflammatory response in asthmatic patients, Rosenkranz and colleagues (2005) enrolled all asthmatic patients into three inhalation challenges (saline, Meth, and Ag) and monitored them for lung function, inflammatory response, and the pattern of brain activity as evaluated using FEV1, the percentage of various immune cells, and functional brain imaging (fMRI), respectively. They demonstrated that throughout the duration of the late-phase response (6–8 hours), there was an increase in the percentage of eosinophils in the sputum sample among asthmatic patients who showed a greater signal change in the ACC and left insula produced by asthma-specific (As)-valence-neutral (Ne) words contrast [7]. Following LPS administration in nonstressed animals, alveolar macrophages produced all the cytokines studied, e.g., TNF- α , IL-1 β , and IL-6, in a dose-dependent biphasic manner as well as NO in a monophasic manner [8]. In stressed rats, LPS injection led to induce the levels of TNF- α and IL-1 β , but not IL-6, and to reduce NO levels [8]. These lines draw the significance of stress situations to alveolar macrophages (Table 10.1).

This influence of emotional problems is not limited to disease exacerbation, but it might become a constraint to routine functioning as well. Allergic rhinitis with or without asthma was demonstrated to associate significantly with “role limitations due to emotional problems,” which was measured using the short-form 36 health survey questionnaire (SF-36) [9].

Autoimmune Diseases (AIDs)

Patients with autoimmune disease (AIDs) commonly confront emotional problems. Moreover, emotional stressors and disorders are capable of causing AIDs. Therefore, emotional stressors have been well established as a potential trigger of some AIDs

Table 10.1 Physiological states/physical diseases associated with the immunoemotional regulatory system

Physiological states/physical diseases
Allergic rhinitis and asthma
Autoimmune diseases (e.g., systemic lupus erythematosus and multiple sclerosis)
Cardiovascular diseases
Cancer
Hemodialysis
Human immunodeficiency virus
Inflammatory bowel diseases
Infections
Neurological diseases
Obesity
Metabolic syndrome
Skin diseases
Sleep disturbances
Stroke
Traumatic injuries
Vaccination

such as pemphigus [10, 11]. Further, human studies provided evidence pointing to the increased development of emotional problems and EDR-related disorders in patients with various types of AIDs, such as SLE and multiple sclerosis (MS), in a disease state/severity-dependent manner [12–17]. For example, among patients with childhood-onset SLE, 95% manifest neuropsychiatric SLE (NSLE). Mood and anxiety disorders were the most common psychiatric conditions with the prevalence rate of 60% and 20% [13]. Even about 40% of patients with SLE without CNS manifestations suffer from psychological distress compared with 6% in controls. It is, thus, not surprising that both emotional coping and depressive symptoms were correlated with non-NSLE [14, 15]. Interestingly, there was an increased activation of the brain regions related to emotion regulation/processing (e.g., the amygdala and superior temporal) in SLE patients. However further analyses led to identifying this increased activity of emotional circuit as a consequence of CNS involvement by SLE [18]. Among patients with MS, emotional troubles were more than twofold more likely to occur in patients who had an exacerbation or progressive nonremitting MS compared to stable patients. This was reflected by an increased rate of using emotion-focused coping styles in patients with relapsing-remitting multiple sclerosis (RRMS) compared to stable patients [16, 17]. Mood disturbance was correlated negatively with sIL-2r levels and positively with joint pain in patients with RA [19]. Consistent with data from human studies, animal experiments have also supported the link between emotionality-related behaviors and AIDs. Clearly, AIDs result from IMMDR. Interestingly, the AIDs-related IMMDR has been observed in the specific brain regions associated with emotional

behaviors, particularly anxiety- and depressive-like behaviors [20]. In this manner, the link between AIDs and IMMERS is strengthened.

