Annals of R.S.C.B., ISSN: 1583-6258, Vol. 25, Issue 4, 2021, Pages. 15301 - 15308

Received 05 March 2021; Accepted 01 April 2021.

Sleep Disorders in Patients with Sickle Cell Disease

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ABSTRACT

Sickle cell disease (SCD) is a recessive genetic disorder caused by mutations in the β-hemoglobin gene on chromosome 11. It affects an estimated 100,000 people in the United States .Sleep disturbance and depression are commonly encountered in sickle cell disease, depression is associated with pain, poor treatment compliance, and lower quality of life. The relationship between pain and fatigue in adolescents and young adults with sickle cell disease (SCD) is not well understood. In fact, little research exists on fatigue in SCD despite the distinctive anemia. The purposes of this secondary analysis were: 1) describe pain, fatigue, and sleep quality in patients with SCD, and 2) explore whether sleep quality mediates the relationship between pain and fatigue.

Keywords: Sickle cell disease, sleep disorders, Hemoglobin S, vaso-occlusion crises, hemoglobinopathy, sleep disturbances.

1- Sickle cell disease:

Sickle cell disease (SCD) is a heterogeneous disorder accompanied by clinical expressing involving a growing vulnerability towardsinfections; severe hemolysis and vaso-occlusion often seek for medical attention. Sickle cell disease patients are able to extend particular and occasionally life-threatening complications, together with an increased organ injury lowering both their feature of life and their life expectation [1]. The genetic aberration is because of the replacement of valine with glutamic acid at the point number six on theglobin beta chain and was initially characterized many years ago. Hemoglobin S (HbS) that is formed is a protein organized into two mutant beta chains and two normal chains. Generally, the extent of SCD overridesother serious genetic disorders [2].

2- Epidemiology:

Generally, sickle cell diseaseis visible through the world but frequently appears in Africans and less common in East Indian, Mediterranean, Latino and Arabs [3]. It is valuated that about 80% of more than 300,000 births a year appear in sub-Saharan Africa (SSA), the highest percent from Congo and Nigeria [4]. The genetic recurrence was at the top peak in the countries of West Africa with 1/4 asHbS carrier in comparison to 1/400 Americans from Africa and is changeable in the countries of Europe [5]. The incidence of the disease in developing populations is elevated partially because of emigration from countries with high incidence of SCD [6]. It was assessed that more than 14,000 of the population live with SCD in France and UK, while countries like Italy and Germany had an increased number of cases than Africa [7]. Recently, there are an increasing number of patients with SCD surviving into adulthood and old age [8]. Nowadays, it has been noticed that more than 94% of cases surviving with SCD into adulthood in the UK, USA and France while about 50–90% of SCD cases in SSA die during the first 5 years of their lives [9].

Received 05 March 2021; Accepted 01 April 2021.

3- Pathophysiology:

The pathophysiological events of the clinical expression of SCD is a single amino acid replacement in the beta globin chain leading to mutant hemoglobin S polymerization, weakening the rheology and permanence of erythrocytes. Clinically, in SCD the erythrocyte aberrations are manifested asvaso-occlusions and anemia progressing to infarction and ischemia. Vaso-occlusion and intravascular hemolysis enhance free radical formation and inflammation that progress to enhanced small- and large-vessel vasculopathy[10]. Sickle cell vaso-occlusion manifested as severe acute pain perhaps because of blood flow obstruction and tissue hypoxia. Additionally; SCD is identified by hemolytic anemia, chronic organ damage and precocious mortality [11]. Depression, sleep disorders and fatigue are suggested to be the main factors in SCD biobehaviour [12].

