Life Sciences 210 (2018) 96–105

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Review article

Does sickle cell disease have a psychosomatic component? A particular focus on anxiety and depression

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ARTICLE INFO

Keywords:
Sickle cell disease
Pain
Fatigue
Anxiety
Depression
Psychosomatic
Quality of life

ABSTRACT

Sickle cell disease, an early-age genetic condition, encompasses a range of blood disorders with severe complications. This disease is characterized by the synthesis of abnormal hemoglobin molecules, which tend to polymerize due to their low solubility upon deoxygenation in the peripheral capillary beds, resulting in sickle-like red blood cells. Sickled cells lose their normal functioning and hemodynamic properties, leading to chronic fatigue as well as to episodes of painful crises. Over the last two decades, a growing body of clinical evidence has pointed out that these somatic complaints can give rise to neuropsychiatric disorders, among which anxiety and depression are the most common, that worsen the health-related quality of life in patients. At first glance, this somatic influence may be unsurprising, as both anxiety and depressive signs are prevalent in almost all chronic diseases. However, in the case of a genetic condition such as sickle cell disease whose somatic disturbances are predetermined, the fact that mood disorders can increase fatigue and pain through a psychosomatic component has attracted increasing attention. In this review, we address the hypothesis of a psychosomatic component in patients with sickle cell disease by underlining the most relevant clinical studies that have highlighted the existence of a bidirectional link between physical and psychological sequelae, which are reported to be relieved not only by pharmacological cotreatments but also by the concomitant application of cognitive behavioral therapy.

1. Introduction

Sickle cell disease (SCD) is a general term that describes a group of inherited blood disorders resulting from a single point mutation in the *HBB* gene, which encodes the β-globin subunit of adult hemoglobin (HbA). This autosomal recessive inheritance produces abnormal hemoglobin, namely, hemoglobin S (HbS), which is found in red blood cells (RBCs) at proportions greater than, or approximately equal to, 50% of the total Hb content in affected individuals. These disorders include homozygous sickle cell disease (HbSS) and a range of mixed heterozygous hemoglobinopathies such as HbS/β-thalassemia and HbSC variants [1,2]. Deoxygenated HbS molecules aggregate and form rigid polymers, leading to deformation of RBCs into sickle-shaped cells. Sickled RBCs acquire a stiff structure and an unstable hemodynamic behavior inside the vascular system and occlude capillary beds. Although reoxygenation allows RBCs to regain their normal shape through HbS polymer dissociation, the sickling/unsickling cycle is thought to cause irreversible membrane damage and lead to both intravascular hemolysis and extravascular removal by the spleen, resulting in sickle cell anemia (SCA) [3]. A broad range of somatic complications have been reported in SCD patients including pulmonary hypertension, leg ulcers, stroke, ocular damage, osteonecrosis, acute chest syndrome and cholelithiasis, as well as bacterial infections due to the progressive loss of spleen tissue functioning [4]. These life-threatening complications have a significant impact on patients' health-related quality of life (HRQoL) by impairing their physical and mental states over time. Although there is no consensus on the definition of HRQoL, the concept is usually considered to be an individual's self-perceived health status. The HRQoL is thoroughly evaluated by healthcare practitioners to determine to what extent a chronic disease interferes with a patient's daily life, weakening its quality and, therefore, the self-perceived significance of being alive. Clinical interest in HRQoL has grown rapidly as a wide range of observations and surveys have provided evidence of its potential effect on the prognosis of life-long conditions. In SCD patients of various ages, studies addressing HRQoL have shown that the physical, psychological, and social

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https://doi.org/10.1016/j.lfs.2018.08.066
Received 2 May 2018; Received in revised form 4 August 2018; Accepted 27 August 2018
Available online 29 August 2018

domains measured by questionnaires are significantly affected by the disease. Consequently, SCD subjects generally display low HRQoL scores compared to those of healthy counterparts [5]. One of the most common hallmarks observed during HRQoL assessment is the emergence of anxiety and/or depression in these patients [6]. While long-lasting somatic complaints have been found to directly cause anxiety and depressive symptoms, other perceptional factors have also been reported as potential sources of these mood disorders in SCD patients as they progressively realize that their condition could result in a shortened life expectancy. These factors include the chronicity of the disease and the unpredictability of the painful crises it causes, the relative growth retardation and physical disabilities, racial prejudice, and financial burden associated with repetitive hospitalizations [7], as well as stigmatization for possible addiction to opioid analgesics [8]. Nonetheless, although the appearance of anxiety and depressive symptoms in SCD patients is understandable, as it generally occurs with most chronic illnesses, the relationship between SCD and psychiatric disorders appears to be bidirectional. In fact, a growing body of clinical evidence suggests that anxiety and depression ensuing from somatic complications may worsen the physical status of patients and further decrease their HRQoL. This raises the possibility of a psychosomatic component in SCD, although the designation *psychosomatic* has not been explicitly stated in the literature thus far. Therefore, this report aims to highlight a psychosomatic hypothesis in SCD by reviewing the most relevant clinical studies relating to the occurrence of psychiatric disorders in SCD patients, with a particular focus on anxiety and depression. A concise description of the HRQoL-related questionnaires that are reported throughout this review is given in Table 1.

