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EDITORIAL

Depression in late life: Linking the immunometabolic dysregulation with clinical features

Depresión en la edad anciana: conectando el perfil fenotípico con la desregulación inmunometabólica

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Depression is the most prevalent psychiatric condition in old age and one of the main causes of disability. Over 15% of older adults may suffer a major depression episode throughout their late life.[1] Prevalence rates may be even higher when a symptom-based approach (e.g., episodes of clinically relevant depression symptoms) is taken.[2,3] Finally, increased mortality and disease burden are associated with late-life depression, even from its earlier (subthreshold) statuses.[4] Epidemiological projections are quite discouraging and point to a steeper increase of depression incidence in next decades, with enduring phenotypes. The challenging times we live due to the COVID-19 pandemic will definitely contribute to this dreadful scenario.

Depression may lead to intense emotional distress and poorer wellbeing, beyond the typical adjustment to highly stressful events facing over the late life (e.g., widowhood, life after work retirement). In fact, the impact of late-life depression seems to be more dramatic than expected. Depression endophenotypes (i.e., internal mechanisms connecting genetic vulnerabilities and elusive disease process) may decisively contribute to depression development and symptom aggravation due to the initiation of pathophysiological cascades (e.g., changes in frontolimbic connectivity, increased glucocorticoid resistance), with substantial impact across varying regulatory systems.[5–7] For instance, it is well known that late-life depression may put individuals at higher risk of neurodegenerative disease development. In this sense, an overproduction of glucocorticoid agents and arginine vasopressin signalling alterations (associated with increased cardiovascular risk) have been commonly found among depressive older adults. The related changes in regulatory pathways may lead to ischaemic vascular damage and glucocorticoid neurotoxicity, both associated with key precipitating factors of dementia disorders, such as loss of hippocampal volume and increased levels of amyloid plaques.[8]

Late-life depression seems therefore to work under the influence of particular control mechanisms, in terms of disease evolution and symptom expression. First, depression tends to become chronic in old age. In this regard, it is likely an adult with a history of depression episodes (also applicable to episodes of clinically relevant depressive symptoms) across their life to present a new episode (or multiple episodes) in late life. Conversely, the probability to show a first episode of depression in the old age is quite lower and highly related to adverse cardiovascular or neurological events.[9 (pp. 248–281),10] Moreover, depression may be featured by more somatic symptoms in the old age

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than earlier in life (e.g., agitation, insomnia, gastrointestinal symptoms, weight loss).[11] In addition, a closer attention should be paid on some depression-related symptoms (e.g., passive suicidal ideation) and problematic symptom profiles (e.g., mainly featured by excessive hypochondriasis and elevated anhedonia) in old age.[12,13] Ageing-related processes (e.g., increasing cytokine production, brain grey matter volume loss in hippocampus), in conjunction with a subjective sense of being physically and mentally frail, may be behind the characteristic presentations of depression in late life.[14,15] Finally, factors associated with social engagement and participation (e.g., feelings of loneliness, perceived social support) may be decisive for depression development in old age.[16]

The pernicious relationship between depression and metabolic syndrome

It is very common older people to deal with varying co-occurring mental and physical diseases on a daily basis. In this vein, an important proportion of people (almost one in four people) with depression may show a comorbid chronic disease (e.g., arthritis, cardiovascular conditions, diabetes, high cholesterol) during their late life.[17,18] Numerous studies point to bidirectional relationships between late-life depression and chronic diseases, especially those related to metabolic processes. For instance, chronic conditions may be a key risk factor for depression onset and symptom aggravation in old age.[19,20] From a longitudinal point of view, a course of elevated depressive symptoms may be associated with altered markers of metabolic function, such as increased levels of triglycerides, blood sugar and adiposity; as well as diminished high-density cholesterol levels.[21,22] Evidence is mixed regarding the relationship between either adverse cardiovascular events (e.g., stroke) or cardiovascular chronic diseases (e.g., hypertension), and late-life depression. Some moderating factors (e.g., gender, the co-occurrence of other metabolic syndromes) seem to play a relevant role in such a relationship.[23,24] On the other hand, depression may contribute to the onset of chronic disorders, as it promotes unhealthy life styles (e.g., sedentary routines, alcohol drinking and smoking) at a behavioural level; and triggers metabolic dysregulation as well as alterations in energy-regulating signalling.

