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Review

Biological determinants of depression following bereavement

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ABSTRACT

There is considerable variability among people in their response to bereavement. While most people adapt well to bereavement, some develop exaggerated and/or pathological responses and may meet criteria for a major depressive episode. Many studies have investigated the effect of psychosocial factors on bereavement outcome but biological factors have not received much attention, hence the focus of this paper. The biological factors studied to date in relation to bereavement outcomes include genetic polymorphisms, neuroendocrine factors, and immunologic/inflammatory markers. In addition, animal studies have shown the alterations of brain neurotransmitters as well as changes in the plasma levels of the neurotrophic growth factors under the influence of peer loss. Recent studies have also investigated the biological basis of stress resilience, and have found a few genetic polymorphisms and potential biomarkers as protective factors in the face of adversity. Longitudinal studies that include data collection prior to, and also after, bereavement and which chart both biological and psychological measures are needed to develop profiles for the prediction of response to bereavement and personalised interventions.

Contents

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1. Introduction

Depression is a major global public health issue due to a relatively high lifetime prevalence of up to 15% (Ustun and Chatterji, 2001). As a result of substantial comorbidity with chronic medical diseases (Molteni et al., 2001, Moussavi et al., 2007) and association with high mortality (Mykletun et al., 2009), depression has been considered as an important contributor to the total disease burden (Üstün et al., 2004) and has been estimated to be the second most common contributor to years lived with disability (Vos et al., 2013). Specific external causes have been reported to promote the occurrence of depression, especially those associated with loss (Ferster, 1973). Loss can take many forms which include bereavement, romantic betrayal and rejection, unexpected job loss, financial ruin, loss of possessions, natural disasters, or negative medical diagnosis in oneself or a loved one (Wakefield and First, 2012). However, it has been shown that interpersonal loss including bereavement, separations, endings or threats of separation, has the most profound influence (Paykel, 2003). Bereavement usually has a profound effect and therefore is understandable as one of the most prominent and consistent risk factors for depression (Cole and Dendukuri, 2003). Bereavement also leads to a grief reaction which may be regarded as a normative process. This raises some important questions: when does grief become pathological and should this be diagnosed as depression? Are there particular psychological and social factors that predict depression in someone who is bereaved? Are there biological factors that predispose a bereaved person to become depressed?

In this review, we address some of these questions and document the current state of knowledge on the biological determinants of depression after bereavement. In particular, we attempt to show how the application of molecular biology and genetic techniques is promoting the identification of biomarkers of major depressive disorder (MDD) following bereavement. Finally, new strategies for future research are proposed.

2. Determinants of depression

Several factors have been identified as determinants of depression. A review by Riso et al. (2002) classified the factors underlying chronic depression into six putative categories: (1) developmental factors such as childhood adversity (early trauma or maltreatment), (2) personality and personality disorders like neuroticism and stress reactivity, (3) psychosocial stressors (life events), (4) comorbid disorders including anxiety and substance abuse, (5) biological factors such as dysregulation of the neuroendocrine and/or immune systems, and (6) cognitive factors (e.g. self-criticism). In studies of chronic depression, the strongest evidence of aetiology has been found for developmental factors, with some support for environmental stressors and heightened stress reactivity (Riso et al., 2002). The vast majority of research on the association between stress and depression supports a strong relationship between stressful life events and depression (Kessler, 1997; Kendler et al., 1999; Pittenger and Duman, 2008), specifically the unique significance of depression following a "loss" (Zisook and Shuchter, 1991; Biondi and Picardi, 1996).

3. Grief as a normal response to bereavement

"Grief" is a normal reaction to a major loss of any kind but will be discussed herein in relation to the particular loss incurred due to bereavement. Bereavement grief is multidimensional, with physical, behavioural and meaning/spiritual components and is characterised by a complex set of cognitive, emotional and social adjustments that follow the death of a loved one (Lobb et al., 2010). Although individuals vary in the type, intensity and duration of the grief they experience (Christ et al., 2003), most grieving people show similar patterns of intense distress, anxiety, yearning and sadness which usually settle over time.

The grief symptoms related to bereavement bear a close resemblance to the symptoms of Major Depressive Disorder (MDD) as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) (American Psychiatric Association, 2000). It has been argued that bereaved individuals who have these symptoms are not experiencing a mood disorder but rather an intense normal sadness in response to losing their loved ones, which should not be pathologized. However, a clinician evaluating a bereaved person is at risk of both over-and under-diagnosis of MDD, either pathologizing a normal condition or neglecting to treat an impairing disorder (Shear et al., 2011). To prevent over-diagnosis of MDD in such individuals, the DSM-IV-TR used the 'bereavement exclusion' criterion where a bereavement-related depressive syndrome had to be either of a longer duration than two months instead of the standard requirement of two weeks, be paired with specific symptomatic manifestations, or be associated with marked functional impairment (American Psychiatric Association, 2000). Although many other types of loss, such as marital dissolution and unexpected job loss, can also trigger intense sadness that may meet the criteria for diagnosis of MDD, the concern about pathologizing grief has been restricted to the loss of a loved one and all depressive episodes following other major stressors were classified as MDD by the DSM-IV, irrespective of whether the response to those losses was complicated or not (Wakefield and First, 2012). There is ample evidence that stress caused by bereavement, like other stressors, has a negative effect on psychiatric and physical morbidity and increases the risk and severity of depressive syndromes (Clayton and Darvish, 1979; Zisook et al., 2012a). The authors of DSM-IV focused primarily on the problem of over-diagnosis, and therefore the revision of DSM-IV-TR leading to the publication of DSM-5, resulted in the removal of "Bereavement Exclusion" clause in the diagnosis of Major Depressive Disorder and has been one of the most contentious changes from DSM-IV to DSM-5, This has led to a lively controversy by grief and bereavement experts (Prigerson et al., 1995; Shear and Shair, 2005; Zisook et al., 2012a; Parker, 2013), and even resulted in some sensational or misleading reports in the lay media; including headlines such as, "Psychiatrists want to make normal grief a mental disorder!" and "DSM-5 medicalizes mourning." (Pies, 2014) (Table 1).

The DSM5 Mood Disorders Work Group believed that, although bereavement should not be 'medicalised', neither should the serious risks of under-recognised MDD be normalised, since these include suicide and cognitive dysfunction. Recognising major depression following a recent bereavement requires careful clinical judgement and does not necessarily warrant psychopharmocological anti-depressant treatment (Pies, 2014). In reflection of this attitude, the DSM-5 itself warns clinicians that they need to distinguish