A high rate of increased emotionality and emotional-like behaviors in AIDs led to propose the term autoimmune-associated behavioral syndrome (AABS). Studies emphasize the pivotal role of cytokines and neuroendocrine factors in the pathogenesis of AABS [21]. B-cell-activating factor (BAFF) transgenic mice model, which is used as an experimental model of systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and Sjögren syndrome, exhibited an anxious phenotype along with the following changes in immune brain signaling, such as increased IgG titers in the hippocampus, hypothalamus, and cortex and increased CD68 (as a maker of activated microglia/macrophages) and GFAP (as a maker of activated astrocytes) immunoreactivity in the hippocampus in mice at 4.5–5 months of age, but not in young (2 months of age) mice [22]. EAE models of MS showed an increase in levels of IL-1 β and TNF- α in the hypothalamus. This indicates an inflammatory central basis behind anxiety- and depressive-like behaviors [20]. These emotional deficits were shown to display before the onset of MS [20, 23]. Consistently, behavioral problems usually manifest before symptoms of impaired cognitive and motor performance in dementia. Moreover, this model showed an early (at day 4) and a meaningful increase in circulating cytokine levels and CD3⁺ T cell counts. Of note, these inflammatory markers began to decrease in the periphery (at day 8) almost when their infiltration in the CNS (at day 10) started [23]. In the MRL-lpr model of AID, which is a well-documented model of emotional deficits [24, 25], a reduced preference to glucose, and as an index of emotionality, was detected in 5- to 6-week-old mice [26]. This deficit could be diminished by immunosuppressive treatment with cyclophosphamide and was pronounced by means of chronic administration of IL-6 [26].

Cardiovascular Diseases

Along with psychosocial stressors, either chronic and acute, and social network-related factors (i.e., social ties, social conflict, and social support), the experience of unpleasant emotions, including anger, depression, sadness, and stress, or, in general, extremely exciting emotions, often promptly, pulls susceptible individuals into a steep road leading to cardiovascular events, particularly ACS (for review see references [27–29]). For example, emotional stress is ranked as the second most common neuropsychological cause of acute myocardial infarction (AMI) owing to its record in approximately 40–50% of these patients [30, 31]. At the molecular levels, these patients have shown increased levels of the proinflammatory cytokines (e.g., TNF- α , IL-1, IL-2, IL-6, and IL-18) and decreased levels of the anti-inflammatory cytokine (IL-10). Thus, it is not surprising that the inflammatory response and respective cytokines are supposed as one of the possible mechanisms linking the experience of negative emotions or ER-related disorders and the progression of cardiovascular diseases, of course along with the neuroendocrine system and apoptosis signaling pathways [27, 30, 32–35]. It is to be noted that when patients with

cardiovascular diseases are stratified according to their emotional background, some cytokines are more highlighted than others, for example, TNF- α and IL-10, but not IL-6, considering depressive symptoms in CHF patients [35]. Cognitive reappraisal is found to correlate positively with the engagement of the lateral and prefrontal regions and inversely with the engagement of the amygdala and medial orbitofrontal cortex [36]. The role of the inflammatory cytokine IL-6 in the progression of cardiovascular diseases is widely appreciated [37]. Studies show that IL-6 is significantly involved in efforts to arbitrate between the sides of the relationship between the reappraisal-related activation of the dorsal anterior cingulate cortex and preclinical atherosclerosis (evaluated by carotid artery intima-media thickness and inter-adventitial diameter) in healthy individuals [38]. The Normative Aging Study carried out a 3-year follow-up study in older men (mean 60.3 ± 7.9 years). There was a dose-response relationship between negative emotions, evaluated by the Minnesota Multiphasic Personality Inventory (MMPI), and incidence of coronary heart disease (CHD) within the duration of the study ($p = 0.005$) [39]. Meanwhile, the circulating levels of IL-6 were positively associated with the reappraisal-related activation of the dorsal anterior cingulate cortex in healthy subjects [38]. However, higher reappraisals and suppressions were positively and inversely associated with the serum levels of CRP, respectively [40]. On the other hand, the reflection of watching the ice hockey match, as a real-life emotional excitement, on serum levels of endothelin-1 (ET-1) and IL-6 was more pronounced in spectators with coronary artery disease compared with healthy spectators [41].

Patients with type D personality display concurrently two absolute opposite, positive and negative, tendencies towards the experience and the expression of negative emotions by themselves and in front of other people, correspondingly. Meta-analysis studies and comprehensive literature reviews have revealed that this type of personality is positively associated with contracting cardiovascular conditions and their consequent mortality and morbidity, as well as with a constellation of non-cardiovascular complaints (for details, see [42–44]). Also, individual studies, either cross-sectional or follow-up, have provided evidence of increased levels of proinflammatory cytokine TNF- α and its receptors, sTNFR1 and sTNFR2 [45–48], an enhanced IL-6/IL-10 ratio, and decreased levels of anti-inflammatory cytokine, IL-10, in CHF patients with type D personality compared to those without type D personality [45]. Interestingly, in CHF patients, the inflammatory effect of type D personality appears to resemble closely the effect of aging. There was a similar increased pattern of sTNFR1 and sTNFR2 in younger CHF patients with type D personality and older patients without this personality trait [46].

