Review Article

Mechanistic Association of Hepatoblastoma with Cerebral Palsy: A Narrative Review

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Abstract

Hepatoblastoma is a rare liver cancer that occurs most often in children who present with lower birth weight. Cerebral palsy (CP) is a neurodevelopmental disorder distinguished by irregularities in muscle tone, movement, and motor skills. CP is caused by damage to the developing brain and is often associated with secondary complications such as severe constipation. Clinicians must be aware of sudden worsening constipation occurring in CP children because it can also be a sign of hepatoblastoma. The aim of this review is to summarize the current understanding of the risks for hepatoblastoma development in children with CP. Cancer risks likely include dysfunction of the immune system surveillance in CP children. Elevated C-reactive protein and tumor necrosis factor-alpha levels may be higher in children with CP, which weakens their innate immune system. Metabolic disruption increases the risk of some cancers, and poor nutrition and reduced growth that occur in CP patients may have an impact on cancer development through a loss in immune function. Increased mobility and physical activity can increase the T-cell, natural killer cell, and neutrophil population. Children with CP tend to engage poorly in physical activity, and consequently, their immune system is affected. There are multiple factors associated with CP that increase the risk of childhood cancers such as hepatoblastoma.

Keywords: Cerebral palsy, child, hepatoblastoma, immune surveillance, liver cancer

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Submitted: 08-Nov-2023 **Revised:** 26-Mar-2024 **Accepted:** 31-Mar-2024 **Published:** 20-Jun-2024

INTRODUCTION

Hepatoblastoma is a type of liver cancer that most frequently occurs during childhood, between the age of 0 to 4 years. The incidence of hepatoblastoma has increased since the 1970s from 0.61 cases per 1,000,000 to currently 2.61 cases per 1,000,000,[1] and is estimated to be 0.5% among extremely low birth weight children.[2] In a case–control study that compared 60 children with hepatoblastoma (with birthweight <2500 g) and 51 control children matched for age, sex, year of birth, and geographical region of birth (within the US), it was found that children with hepatoblastoma had a higher probability of being born at lower birth weight, low birth length, younger gestational age, and had longer neonatal intensive care unit stays to support organ development and growth. The hepatoblastoma cases in this study also received antenatal steroids more often and were more likely to be exposed to mechanical ventilation.[3] Individuals with hepatoblastoma are more likely to experience anorexia, unexplained weight loss, abdominal distention, abdominal

Access this article online	
Quick Response Code:	Website: https://journals.lww.com/sjmm
	DOI: 10.4103/sjmms.sjmms_519_23

How to cite this article: Hasan NS, Thomas W. Mechanistic association of hepatoblastoma with cerebral palsy: A narrative review. Saudi J Med Med Sci 2024;12:203-9.

pain, isosexual precocity, elevated liver enzymes, jaundice, and constipation throughout their lifetime.[4] A study in Michigan found that 40% of hepatoblastoma cases occurred in premature infants of gestational age ranging from 26 to 36 weeks.[5]

Cerebral palsy (CP) can defined as a group of motor disorders caused by non-progressive lesions of the premature brain with lifelong pathophysiological consequences that include dysregulation of innate immunity.[6] The overall prevalence of CP is approximately 2 per 1000 live births, much higher than for hepatoblastoma at 1.76 per 1.000.1000 live births in the US.[7] A population-based study from the USA reported a relatively stable rate of CP at 1.86/1000 in 1985 to 1.76/1000 in 2002.[8] Risk factors for sustaining a brain injury early in life include preterm birth, where infants born prior to 28 weeks of gestational age have a 50 times higher risk of CP compared with infants born at 38 to 42 weeks,[4] and also perinatal infection, particularly chorioamnionitis.[9] CP is characteristically most associated with irregularities in muscle tone, movement, and motor skills.[10] CP is often associated with immature muscular responses and patients with CP tend to experience physical weakness as well as visual and hearing dysfunction due to a lack of coordination between movement and sensory responses through development. People with CP may develop constipation as a secondary condition; a sudden worsening of the constipation may also be a clinical presentation of hepatoblastoma.[4] While the mechanistic links remain to be established, Table 1 outlines the cases of three patients who have a diagnosis of CP prior to being diagnosed with hepatoblastoma.[4,11]

Hepatoblastoma and CP are both conditions that disproportionately affect children with premature delivery and low birth weight. Case studies suggest a causative link, and this paper aims to review current literature to identify the mechanisms by which CP and its associated pathophysiology can increase hepatoblastoma risk. Understanding the underlying causes of hepatoblastoma, as a rare malignancy, will help to more precisely identify children most at risk and design more effective interventions.