4- Depression:

As it is known; depression and catastrophizing behavior participate in alteration of pain conception and are supposed to contribute in pain modification[13]. The incidenceof depression is about 18 to 44% in SCD adults [14-17],which is virtually greater than it´s incidence in the United States [18]. In SCD patients, depression is correlated with low quality of life, great pain and low response to treatment. The disorders of sleep probably correlated with great SCD symptoms involvement[19-21], though it is a quite recognized risky agent for main depression in well persons[22]. Previous studies suggested thatvaso-occlusive pain crises as well as depression greatly increase disturbed sleep and daytime action in SCD [23]. Sleep disorders and depression were linked with severe diseased effects in bothadults and children, though those investigations estimated depression applying the SF-36 and the Patient Health Questionnaire rather than a screening instrument for depression [17- 24]. In spite of applying a group of traditional indicators used for SCD determination, only anemia was correlated with high lineage of depression. Hematocrit, adult and fetal hemoglobin levels are classical indicators correlated with modifying the recurrence of pain in SCD. Yet, the combination between anemia and depression simply agreed with the standard for prominence, proposing that the extent of this impact is comparatively little in comparison to the combination of vaso-occlusive pain with elevated hemoglobin. No parameter of these was linked with sleep disorders. In general, sleep disorders examination and global depression are advocated in SCD adults, irrespective of disease intensity or genotype (i.e. SC vs. SS) [25].

5- Pain:

Previous studies suggested that bad sleep probably foretells growing in experimental and clinical pain [26].Particularly, fewstudies have confirmed that evidences of sleep continuation, such as delayed sleep onset latency (SOL; > 30 minutes), decreased sleep duration and increased sleep fragmentation (i.e. wake after sleep onset; WASO) indicate elevated pain intensity [27, 28].

Former studies explained that in experiment perturbing sleep continuation considerably reduced endogenous pain-suppression and raised involuntary pain in healthy individuals [29]. In two monitoring studies, elevated sleep discontinuation significantly proposed greater the following-day pain in between adults and adolescents with severe pain[30, 31].

The relationship between pain and continuation of sleepin SCDadults have been studied for several causes. First, pain is the extremely widespread symptom in patients with SCD and displays variation from day to day [32, 33]. Second, more than70% of SCD patients declare sleep disorders involving hardness in initiation and continuation of sleep[34, 35]. Although sleep disorders are linked with vaso-occlusive crises, however pain and sleep-disturbance breathing (e.g. obstructive sleep apnea) are the most popular causes[36, 37]. Previous studies recorded

Received 05 March 2021; Accepted 01 April 2021.

variations in sleep from day-to-day also the amplitude to who perturbed sleep continuation effects SCD pain each day[38].

6- Sleep disordered breathing:

Sleep disordered breathing (SDB) is a set of events recognized by partial or complete discontinuation of respiration during sleep. Obstructive sleep apnea (OSA), the utmost common form of SDB, is a disturbance that involves about 2% to 4% of the adult people [39, 40]. It is realized by sleeping during day, as well as 5 or more respiratory obstructions per onehour of sleep [41]. Obstructive sleep apnea (OSA) and its polysomnographic (PSG) specialties have been investigated in SCD children who were pointed out to a sleep laboratory and they showed a high incidence (69%) of OSA [42, 43]. Although, a raised percent of patients with SCD continue living till adulthood[44]. The high body mass index with increasing the size of neck is considerable factors for SDB in patients with SCD;this supports the idea that an increase in the adipose tissue is substantial for SDB pathogenesisin patients with SCD [45]. A previous study stated thatthe slow growth of children with OSA is linked to raised respiratory strain throughsleep that leads to higher calories expense; also, respiratory obstructions lead to a decrease in the release of growth hormone. Persons with SCD usually had reduced level of serum growth hormone along with adecrease in the response to this hormone due tohypoxic-ischemic damagecaused by incidents ofvaso-occlusive crisis, which leads toa growth delay[46]. In addition, it was approved that persons with OSA had high level of plasma fibrinogen with greater platelets activitytogether with a decrease in fibrinolysis identified as hypercoagulability state. The relationship between OSA and hypercoagulability state can be interpreted by the increase in inflammation and oxidative stress that will increase the chance for cerebrovascular attacks[47].

