



CLINICAL REVIEW

Sleep and fatigue in pediatric oncology: A review of the literature



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SUMMARY

Cancer in children has detrimental effects on sleep patterns and sleep quality, which in turn impacts on the perception of, and the ability to cope with, the emotional and physical challenges associated with both the disease and its treatment. This places an added burden on their quality of life that can last many years beyond diagnosis and treatment. In addition to the effect of the cancer itself, surgery, chemotherapy and radiotherapy can all contribute both short and long term to sleep disruption. Sleep disorders have also been associated with pain, fatigue, medication and hospitalisation in children suffering from cancer. This review will explore the relationship between childhood cancer and associated sleep disorders, in the acute stage of diagnosis, during treatment and in the years following. We will discuss the possible causes and the current treatment modalities used to treat sleep disorders in children with cancer, and in childhood cancer survivors. It has been estimated that the recent advances in treatment have improved the overall five year survival rate for all childhood cancers to over 80%, with some cancers achieving a near 100% cure rate such as early stage Wilms' tumour. Thus, recognition and appropriate treatment of associated sleep disorders is essential to optimise long term quality of life.

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Introduction

Most commonly thought of as a modern disease, in fact evidence of cancer has been identified in Egyptian mummies that were dated to 3000 BC. Currently, even though the combined cancer death rate for adults has been declining in the last two decades, cancer accounts for one in four adult deaths [1] and is the second commonest cause of death in children in developed countries [2]. Whilst three out of five children with cancer will survive, they are at increased risk for psychological distress, neurocognitive dysfunction and poor health-related quality of life (QOL) [3]. Sleep plays a fundamental role in the psychological health, neurocognitive ability and QOL of

healthy children; a role which is even more important in a child suffering illness, pain, anxiety and emotional distress [4]. Poor sleep patterns and sleep quality impacts on the perception of, and the ability to cope with, the emotional and physical challenges associated with childhood cancer and its treatment. To increase recognition of sleep problems associated with cancer by health professionals, a practice guideline has been published for the prevention, screening, assessment and treatment of sleep disturbances in adults with cancer in Canada [5]. However, there is no similar guideline for children with cancer, indicating that identifying and treating sleep disorders in pediatric oncology remains an area of research that is sadly lacking. This is even more apparent in the case of young children with cancer, where there is almost a complete dearth of research. This review will provide an overview of the current literature on sleep and fatigue in pediatric oncology.

Childhood cancer

Childhood cancers encompass a wide range of malignancies which are differentiated by histology, the sex, age and race of the child, and the site of origin of the cancer [6]. The most common

Abbreviations: ALL, acute lymphoblastic leukaemia; BMI, body mass index; CCSS, childhood cancer survivor study; CNS, central nervous system; EDS, excessive daytime sleepiness; MSLT, multiple sleep latency test; SDB, sleep disordered breathing; QOL, quality of life.

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cancers diagnosed during childhood overall, are leukaemia, malignancies of the brain and central nervous system, and lymphomas, accounting for 34%, 23% and 12% of all childhood cancers respectively [2] (Fig. 1). Acute lymphoblastic leukaemia (ALL) is in turn the most commonly diagnosed leukaemia with approximately 78% of leukaemia being ALL [7]. Astrocytoma is the most commonly diagnosed central nervous system (CNS) tumour, and Non-Hodgkin lymphoma the most common lymphoma, accounting for 47% and 46% of these types of cancers respectively [2]. However, the pattern of diagnoses of childhood cancers is very much age-dependent. Neuroblastomas represent 33% of the malignancies diagnosed in infants less than one year of age, 45% of malignancies in one to four year olds are leukaemias, in children from five to fourteen, leukaemias, CNS tumours and lymphomas make up 75% of malignancies, while in fifteen to nineteen year olds carcinomas and germ cell tumours predominate (32%) [2]. Although dependent on tumour type, overall the highest incidence of childhood cancer is in the under five years age group and is slightly higher in boys (55%) [7]. This age group is characterised by rapid cerebral and functional development and is therefore a period when the brain is particularly vulnerable to the pathological effects of disruption to sleep. There is also a second peak in incidence that occurs during puberty.

Sleep in childhood

Sleep is a major physiological drive which is essential for normal growth and development of both the body and the brain. During childhood, sleep is at a lifetime maximum, with children between the ages of two and five spending about half of each 24 h asleep [4].