Immunosenescence

Plasminogen activator inhibitor-1 (PAI-1) is a factor contributing to thrombosis-related cardiovascular diseases in elderly people. Both cytokines and hormones take part in the regulation of the gene expression of PAI-1 (for review, see

reference [49]). In a model of premature immunosenescence, mice were assigned to either fast or slow group if the amount of time taken to explore the first arm of the maze was ≤ 20 s or >20 s, correspondingly [50]. When compared to fast mice, slow mice expressed high emotional response to stress and had lower life span [50]. At the immunological levels, slow mice showed a reduction in proliferative response to concanavalin A (Con A) and related release of IL-2 and IL-1 β and NK cell activity, while increasing the production of TNF- α [50].

Cancer

An investigation on women who had to undergo breast biopsy indicated that this procedure should be considered as an emotional stressor if the final diagnosis is determined benign. In parallel with this emotional stress, the immune system prepares itself before the procedure and seeks for ways to prolong this preparation even 4 months after the procedure. This is a reflection of the joint regulation of our body by both the immune system and the emotional brain [51]. The immune system responds to this challenge by decreasing NK cell activity, decreasing production of IFN- γ , and increasing production of IL-4, IL-6, and IL-10 [51]. Further, there was a significantly positive relationship between mothers with breast cancer and their adult daughters on distress levels. This persuaded scientists to investigate the immune profile and its association with distress in daughters' group. Daughters' distress levels were inversely associated with IL-2, IL-12, and IFN- γ production and also with IL-2-induced natural cytotoxic activity (NCA) [52, 53]. Further, NCA activity and the production of Th1 cytokines were both negatively related to the emotional distress degree [53]. Antoni and his colleagues accomplished a genome-wide transcriptional analysis on leukocyte samples taken from women subject to the treatment of stage 0–III breast cancer and demonstrated that the negative affect, evaluated by the affects balance scale (ABS), was significantly associated with greater than 50% increased expression of leukocyte transcripts such as proinflammatory marker-related genes [54]. Another multiplex analysis on circulating concentration of 27 cytokines identified the IL-6 profile as the predictor of physical and cognitive functioning and also the vascular endothelial growth factor (VEGF) profile as the predictor of emotional functioning [55]. Further, the experience of childhood emotional neglect/abuse was associated with lower levels of NCA at the first evaluation after breast cancer surgery [56].

Emotional processing and expression (evaluated by emotional approach coping scale), respectively, tended to be inversely and positively correlated with plasma levels of IL-6, soluble TNF-receptor type 2 (sTNF-RII), and CRP in male patients with prostate cancer [57]. However, among those correlations, two of them, the correlations of emotional expression with IL-6 and CRP, were not found significant ($p < 0.10$) [57].

In vivo model of ultraviolet-B light-induced squamous cell carcinoma concluded that the high stress and anxiety levels can leave mice prone to the more

considerably progression of the tumor through increasing the expression of immunosuppressive (CCL2 and T regulatory cells) and angiogenic (VEGF: vascular endothelial growth factor) markers and decreasing the expression of antitumor immune markers (CTACK/CCL27, IL-12, and IFN- γ) [58]. On the other side, a peripheral tumor, by itself, could lead to a reduction in the hippocampal function, as reflected in increased depressive-like behaviors and memory impairment. This was, at least in part, underpinned by triggering an inflammatory process both in the hippocampus (\uparrow IL-1 β , \uparrow IL-6, \uparrow IL-10, and \uparrow TNF- α) and in the circulation (\uparrow IL-6, \uparrow IL-1 β , and \uparrow IL-10) [59, 60]. This process was found to be significantly strengthened in infection models compared to peripheral tumor models, explaining the presence and absence of the sickness state in these models, respectively [60].

Hemodialysis

Using Hospital Anxiety and Depression Scale (HADS) test, it was estimated that nearly half of patients with hemodialysis (HD) were in a depressive mood, which was significantly higher than what was reported for control group [61]. Also, there was a higher production of IL-6 in HD patients with anxiety (HADS \geq 8) than those without anxiety (HADS \leq 8) [61].

Human Immunodeficiency Virus (HIV)

At least one major psychiatric illness, particularly depression, affects greater than 60% of HIV patients [62]. By virtue of the fact that specific substances of abuse aggregate further the situation of HIV patients at the neuropathological level [62], the inverse correlation between affect regulation and regular substance motivates us to utilize ER as a therapeutic intervention in this population [63].