The metabolic disease which has been studied the most is type 2 diabetes. Mounting evidence has proven diabetes to be influential in late-life depression onset. Robust evidence suggests that older individuals with depression may show higher insulin resistance than healthy controls.[20] A mechanistic candidate connecting depression and diabetes may involve stress hormones. In this regard, alterations in the regular activity of the hypothalamus-pituitary-adrenals (HPA) axis may be responsible for the high comorbidity between depression and type 2 diabetes seen across studies. It is well known that older patients with depressive symptoms often show elevated levels of basal cortisol and a flatter releasing curve over the course of the day.[25] Moreover, variation in genes that encode glucocorticoid and mineralocorticoid receptors have been shown among depressive patients. Consequently, increased levels of circulating glucocorticoids have been shown as well as impaired receptor function (i.e., receptor hyposensitivity). The overproduction of glucocorticoid agents and reduced glucocorticoid resistance may initiate pathophysiological cascades that alter regular metabolism (e.g., elevated levels of visceral adiposity, lipolysis with free fatty acid release, decreasing insulin secretion, increasing hepatic glucose production and dysfunctional insulin receptors). Besides, alterations in the inflammatory response have also been derived from HPA dysregulation (i.e., increased cytokine release). Cytokines are involved in the HPA regulation by means of negative feedback loops. In addition, these inflammatory factors are involved in the neurodegenerative response by inducing increased apoptosis by astrocytes.[6,26]

On the other hand, robust evidence points that obesity may constitute a major contributor of depression onset and symptom aggravation. Even though the relationship between depression and obesity seems to be bidirectional. First, depression may put individuals at higher risk of obesity as some of its behavioural precipitating factors (e.g., unhealthy life styles and fatty food preference) have been associated with depression symptomatology (e.g., anhedonia, lack of energy).[17] Second, the overproduction of glucocorticoid agents (a main neurobiological feature of the depressive syndrome) may lead to higher levels of visceral adiposity, as aforementioned. Finally, alterations in leptin signalling (i.e., a hormone involved in appetite regulation) have been shown among depressive patients.[27,28]

It is worth noting the distinctive role of obesity among the metabolic syndrome factors. In this regards, Jokela et al.[29] conducted an interesting meta-analysis (pooled $N \approx 30{,}000$ participants) to evaluate the relationship between metabolic profiles and depressive symptoms. As a result, they found that metabolically healthy obesity (i.e., a condition featured by showing obesity and no more than one additional metabolic risk factor) put individuals at meaningful risk of elevated depression symptoms ($OR = 1.29$, $CI_{95} = 1.12,\ 1.50$). The risk grew linearly with every additional metabolic risk factor. Moreover, individuals showing a metabolically unhealthy obesity profile (i.e., obesity plus two or more metabolic risk factors) obtained the most elevated risk for depressive symptoms ($OR = 1.71,\ CI_{95} = 1.40$, 2.09). Conversely, metabolically unhealthy non-obesity profile showed risk rates quite similar to metabolically healthy obesity ($OR = 1.31,\ CI_{95} = 1.16,\ 1.48$). More recently, large-cohort studies have provided mixed evidence about the higher risk of increased depression symptoms in metabolically unhealthy obese adults.[30,31] In this regard, alterations in the inflammatory response should be considered as its relationship with obesity and depression is far from evident.

It is also important to mention the dyslipidemic syndrome. Dyslipidemia (i.e., elevated concentrations of triglycerides as well as low high-density lipoprotein cholesterol) have decisively been related to depression in late life. Dyslipidemia involves metabolic alterations in energy homeostasis and higher risk of cardiovascular disease. Some studies have associated dyslipidemia with more severe depression presentations as well as higher risk of dementia.[32] An unregulated inflammatory response seems to mediate the dyslipemia impact on late-life depression.

An inflammatory path remains open

Some authors conceptualise depression as a part of the defensive response from the organism. From this standpoint, depression comprises a variety of behavioural repertoires that helps the immune system combat existing infections and reduce pathogen exposure.[33] In this regard, robust evidence points that depression and systemic inflammatory response share a common genetic liability. Moreover, neurochemical pathways involved in mood regulation (e.g., dopamine, serotonin and glutamate signalling systems) may also play a relevant role in inflammatory response modulation. Finally, some depressive symptoms (the so-called sickness behaviours) seem to play a protective role in terms of fighting against external attacks and pathogen entry restriction (e.g., anorexia, insomnia, irritability, hypervigilance). Moreover, some cytokine families (e.g., tumour necrosis factor alfa [TNFα]) are involved in regulation of varying cerebral systems (e.g., motivational system, appetite and satiety or mood) by activating the kynurenine pathway and altering glucose cerebral metabolism.[34]