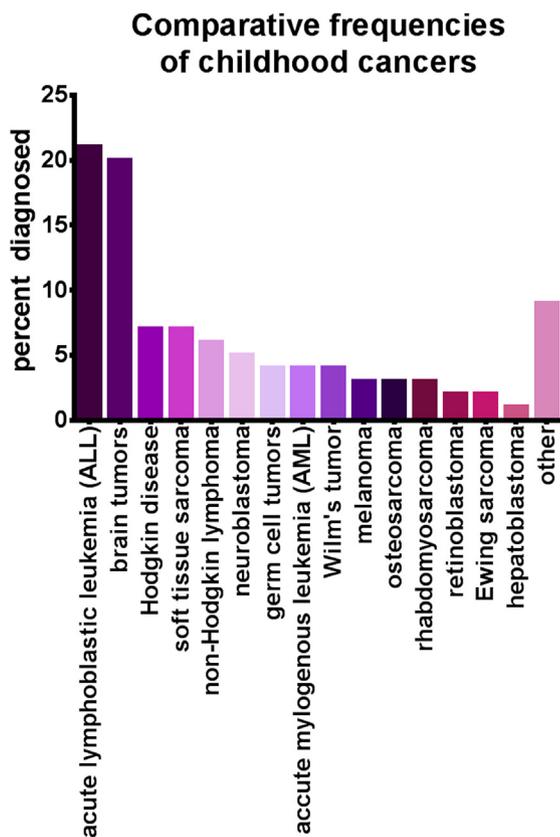


Fig. 1. Comparative frequencies of childhood cancers, represented as a percentage of the total number of childhood cancers diagnosed ($n = 13,500$). Adapted from: *Childhood Cancer Statistics*. CureSearch for Children's Cancer <http://www.curesearch.org/Childhood-Cancer-Statistics/>.

Sleep problems are common in children affecting 20–50% of otherwise healthy children [4]. Dysomnias and parasomnias are the most common sleep problem in children (up to 80% in preschool-aged children), followed by snoring, obstructive sleep apnoea and circadian rhythm disorders [4,8]. While the amount of sleep each child needs is to some extent dependent upon the individual, insufficient or poor quality sleep, impacts a child's mood, cognitive function, behaviour and the propensity for obesity (Table 1).

Sleep has also been shown to significantly affect a child's resilience, that is, the ability to recover normal functioning following stressful situations. The greater the sleep disturbance, the more resilience was reduced and increased problematic behaviour (both internalising and externalising), depression and anxiety were noted [9]. Therefore, maintaining a normal sleep pattern in situations of stress, such as those associated with cancer is of vital importance for improving a child's long-term QOL.

Fatigue and sleepiness

Although interrelated, fatigue and sleepiness are distinct phenomena. Sleepiness is a normal physiological state, and reflects an individual's propensity to sleep. Sleepiness becomes pathological when it becomes pervasive such as in narcolepsy or is reduced as in insomnia [10]. In contrast, fatigue relates to an overwhelming lack of energy and a feeling of exhaustion that is associated with impaired physical and/or cognitive function [10] but which does not lead to sleep. Fatigue can be either central or peripheral. Central fatigue originates in the areas of the brain related to mood, emotion and psychological arousal, and is associated with increased serotonin release [11]. Peripheral fatigue is related to mechanisms such as neuromuscular transmission and impulse propagation, dysfunction of the sarcoplasmic reticulum, and other metabolic factors that disrupt energy provision and muscle contraction [11]. There is scant knowledge of the impact of central versus peripheral fatigue in cancer patients, although a recent study reported that post-cancer fatigue in adults was not characterized by either high central muscle fatigue or low peripheral fatigue, suggesting a different underlying physiological mechanism to cancer-related fatigue compared with other fatigue syndromes [12]. The adverse effects of fatigue and sleep disorders on children with cancer are currently being under-rated by clinicians. Highlighting this, one study of 158 children receiving intravenous antineoplastic therapy identified that 80% of the children suffered from symptoms of fatigue and 41% from significantly severe sleep problems [13].

Table 1
Impact of insufficient or poor quality sleep.

Mood	Irritability Increased emotional lability Moodiness Depression Anxiety
Cognitive function	Inattention Poor concentration Impaired vigilance Decreased executive functioning Learning difficulties Poor academic performance
Behaviour	Overactivity Noncompliance Oppositional behaviour Poor impulse control Increased risk taking
Obesity	Reciprocal amplification effects on sleep quantity, sleep quality and obstructive sleep apnoea

Adapted from [4,10,11].

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