HIV patients encounter commonly with situations where the social self is threatened. This threat causes shame feelings, which have been associated with increased proinflammatory cytokines [64].

Inflammatory Bowel Diseases

Both emotional and environmental factors affect the gut [65]. Similar to that mentioned for asthma, this affect is mediated by CRF and similar neuropeptides and also by mucosal mast cells [65]. Immunoregulatory factors along with genetic and environmental factors contribute to the pathogenesis of inflammatory bowel disease (IBD). Patients with IBD confront various ER-related problems in their social

life in a disease severity-dependent manner, such as higher sensitivity to negative emotions, fewer dropping into bar/disco and delayed falling in love, and experiencing more depressive and anxious symptoms, not only compared to controls, but also compared to patients with other chronic conditions [66–70]. Neuroimaging studies have indicated a reduction in both the volume and the activation of brain regions related to emotional processing [71, 72]. The gray matter (GM) volume of both the frontal cortex and the anterior midcingulate cortex was reduced in patients with Crohn's disease (a type of IBD) compared to controls. More interestingly, disease duration was found to correlate with the GM volumes of some brain regions, importantly, limbic areas [71]. Also, patients with ulcerative colitis (another type of IBD) showed reduced activity, evaluated by BOLD signal, within the amygdala, thalamic regions, and cerebellar areas during the emotional visual task, compared to the control group [72].

Infections

For the first time in 1991, Cohen and his colleagues demonstrated that higher psychological stress is associated with lower resistance to respiratory viruses (rhinovirus type 2, 9, or 14, respiratory syncytial virus, or coronavirus type 229E) in a dose-response manner [73], while positive emotional style (PES), but not negative emotional style (NES), was found to correlate inversely with susceptibility to common cold and upper respiratory infections following exposure to rhinoviruses and influenza A virus in a dose-response manner [74, 75]. Various regression analyses showed that this correlation is independent of prechallenge virus-specific antibody, virus type, age, sex, education, race, body mass, season, and NES, optimism, extraversion, mastery, self-esteem, purpose, and self-reported health [74, 75]. By contrast, childhood socioeconomic status, as assessed by “the number of childhood years during which their parents owned their home,” was found to correspond negatively with both the risk of illness and infection and, in a word, with vulnerability to common colds [76]. This finding along with approximately the similar increased risk of common colds in “those whose parents did not own their home during their early life but did during adolescence” in “those whose parents never owned their home” [76] indicate that (a) the childhood period takes more impression of socioeconomic status of their family than other lifetime periods (e.g., adolescence) such that (b) it would influence the mind-body background of future life. Meanwhile, PES and NES were negatively and positively related to the subjective report of unfounded symptoms of common cold, respectively [74, 75].

However, the basal protein levels of all the investigated proinflammatory cytokines, e.g., IL-1 β , IL-6, and IL-8, were associated with illness symptoms/signs after exposure to rhinoviruses. However, IL-6 was the best cytokine which could predict nasal symptoms/signs [77]. Further, daily evaluation of emotional style and cytokine production in infected individuals on each one of 5 days after

exposure to rhinoviruses and influenza virus showed that the production of inflammatory cytokines including IL-6, IL-1 β , and TNF- α was negatively related to positive affect (PA) on that day or on the next day [78].

Neurological Diseases (NDs)

Neurological diseases including Parkinson's disease (PD) and Alzheimer's disease (AD) are accompanied by serious shortfalls in emotional processing in a severity-dependent manner. For example, patients with frontotemporal dementia (FTD) represent a poor recognition of several basic emotions, e.g., anger, sadness, disgust, fear, and contempt. Also, patients with the probable AD are more likely to fail to recognize fear and contempt compared with controls [79]. In patients with mild AD, the recognition of more basic emotions are missed, and they are less able to differentiate between some emotions, e.g., happiness and sadness [80]. Apathy in patients with AD was found to correlate positively with dysfunction in the prefrontal and anterior temporal regions [81]. Regarding memory recall, individuals with AD presented no preference to recall better emotional memories other than nonemotional ones, standing in stark contrast to healthy subjects, either young or older [82]. Experimental models provided evidence that there are deficits in the emotional memory performance in AD, which can be diminished by treatment with cytotoxic necrotizing factor 1 (CNF1) [83]. This pleasant effect of CNF1 was accompanied by a reduced IL-1 β expression in the hippocampus, along with other encouraging events, especially enhancing the energy amount evaluated by the ATP (Adenosine triphosphate) levels [83]. There is a spectrum of behavioral problems in patients with AD [84]. Agitation is the second most common behavior in AD, after apathy. It has been associated with cognitive impairment [84]. Inflammatory changes appear to pave the way for agitation. There were higher IL-1 β levels and decreased NK cell activity in both the morning and evening periods corresponding with preagitation and agitation phases of AD [85].