2. Fatigue and pain as potential somatic disruptors of health-related quality of life in patients with sickle cell disease

Clinically, fatigue and pain are the main somatic symptoms of SCD. Fatigue develops because of chronic hemolytic anemia due to excessive extravascular destruction of sickled RBCs, particularly by the mononuclear cells of the spleen. The resulting anemic state causes arterial oxygen desaturation and, consequently, tissue hypoxia in all organs, including the skeletal muscles. The decline in oxygen supply to skeletal muscles in SCD patients is thought to alter their normal locomotor functioning at rest and yield abnormal metabolic responses to daily physical activities and exercise, which are almost always accompanied with pronounced metabolic acidosis and muscle fatigability. In turn, this pathological acidosis is suspected to be involved in further RBC sickling, exacerbating the somatic complaints of the disease [9]. Another hallmark relating SCD to fatigue lies in the fact that SCD patients display impaired electromyographic measures, suggesting disturbed neuromuscular coordination due to hypoxia-induced central disorders [10]. However, pain is considered the most recurrent complication experienced by SCD patients and significantly interferes with their HRQoL. Acute pain episodes, which are more common in SCD patients than chronic pain is, are usually referred to as vasoocclusive crises (VOCs) [11]. Due to their low flexibility, sickled RBCs are trapped in the microcirculation, leading to vascular obstruction (occlusion) and tissue ischemia, which are eventually followed by infarction-reperfusion injuries. During VOCs, sickled RBCs abnormally interact with multiple humoral, cellular, and endothelial factors to cause intravascular inflammatory responses leading to pervasive hyperalgesia through substantial nociceptor activation [12].

SCD is characterized by the chronicity and severity of its complications. Pain and, to a lesser extent, fatigue are primarily involved in HRQoL impairments since these ensuing somatic problems, through their recurrent and unexpected occurrence, create a negative mood and excessive worry in patients regarding their health and life progress. However, the role of somatic complications in inducing anxiety and depressive disorders leading to psychosocial difficulties remains a subject of debate [5]. From a genetic point of view, the SCD variant is thought to be a key factor contributing to HRQoL decline. A cross-sectional study that enrolled 110 adult SCD patients demonstrated that disease genotype could influence HRQoL [13]. Patients with the most severe genotypes (i.e., SS and Sβthal0) had the worst general and physical HRQoL scores based on the Short Form 36 (SF-36) questionnaire. Nevertheless, although several patients were suffering from anxiety and depression, no interference from these psychiatric symptoms on their mental HRQoL indexes was found, indicating that mental health status should be carefully analyzed and interpreted when evaluating various HRQoL aspects in SCD patients. In this respect, the emotional state of patients and their adaptive capabilities are very important for properly assessing their HRQoL. In a sample of 44 SCD adolescents, questionnaires that targeted a range of resilience factors (e.g., attributional style, hope, stress coping) and internalized signs of anxiety and depression did not show a statistically significant difference between these patients and their healthy siblings. However, self-esteem in SCD subjects correlated with less internalized signs, and a sense of inadequacy was associated with poor psychosocial functioning [14]. Although these findings clearly elucidate the high resilience rate in these SCD patients, they also highlight the emergence of some psychosocial disturbances, which could develop into severe neuropsychiatric disorders if the somatic sequelae appear over time as the result of both age and disease progression. Of interest, even if the patients' emotional state is stable, there is the possibility that anxiety and depressive comorbidities develop from past VOCs and vasculopathic complications, such as stroke, which has been suggested. For instance, Nunes et al. [15] diagnosed a range of neurocognitive complications in a sample of 15 young SCA patients (children and adolescents) using the Wechsler Intelligence Scale for Children (WISC-III), the Developmental Neuropsychological Assessment Test (NEPSY-II), and the Child Behavior Checklist (CBCL). The authors found that patients who had a history of stroke as a result of VOCs suffered from severe cognitive declines that included attention deficits, sensorimotor difficulties and verbal and mnemonic disabilities, suggesting that SCA can progress as a condition of cerebral vasculopathy that alters the normal brain functioning and psychosocial development of young SCD subjects, thus predisposing them to higher levels of anxiety and depression. However, it is noteworthy that anxiety and depression do not necessarily include a cognitive decline, and anxious or depressed patients might have no cognitive decline. In particular, the occurrence of VOC-related complications during childhood is thought to induce behavioral inhibitions, probably due to a cumulative fear of eventual recurrence. Behavioral inhibition is a temperamental factor referring to the tendency to exhibit remarkable shyness or to react with fear/withdrawal in novel or unfamiliar social situations [16]. The role of behavioral inhibition in the progression of neuropsychiatric disorders was investigated in another study of 30 adolescent SCD subjects [17]. The authors found that patients who classified themselves as ‘high’ on behavioral inhibition scales displayed higher scores of anxiety and depression than did those with low behavioral inhibition. These results are reinforced by the fact that patients in the middle behavioral inhibition group generally had medium anxiety and depressive scores. This finding suggests that SCD-related neuropsychiatric disorders can develop from somatic (motor) disabilities, making SCD a condition that alters general HRQoL at adolescence. Otherwise, pain is still considered as the main cause of anxiety and depression, even in the absence of VOC-related complications. A descriptive study with 100 adult SCD patients under analgesic treatment (108 ± 87 mg of morphine) who took part in the Patient-Reported Outcomes Measurement Information System (PROMIS) survey network showed a statistically significant, positive correlation between pain intensity and interference, depression and anxiety, indicating that SCD individuals are prone to develop these psychiatric disorders in the presence of considerable pain sensitivity, even in combination with a chronic opioid medication. With the exception of employment status, none of the demographic (i.e., age, sex, and marital status) and educational indexes were related to quality of