Some evidence supports that late-life depression is associated with heightened inflammatory response. In this sense, increased levels of circulating cytokines and low-grade inflammation agents have been observed among depressive patients.[35] Inflammation may be of particular interest in older age due to the ageing-related imbalance between inflammatory and anti-inflammatory response. Consequently, a low-grade chronic pro-inflammatory status becomes predominant in late life.[15] This may predispose individuals to develop varying diseases throughout the late life (e.g., metabolic diseases, kidney disease). In turn, this predisposition may play a relevant role in depression episode emergence, especially in older adults with a history of previous depressive episodes.[10]

Alterations in the inflammatory response have been observed among older adults with depression. Low-grade systemic inflammation (e.g., circulating levels of fibrinogen and c-reactive protein) may be upregulated in acute stages of late-life depression and over a heightened course of depression symptoms.[33] Moreover, cytokine overproduction is associated with depression in old age.[35] Inflammatory response dysregulation is also evident in subthreshold depressive statuses. A recent study using a large cohort of community-dwelling older adults stressed an altered inflammatory profile in individuals with a course of heightened depressive symptoms over a 10-year follow-up.[21] Dysregulation in inflammatory response was also present in participants showing a subclinical course of increasing depressive symptoms towards reaching the level of clinical meaningfulness.

Elevated inflammatory levels have been associated with worse treatment prognosis and symptom aggravation in depressive patients. Numerous anti-inflammatory drugs have been used to tackle depression (e.g., selective and non-selective inhibitors of cyclooxygenases, such as celecoxib or naproxen; cytokine inhibitors, such as ustekinumab; or statins).[36,37] The rationale to deliver these types of agents is because of its inhibiting effect on the production of mediators involved in the pro-inflammatory signalling pathway. In this sense, anti-inflammatory drugs seemed to be promising treatments for symptom amelioration, but no effects were found in older adults.[38] Basal pro-inflammatory status seems to play a moderating role in this effect.

From a symptom-based standpoint, robust evidence suggests a relationship between elevated levels of circulating cytokines (e.g., interleukin 6 [IL-6]) and low-grade systemic agents (e.g., C-reactive protein) and specific symptoms featuring late-life depression, such as cognitive deficits, lack of energy or sleep difficulty.[39,40] A recent line of research highlights that inflammatory dysregulation may be not characteristic of depression but certain depressive profiles. In this regard, a depression presentation featured by atypical behavioural symptoms (e.g., hyperphagia, weight gain, hypersomnia, fatigue) was proven to be related with altered energy homeostasis and increased levels of circulating cytokines (e.g., IL-6, TNFα).[28,41] Further research should be done using older adult samples to disentangle the specific pathways involved in the depression and inflammation relationship.

Conclusions

Some questions remain open regarding late-life depression in nosological and clinical terms. First, depression seems to have some distinctive features in old age, such as a predominance of somatic symptoms and an increased probability of episode repetition. Moreover, comorbidity with chronic diseases (particularly, those derived from metabolic alterations) and their management turn into crucial to forecast the course of depression and its phenotype over the old age. Finally, inflammatory dysregulation may constitute a major contributor to depression onset and symptom aggravation in old age, due to the regulatory of inflammatory markers in key neuroendocrine systems and the ageing-related pro-inflammatory status.

Further research should be done to disentangle key pathophysiological pathways of late-life depression. The study of oxidative stress and microbiome may help gain insight into distinctive features and maintaining factors. Depressive symptoms are connected with increased oxidative stress, which may lead to inefficient anti-inflammatory response. In addition, alterations in gut mucosal permeability and related dysbiosis (i.e., microbial imbalance) in the intestinal tract have been shown in depressive patients.

From a clinical point of view, some lessons can be learnt from research on late-life depression. First, a physical exploration should be mandatory to explore the potential risk factors contributing to depressive symptom maintenance. Second, depression may have an important impact on people's wellbeing and physical health even from its earlier stages. On the other hand, numerous researchers claim for a lifelong management of depression. In this regard, interventions focused on providing coping skills (e.g., problem-solving skills, resilience) might be quite beneficial to tackle depressive episodes in old age. Moreover, it is important to optimise pharmacological anti-inflammatory treatment to enhance its effectiveness in promoting depressive symptom amelioration. For that reason, new targets deserve being explored towards more effective and integrated therapeutic strategies for depression in late life, such as probiotics, dietary supplements (e.g., omega-3 polyunsaturated fatty acids) or some antibiotics (e.g., minocycline).

Conflict of interest

None declared.

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