Even, Esterling and his colleagues demonstrated changes in the immune profile of AD patients' spousal caregivers, either former or current. There was a reduced response of enriched NK cells to either rIL-2 or rIFN- γ cytokines in patients' caregivers than controls [86]. Interestingly, this response was related positively to the emotional and tangible social support levels [86].

Obesity

Women with severe or morbid obesity had significantly increased levels of proinflammatory markers IL-6 and hsCRP in a BMI-dependent manner, which were closely related to anxiety and depression subscales of neuroticism, even after the BMI adjustment [87]. Since these patients had to undergo gastric surgery, these

markers were measured again after surgery. Interestingly, decreased levels of IL-6 and hsCRP were correlated with lower anxiety and depressive behaviors post-operation [87].

The long-term maternal exposure (4 weeks before mating and during pregnancy and lactation) to a high-fat diet (HFD) led to a decrease in the basal serum levels of CORT in offspring [88]. In addition, the steps toward normalizing the stress-induced CORT levels were made with the lower speed in long-term HFD-exposed offspring than standard chow diet (SD)-exposed offspring at the end of stress challenge [88]. Regarding inflammation-related markers, the increased expression of IL-6 and IL-1Ra in long-term HFD-exposed offspring than chow-exposed ones in the amygdala was found in both females and males [88], while changes in the expression of NF- κ B and I-kappa-B-alpha (IkBa) were observed only in female, but not in male, offspring [88]. Mice subjected to short-term (1–3 weeks) HFD also exhibited anxiety-like behaviors in addition to learning and memory impairments and had significantly higher levels of homovanillic acid—a metabolite of dopamine—in their hippocampus and cortex but without any alteration in the gene expression of inflammatory markers [89]. Further, chronic western diet (WD) intake led to the increased responsiveness to LPS, which was represented in higher and more prolonged protein/mRNA measures of IL-6 in both plasma and hypothalamus, while there was no significant difference in the plasma levels of other proinflammatory cytokines such as TNF- α , IL-1 β , and IFN- γ between WD and SD groups [90]. In parallel with the increased expression of IL-6, there was significantly increased mRNA expression of SOCS-3, which belonged to the suppressors-of-cytokine-signaling (SOCS) family of proteins, in the hypothalamus in WD than SD mice [90]. However, the LPS-induced mRNA expressions of TNF- α and IFN- γ in the hippocampus were significantly higher in WD than SD mice. Also, LPS augmented the levels of adipokines, e.g., CST, leptin, and resistin, more significantly in WD mice when compared with mice exposed to SD [90]. Altogether, both short-term and long-term obesity in either young adult or maternally can lead to display disturbed anxiety-like behaviors and impaired learning/memory, and brain inflammation might be one of the reasons behind these HFD-related events [88–91]. Chronologically, at first, learning/memory and then anxiety-like behaviors are impaired, and disturbance in depressive-like behaviors is subject to exposure to an immune challenge, such as LPS [90].

Metabolic Syndrome

A high age-adjusted prevalence rate of ~24% is estimated for metabolic syndrome (visceral obesity, dyslipidemia, hyperglycemia, and hypertension) in the United States [92]. Both ER- and EDR-related subscales have been associated with the metabolic syndrome factor [93]. Even, a disease pathway involving EDR can be proposed, which is triggered by low socioeconomic status (SES), followed with low reserve capacity for high negative emotions and eventuated in the metabolic syndrome factor [94].

Inflammation plays a major role in metabolic syndrome [95]. It has also been indicated that this role is not performed in the periphery merely, but a mice model of metabolic syndrome proved the presence of central inflammation (\uparrow TNF- α , \uparrow IL-1 β , and \uparrow IL-6) in the hippocampus, explaining the anxiety-like behavior in this model [96].

A possible pathogenic pathway for metabolic syndrome is initiated by emotional stress and ensuing enhancement in the levels of proinflammatory cytokines, e.g., IL-1, IL-6, and TNF- α . Then, these cytokines lead to increased levels of NGF, which in turn stimulates a series of cascades toward insulin resistance and finally resulting in diabetes mellitus (for review, see [97]).

