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Mini Review

Non-Adherence in Transplantation: Toward A Biological Explanation

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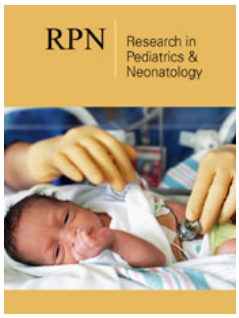

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Abstract

Non-Adherence (NA) to medical regimen after transplantation remains as the leading cause of graft loss. The adolescents and young adults are at higher risk for NA than adults. It has been stressed the multi-factorial nature of NA, however biological mechanisms of NA have not been investigated. Adverse Childhood Experiences (ACE) are related to short and long-term negative physical and mental health consequences among children and adults, more over depression in adolescents and adults observed in chronic kidney disease and after transplantation are characterized by cell-mediated immune activation and inflammation. This article examines the current literature regarding each of these factors, proposes a biological hypothesis for NA and gives suggestions for the prevention of ACE, depression and therefore of the NA.

Keywords: Adherence; Transplantation; Depression; Adverse Childhood Experiences(ACE)

Abbreviations: ACE: Adverse Childhood Experiences; CKD: Chronic Kidney Disease; HPA: Hypothalamic-Pituitary-Adrenal; IDO: Indoleamine-2,3-Dioxygenase; IL: Interleukin; INF: Interferon; NA: Non-Adherence; Stnf: Soluble Tumor Necrosis Factor; sTNFR: Soluble Tumor Necrosis Factor Receptor; TCMR: T cell Mediated Rejection; TNF: Tumor Necrosis Factor.

Introduction

NA to immunosuppressive therapy increases the risk for adverse outcomes after kidney transplant. Among children, adherence depends on their parents because they are not capable of maintaining a strict adherence. NA in the pediatric population is 37%, but it is higher among adolescents and young adults (48%) [1] than older adults (36%). The causes of NA among youth include forgetfulness (29%-56%) or organizational problems (58%), but in most cases, NA is unintentional [2]. However, these patients know that not taking immunosuppressive medication implies the loss of the transplanted organ, and in some cases their life.

Although NA is the result of multiple factors, personal factors and the fact that NA is unintentional suggest that neuropsychological factors play a role in these patients. Moreover, NA among adolescents and young adults suggests an alteration in mental health. ACE [3] in early life and long before transplant, namely exposures such as neglect, abuse, alterations in attachment, low socio-economic status, chronic disease, caregiver mental illness, family or community violence predict poorer long-term outcomes across health and social domains. Therefore, is it possible that the history of ACE in early life could be related to NA behavior after organ transplantation? The objective of this article is to provide a view of NA related: to physiopathology of ACE, chronic stress and the role of cytokines and inflammation in depression, suicidal behavior, in CKD and transplant patients and discuss a biological hypothesis on NA, that may account for part of NA patients.

Methods

This mini review provides a synthesis of literature on ACE, depression, suicidal behavior, chronic stress in CKD, and their relationship with inflammation.

ACE in early life

ACE cause three levels of "programming" in children or adolescents:

Immunological, neurological and endocrine changes: Children with ACE show higher inflammatory activity (increased fibrinogen, C-reactive protein, E-selectin) [4] and increased nuclear factor κβ activity, which regulates the expression of proinflammatory cytokine genes [5]. Chronic stress during childhood program a proinflammatory phenotype of Th1 cells and mast cells/macrophages. Patients with depression who have suffered ACE during childhood have increased proinflammatory cytokine levels: IL-6, IFN-γ, IL-Iβ, IL-2, IL-8, and reduced anti-inflammatory cytokine levels: IL-4, IL-10 [6]. In addition, ACE activate the HPA axis and the autonomic nervous system [7]. Through the hypothalamus, cytokines activate the HPA axis, and cortisol, epinephrine, and norepinephrine are released. These hormones increase the inflammatory response of monocytes and the release of proinflammatory cytokines. The parasympathetic nervous system produces a cholinergic release, with an inflammatory action. Moreover, oxytocin, a hypothalamic neuropeptide involved in feelings of love, truth, justice, attachment and safety, is reduced in the presence of ACE [4].

Brain changes: ACE cause anatomic changes in children younger than 16 years: reduced amygdala, hippocampus, and prefrontal cortex size. HPA axis hyperactivity has been associated with reductions in these brain areas [8]. The consequences include alterations in corticolimbic and corticostriatal connectivity. These reduce the emotional regulation capacity and increase the reaction to threats.

