

Current views of depressive disorders in children – a review

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Abstract. – OBJECTIVE: Depression is one of the most debilitating worldwide mental illnesses, which is included in the Diagnostic and Statistical Manual of Mental Disorders. The main risk factors for the development of depression are female gender, early life stress family history of mood disorders, former anxiety disorders, substance abuse and life events. The present review article is focused on the various causative factors like childhood early life stress, cortisol or cortisol awakening response. The review would update readers with regards to the current view of factors responsible for pediatric depression, which in turn helps to plan better therapeutic approaches in the near future.

Key Words:

Depression, Children, Mental illness.

Introduction

Depression is a form of mental illness involving a core feature of persistent low mood and/or anhedonia¹. People who have five or more of these following symptoms over a two-weeks period are recognized as having major depressive disorder (MDD): depressed mood for most of the day, anhedonia, significant weight loss, insomnia or hypersomnia, psychomotor agitation or retardation, loss of energy or fatigue, feeling guilt, poor concentration or having no ability to make a decision, and repetitive suicide thoughts. Social or occupational aspects of a person's life must be impaired, and there must not be any relation to the physiological effects of substances or a medical condition. Further, depressed mood, anhedonia and reduced energy are the three core symptoms that should be kept in mind while diagnosing depression².

Longitudinal Course of Major Depressive Disorder

A large number of studies have shown that the average age of the onset of depression is in

late adolescence or emerging adulthood, although this varies between studies³. MDD is a recurrent disorder and around 45% of adolescents who experienced an episode of depression suffered a second episode before the age of 24^{4,5}. Moreover, Rohde et al⁶ conducted a work in MDD patients about incidence, recurrence, gender, comorbidity, duration, and suicide attempts during childhood (age 5-12.9 years), using the data from 816 participants (56% female). They found that around 50% of adolescents had a second episode by the age of 30, reinforcing the recurrent nature of depression. Regarding treatment, a substantial minority of MDD patients does not respond to initial treatment, and are defined as having treatment resistant depression (TRD). In the short term, TRD patients have greater tendencies to be recurrent⁷. Specifically, Rush et al⁸ showed that more than 80% of those who followed up after a response to treatment relapsed within a year. Moreover, the duration of depressive episodes varies substantially between subjects and the average time of recovery varies from 5 to 13 months⁴.

Treatment of Major Depressive Disorder

Several forms of treatment are used for MDD. While antidepressants and psychotherapies are the main treatments, stimulation treatments including transcranial magnetic stimulation, deep brain stimulation, vagus nerve stimulation and electroconvulsive therapy represent other more rarely used treatment options. In association with this, recently, Ketamine has been used for the treatment of depression. It is of the noted combinations of treatments that may be more efficacious than monotherapies; for example, Nemeroff et al⁹ demonstrated that antidepressants and psychotherapies have broadly equivalent effectiveness, but remission rates are higher when using both treatments in combination. There is little evidence suggesting preferential efficacy of individual antidepressants for the treatment of depression among all subjects¹⁰. Moreover, there

are more than 7 classes of antidepressant being used worldwide in clinical settings¹¹. Notably, one meta-analysis by Cipriani et al¹² assessed the effects of 12 new-generation antidepressants on MDD. The results suggested that, for the initial treatment of moderate to severe MDD in adults, Sertraline could be the best choice, balancing efficacy against adverse effects.

Early Life Stress- One of the Main Contributors of Depression in Children

Child abuse is a serious social problem and is a complex global phenomenon, which does not respect boundaries of class, nationality, race, religion, age, or educational level and could happen both publicly and privately¹³. The consequences of child abuse might include biological, physiological, behavioral and cognitive dysfunction. It has been argued that child abuse could be a specific risk factor for psychiatric disorders such as unipolar depression. Rates of depression in adulthood are higher in those who have experienced child abuse. In a health maintenance organization (HMO) population, a dose-response association between the number of childhood abuse experiences and the presence of a recent-in the past year- depressive episode or lifetime chronic depression has been observed¹⁴. Heim et al¹⁵ argued that the underlying mechanism of the higher risk of depression in the subjects that experienced early life stress could be due to persistent changes in corticotropin-releasing hormone-mediated (CRH-mediated) stress¹⁶. Furthermore, increase in the concentrations of CRH in cerebrospinal fluid (CSF) has been observed to be an important contributor for MDD in children. Some clinical studies suggested that childhood abuse could contribute to CRH and Hypothalamus-Pituitary-Adrenal (HPA) axis changes observed in depressed patients¹⁶. The exact prevalence of child abuse is unclear for a variety of reasons, but estimates vary from 25% to 45%¹⁵. Considering the definition of early childhood experiences that is a broad concept, the four main types of early life stress include: emotional abuse, physical abuse, sexual abuse, and neglect (physical and emotional)¹³.