Skin Diseases

Skin diseases are frequently associated with troubled ER, reflecting in problematic emotional expression. For instance, patients with psoriasis, who are more likely to be alexithymic, employ more control over negative emotions and more avoidance of emotional closeness and intimacy compared with controls [98]. It may explain the negative relationship between psoriasis symptoms and affective expression in a severity-dependent manner [99]. When patients with atopic dermatitis were compared to healthy controls, the effect of psychological stress on the various immune parameters, such as \uparrow eosinophil count, \uparrow CD8⁺/CD11⁺ and CLA⁺T cells, and \uparrow cytokines (IL-5 and IFN- γ), was significantly strengthened [100].

The route from EDR to IMMDR in acneogenesis has been explained elsewhere [101]. In summary, emotional distress would make sebocytes prone to the increased expression of receptors for CRH, melanocortins, b-endorphin, vasoactive intestinal polypeptide, neuropeptide Y, and calcitonin gene-related peptide, and then the production of proinflammatory cytokines are stimulated by means of these receptors and binding to their ligands.

Sleep Disturbances

This notion that sleep disturbances are, irrespective of their cause, seen as chronic stressors is supported by evidence at different levels, e.g., immunological, neuro-pathological, and neuroimaging studies (for review, see [102]).

To assess the effects of sleep and its efficiency on susceptibility to respiratory infections, Cohen and his colleagues conducted an investigation on healthy individuals and recorded at first their sleep duration and its efficiency within 14 consecutive days and then made them exposed to rhinoviruses, and after 5 days postchallenge, calculated the rate of clinical cold development [103]. This investigation indicated that those who had average sleep duration (ASD) \leq 7 hours were three times more susceptible to clinical cold than those with ASD \geq 8 hours.

Further, there was a 5.5-fold increased risk of clinical cold in individuals with sleep efficiency <92% compared to those with an efficiency of $\geq 98\%$.

Therefore, it is well expected that circadian arrhythmia has been associated with EDR-related parameters, e.g., decreased social motivation/functioning, decreased exploratory anxiety, and decreased emotional functioning [104, 105]. In a cancer population, the presence of circadian arrhythmia was associated with decreased levels of all the investigated cytokines, e.g., TNF- α , TGF- α , and IL-6 [105].

Stroke

Alexithymic patients were more likely to suffer from severe forms of stroke when compared with non-alexithymic patients. This alexithymia trait appears to contain an inflammatory component either as a cause or an effect [106]. Study of patients with a first-ever symptomatic ischemic stroke revealed that (a) the circulating levels of IL-18 were correlated positively with the severity of alexithymia, (b) stratification of patients made this correlation more statistically significant in those who had right hemisphere lesions, and (c) these increased IL-18 levels were pronounced in alexithymic (TAS-20 score 61) than non-alexithymic patients [106].

Traumatic Injuries

In patients hospitalized for orthopedic injuries, the use of emotion-focused coping was found to correlate positively with the levels of proinflammatory cytokines, IL-6 and IL-8, whereas it was negatively correlated with TGF- β levels [107].

Vaccination

Compared with controls who received placebo, circulating levels of cytokines, in particular, IL-6, were increased at 3 hours after the first-ever typhoid vaccination. It coincided with significant mood impairment [108, 109]. It has been elucidated that when subjects perform psychological tasks (i.e., stress condition) after injection, the IL-6 response is inversely related to optimism in either the Typhim Vi typhoid vaccine or saline placebo group [110].

In response to the implicit emotional face perception task, there was an increased activity in the subgenual anterior cingulate cortex (sACC) along with reduced functional connectivity between sACC and reduced activity within the anterior rostral medial prefrontal cortex (arMPFC), MNI coordinates, nucleus accumbens, right amygdala, STS, and FFAs. These changes were observed in inflammation-associated mood change compared to the placebo group [108].

Conclusions

Chapter 10 presented evidence supporting the notion that there are a variety of psychological states/psychiatric diseases where the immune responses, as well as the emotion regulation, are impaired. This chapter provided evidence linking physiological states/physical diseases to the impairment of both the immune system and emotion regulation. Altogether, the immunoemotional regulatory system (IMMERS) covers both psychological states/psychiatric diseases and physiological states/physical diseases. Inevitably, such a system must comprise both the immune mediators and the neuroendocrine messengers, which will be discussed in the next chapter.

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