Epigenetic changes: ACE cause DNA methylation in the genes related to immune regulation in human beings. The hypermethylation of glucocorticoid receptor-related genes results in a reduced expression and HPA axis hyperactivity [9].

We may imagine the primitive "Homo sapiens": from the moment they woke up, they were surrounded by stressful situations, were alert, scared of being attacked by others or animals, had to figure out how to get food, could not think about the following day or the future, and had an activated immune system to cure their wounds or infections. Their lives were not long. Over time, human beings evolved in personal and social terms. The "programming" to which they were exposed is buffered by resilience (family and social support, partner quality). However, those human beings exposed to ACE will be strongly sensitive to future stressful situations (diagnosis of a chronic disease, loss of a loved one, family tragedy, dire socioeconomic situation); this results in psychological (depression/anxiety) and physiological (immunological, neurological and endocrinological) alterations, which will predispose them to adult diseases [3,10].

Depression, is characterized by an inflammatory state with activation of cell-mediated immunity [6]. As an expression of inflammatory activity, IL-6,11 INF-γ, TCMR-1 or sTNFR-2 levels are increased. It is interesting that INF-α immunotherapy is associated with 30-50% of depression symptoms [11]. Moreover, antidepressants have anti-inflammatory effects by suppressing the production of IL-2, INF-γ, IL-Iβ, and TNF-α [12].

Proinflammatory cytokines, particularly IL-6, induce IDO, which in turn induces tryptophan depletion and an increase of kynurenic and xanthurenic acids, which are associated with depression symptoms [13]. Treatment with antidepressants acting on tryptophan metabolism improve depression symptoms. Suicide encompasses three stages: suicidal ideation, suicidal behavior or action, and suicide. Similar to what we see in depression, immune and hormonal dysregulation affect the risk of suicide. High IL-6 levels have been observed in blood, cerebro-spinal fluid, and brain of suicide victims. In addition, HPA hyperactivity has been associated with suicidal behavior [14].

HPA Axis in Patients with CKD, Cytokines, Inflammation, and Depression in Solid Organ Transplant Recipients

The HPA axis was studied in a group of young patients receiving chronic hemodialysis [15]. Findings were that 100% of patients had high serum cortisol levels. Cortisol levels responded to the exogenous administration of adenocorticotropic hormone, but there was no suppression with the administration of dexamethasone, thus indicating partial resistance. Such endocrine profile has been observed in patients with depression, and chronic stress.

Cytokines play a critical role as effector mechanisms on graft rejection. To mimic this situation in vivo, we measured the secretion of cytokines related to Th1 cells (INF-γ and TNF-α), Th2 cells (IL-10) in the supernatant of mixed lymphocyte culture stimulated with third-party lymphocytes. In pediatric patients with kidney or liver transplant and without graft rejection, proinflammatory cytokine levels were normal, except for IL-10, which was high. However, when patients developed graft rejection, INF-γ and TNF-α were high [16]. The levels of IL-10, related to the role of limiting rejection remained high, with an inhibitory action on Th1 cells.

Among adult transplant recipients, 63% have depression in the first years after the transplantation, contrary to the 3% observed in the general population. Moreover, depression was associated with a 65% risk for mortality and a 66% risk for graft loss [17]. Although no studies have been conducted about the impact of depression on graft progression in pediatric transplant recipients, it has been reported that NA is related to psychological distress [1]. Among school children with moderate CKD and young adults admitted to transplant waiting lists, depression was observed in 7% and 22.8%, respectively [18,19]. Recently, it has been observed that individuals with stress-related diseases had a high risk for CKD progression and acute kidney injury, compared to a control group [20]. This suggests that alterations in mental health caused by stress lead to immunological, neurological, endocrine, and psychological stimulation and kidney damage.

Toward a Possible Biological Explanation of NA

Based on the studies mentioned above, the changes caused by ACE in children and adolescents, the chronic stress of patients with CKD, and the acute stress of daily life in patients who already have chronic stress, we developed the hypothesis that in some patients, especially in pediatrics, may be a biological explanation of NA (Figure 1).