HPA Axis, Cortisol and Depression

The HPA axis is one of the most crucial endocrine systems of the body and is one of the main biological systems involved in the stress response. The endocrine system plays an important role in the integration and regulation of several functions of the body and is functionally integrated with

the nervous as well as circulatory system. CRH is released from the paraventricular nucleus of hypothalamus (PVN) into the portal venous circulation in response to stress. CRH has the major role in stimulating the synthesis of proopiomelanocortin (POMC) by the corticotroph cells, which is the precursor of Adrenocorticotrophic hormone (ACTH) subsequently released from the anterior pituitary cells. Therefore, three main roles of CRH are the stimulation of the POMC transcription, ACTH biogenesis and stimulation of the ACTH release. Increasing ACTH release activates glucocorticoid secretion from the adrenal cortex, which is the final part of the HPA axis. The adrenal cortex has the main role in cortisol production. Cortisol has been supposed to have a crucial role in the onset and course of MDD, but its exact role is still not clearly confirmed. The optimal level of cortisol is not clear, which raises more doubts around reaching a conclusion about the exact role of cortisol¹⁷. It has been assumed that the optimal range of cortisol is not the same for all individuals. Cortisol could be characterized in terms of absolute levels, or as the shape or amplitude of the cortisol rhythm over 24 h. The normal range values for each of these might vary depending on subjects' circumstances. The cortisol awakening response (CAR) has been increasingly researched, and found to be a reliable and useful measurement of HPA axis activity. Assessing the cortisol awakening response is not an invasive test, and is now often used for capturing information about stress reactivity in numerous studies¹⁸.

Cortisol Awakening Response (CAR) and Depression

The cortisol awakening response (CAR) is a rapid increase in the cortisol level within the first hour after awakening¹⁹. The CAR is a genuine response to awakening and is distinct from the 24 h diurnal cortisol profile²⁰. During the CAR phase, cortisol concentration increases to a variable extent compared to the cortisol level at the awakening time, reaching its highest point between 30-45 min after awakening. Adam et al¹⁸ found that on adolescents aged 16 to 18 years the CAR is an important prospective predictor of MDD. In detail, salivary cortisol was collected six times during a 24-h period over three consecutive weekdays. The outcome of the study showed that the increased CAR might be a predictive factor for both onset and recurrence of MDD. However, further research is required to know more about the CAR and its function.

The Reliability of the CAR

The CAR is recognized as a reliable index of HPA axis activity²¹. In particular, assessment of the CAR is a non-invasive test and is a useful way of capturing information about stress reactivity²². However, it has been argued that the reliability of calculating the CAR is increased when CAR assessments were done consecutively over 48 h²³. Moreover, the CAR has been widely investigated either in healthy subjects, or in association with cardiovascular, autoimmune, atopic, allergic, and psychiatric diseases¹⁹.

Functions and Regulation of the CAR

The functions of the CAR are not yet fully clarified. It seems that it is associated with anticipation of the demand of the day ahead, supported by evidence showing that the CAR is higher on weekdays compared to weekends. Thus, numerous studies have observed a higher CAR during weekdays²⁴. The CAR might show changes in association with stress levels along with feelings of happiness²³. It might also play a role as an adaptive response²⁵. Both the limbic system and the prefrontal cortex are involved in the regulation of the CAR. The other part of the brain that could influence the CAR is the suprachiasmatic nucleus (SCN)²⁴.

Factors Affecting the CAR

Previous studies have shown that several factors might influence CAR, although there have been inconsistent outcomes about these factors. Age and gender are important factors that should be considered. Some studies²⁶ have found an impact of age on the CAR. In regards to gender, some studies have found that women have a larger CAR compared to men²⁷. An association between Body Mass Index (BMI) and elevated cortisol levels was recently reported²⁸. Furthermore, Therrien et al²⁹ assessed the CAR in obese and reduced obese- men and women. The results showed that men with visceral obesity showed an increased cortisol response. In particular men with visceral obesity showed an increased cortisol, whereas this response tends to return to normal in a reduced obese state. Reduced obesity in women presented a significantly higher CAR compared with lean subjects, but there was no difference in this variable between lean and obese subjects. No gender difference was observed in CAR between lean men and lean women. Further, stress is the key factor

that could affect the CAR. For example, there is an association between chronic overload and increased CAR³⁰.

Lifestyle, CAR and Depression

Smoking and alcohol consumption have been observed to be responsible for the development of depression by affecting CAR production. Mixed results were reported about the effects of smoking on the CAR. Badrick et al³¹ showed that smoking status is related to the elevated CAR, but had short-term effect on the neuroendocrine system. Junghanns et al³² pointed out that there is an association between alcohol consumption and CAR. In particular, heavy drinkers have higher CAR.

Conclusions

Multiple factors are responsible for the development of depression in pediatric patients. Of these, early child hood stress, cortisol and cortisol awakening response are the prominent ones. Future studies focused on these factors could help in the better treatment planning for the affected patients.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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