7- Nocturnal Enuresis:

Adolescents and children with SCD are more probable to display nocturnal enuresis than healthy persons of the same age[48]. Previous studies documented that there are no differences between healthy children and children with enuresis in sleep pattern (stages of sleep during night); knowing that, enuresis can be disturbing for both parents and the child [49]. Enuresis appeared predominately in boys. Parents may think that there is no association between enuresis and SCD, and thus they start preventing fluid intake for their children to inhibit enuresis, in spite that fluid ingestion is significant for the management of the disease, this proposes that alternative methods are more likely for screening and treating the disease [48]. There are hypotheses stated that dehydration may cause renal damage which will lead to an increase in consumption of fluids and increase urine volume, this can be explained by the low level of anti-diuretic hormone and thus an increase of enuresis. In addition, it has been reported that SDB is usually associate with enuresis in SCD children [50].

8- Periodic Limb Movements in Sleep and Restless Legs Syndrome:

Although PLMS and RLS are separated neurological situations that take place in patients with SCD, they are related to each other. PLMS are short, repeated motions of the legs and arms that happen during sleep and are occasionally correlated with wakefulness and/or fragmentation of sleep[51]. Prior studies stated that dopamine and their receptors dysfunction contribute in the pathogenesis of PLMS [52].

The patients may record paresthesia in legs that can be alleviated by movement. Though this case usually happens during the daytime, it mayoccur upon reclining to sleep [53]. The PLMS diagnosis is manifested through PSG, whereasRLS isdiagnosed clinically. Both PLMS and RLS are correlated with a decrease in serum iron level; therefore measuring serum ferritin level is substantial for theirdiagnosis and treatment[51].

Received 05 March 2021; Accepted 01 April 2021.

9- Endothelial dysfunction:

In SCD patients, the vascular endothelium expresses abnormal adhesion molecules related to other activator molecules that stimulate endothelium during vaso- occlusive crises via an inflammatory pathway these comprise cytokines such as tumor necrosis factor alpha (TNF-α), interleukin 1 (IL-1)and thrombin. Endothelial dysfunction (ED) usually produced by sickle cells and inflammatory activated molecules. Nitric Oxide (NO) created by vascular endothelium regulates vascular wall movements in response to stimuli [54, 55]. Abnormalities in vascular endothelium had been reported in patients with SCD. Previous studies reported that flow mediated dilatation (FMD) in patients with SCD crisis was lower thanFMD inthe steady state and both were lower than healthy control.Moreover, there was an increased level of serum biomarkers that increase the risk for endothelial cell activation, inflammation and endothelial dysfunction [56]. The increase in serum inflammatory cytokines such as TNF-α, IL-6, IL-10 and C- reactive protein in adults with OSA and increase C- reactive protein in children with OSA explains the correlation between inflammatory cytokines level and apnea- hypopnea index (AHI) [57].

Prior studies found a positive relationship between adhesion of RBCs toendothelium, platelets and WBCs activation markers[58]. Others reported important issues in relation to sleep disorders in patients with SCD involving SDB [59]. Upper airways occlusion may leads to hypoventilation with eventual hemoglobin desaturation through sleepthat may contribute in hypercapnia, hypoxemia and acidosis development leading to polymerization of sickle cell hemoglobin and thus encouraging the appearance of vaso-occlusive crisis[60]. Thus, there are several molecular pathways that explain the relationship between SCD and OSA and that may contribute to development of the clinical manifestations in these patients [61]. Other studies examined SCD children and assessed that they have several clinical manifestations such as repeated awakening through the night, hardly falling asleep, and sleeping during the day and they had reported that SCD and SDBshare some current pathophysiological pathways such as repeated cycles of hypoxia- reoxygenation, lowering the bioavaibility of nitric oxide, increased signaling of inflammatory pathways and endothelial dysfunction [58, 62].

10- Conclusion:

The present study concluded that patients with SCD experienced insomnia and sleep impairment. Significant association existed between pain and sleep impairment, also, there was a significant association between depression and pain. Sleep disordered breathing may also interrupt sleep. Nocturnal enuresis and PLMS occurred in patients with SCD and were increased in sever diseased state mainly vaso-occlussive crisis. Endothelial dysfunction contributes in the development of SCD clinical manifestations by expressing high level of inflammatory markers and C- reactive protein.Thus, taking in consideration these factors may assist in treatment and management of sleep disorders in patients with SCD.

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