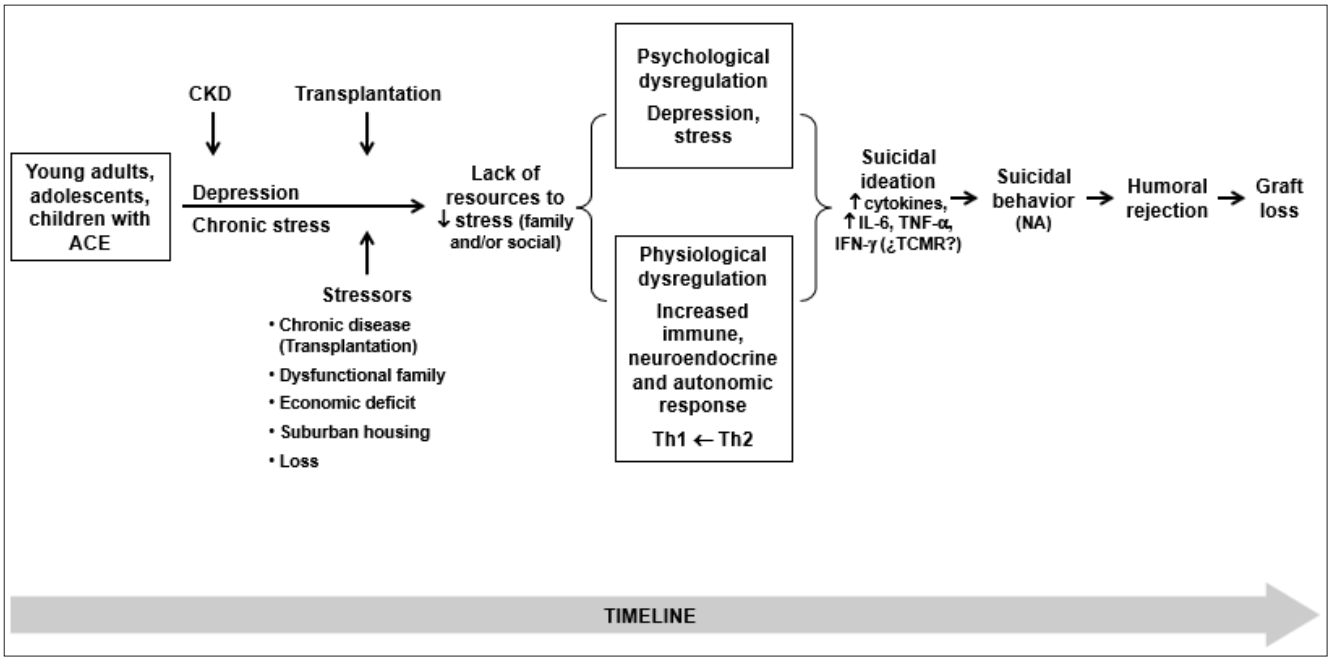

Figure 1: Biological hypothesis of NA.

Our pediatric patients who suffer ACE early in their life and all patients with chronic stress/depression due to their CKD will be more susceptible to new stressful situations (transplant, new disease, dysfunctional family, socioeconomic difficulties, loss, long distance from the transplant center). If they lack the resources to reduce and counterbalance such situations (social, family, and personal factors), they will suffer psychological and physiological dysregulation, with activation of the immune system. This is followed by the release of proinflammatory cytokines (IL-6, IFN-γ, TNF-α), the activation of the IDO pathway (reduced tryptophan), and the onset of psychiatric symptoms: suicidal ideation and possibly TCMR, followed by suicidal action (stop taking the medication) and, therefore, humoral rejection and graft loss. This reasoning suggests that NA may be treated with antidepressants in addition to psychotherapy.

In summary, according to this hypothesis, children, adolescents, and young adults who have suffered ACE in early life and have CKD and, therefore, chronic stress/depression, and receive a transplant, are at a higher risk for immune system dysregulation because they are more psychologically and physiologically sensitive to stress, especially if they lack a favorable social and family context. ACE in pediatric transplant recipients may account for a higher NA compared to the adult population, who may probably have a greater ability to deal with stress.

This perspective poses several limitations, which may be addressed in future research:

A. psychiatric assessments since the diagnosis of CKD, upon admission to dialysis, and before and after transplantation,

B. frequent psychological controls during the course of the disease, with assessment of symptoms and signs of depression,

C. immune markers that indicate their alteration and predict NA ideation.

To conclude, psychosocial factors are the most important predictors of NA. In addition, primary, secondary, and tertiary prevention measures should be put into place. That is to say, prevention of ACE, chronic stress, and depression; reduction of their consequences; and, lastly, management in all age groups before, during, and after transplantation.

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