GENERAL EFFECTS OF CEREBRAL PALSY ON THE IMMUNE SYSTEM

Children with CP have marked upregulation of circulatory proinflammatory cytokines.[6] There is also evidence that CP children have lower levels of erythropoietin (EPO) compared with non-CP children,[4] EPO is a pleiotropic protein cytokine that not only promotes erythrocyte production but also protects the neurons of the central nervous system from damage by proinflammatory cytokines.[12] The cytokines that are most elevated in children with CP include interleukin (IL)-6 and tumor necrosis factor (TNF)-α.[4] While EPO promotes neuroprotection through the JAK/STAT pathway, the proinflammatory cytokine-mediated signals lead to brain damage, and then, CP development also potentially uses this common JAK/STAT pathway.[12] Under high stress, the proinflammatory cytokines promote JAK/STAT pathway activation, which activates negative feedback inhibition factors such as suppression of cytokine signaling proteins. This renders the JAK/STAT pathway unavailable for EPO action.[12] Thus, the neuroprotective effect of the EPO is reduced due to the high inflammatory cytokine background.[12] This may cause a more general suppression of specific immune reactions that rely on the JAK/STAT pathway, and this elevation of proinflammatory cytokines counter intuitively inhibits the natural defenses of the body.

Receptor-associated JAKs form binding sites for STATs through phosphorylation after becoming activated by ligands. STATs are cytoplasmic transcription factors that are latent until recruited by JAKs, which then undergo tyrosine phosphorylation and dimerization. Activated STATs are transferred to the nucleus and bind to DNA, thereby converting an extracellular signal to a

Table 1: Summary of three cerebral palsy patients who developed hepatoblastoma

Case	Age and gender	Gestational age	Diagnostics	Treatment
Case 1	6-year-old female	26 weeks	Spastic dystonic quadriplegic cerebral palsy with GMFCS level IV, MACS level IV, and CFCS level II	Chemotherapy with cisplatin, vincristine, fluorouracil, and adriamycin Resection of the hepatoblastoma approximately 3 months after initiation of chemotherapy Following recovery from surgery, the patient completed another 3 months of chemotherapy
Case 2	3-year-old male	28 weeks	Spastic diplegic cerebral palsy with GMFCS level II, MACS level I, and CFCS level I	Multiple rounds of chemotherapy Resection of the tumor and liver transplantation
Case 3	17- month-old male	25 weeks	Chronic lung disease, laryngomalacia, GERD, ROP, and cerebral palsy	Four cycles of neoadjuvant chemotherapy Complete resection Two cycles of adjuvant chemotherapy

GMFCS – Gross Motor Function Classification scale; MACS – Manual ability classification system; CFCS – Communication function classification system; GERD – Gastroesophageal reflux disease; ROP – Retinopathy of prematurity

transcriptional response. Members of the IL-6 family bind to receptors and activate the JAK/STAT pathway, activating the transcription of other inflammatory genes.[13] Due to elevated proinflammatory IL-6 in individuals with CP, there may be dysregulation in this JAK/STAT pathway, which then influences gene transcription, proliferation, and the normal cancer surveillance function of the immune system [Figure 1].

The dysregulation of the mitogen-activated protein kinase (MAPK) pathways is well-documented in many malignancies, including in the liver.[14] MAPKs are a diverse collection of serine/threonine protein kinases, which regulate cellular responses to a variety of stimuli, such as osmotic stress, mitogens, heat shock, and inflammatory cytokines that impact cell proliferation, differentiation, survival, and apoptosis (i.e. IL-1, TNFα, and IL-6).[13] Any disruption in the MAPK pathways leads to dysregulated cellular activity and increased cancer risk, and thus, the elevated levels of proinflammatory cytokines seen in CP may activate MAPK pathways in synergy with the JAK/STAT pathway links to promote inflammatory, autoimmune, metabolic, and cancer-related disorders.[13]

The nervous system can have a direct effect on cancer pathogenesis through multiple mechanisms.[15] Nerve growth factor (NGF) not only affects neuronal growth but also impacts immune function, the NGF receptor is expressed by B and T lymphocytes as well as monocytes and is upregulated in response to inflammation.[16] NGF is released at high levels in CP and activates nociceptors that are associated with the chronic pain experienced by CP patients.[17] There has recently been great interest in understanding the role of the nervous system in directly promoting the development and spread of cancer.[15] Tumors of the liver are highly innervated by the sympathetic and parasympathetic nervous systems and this has led to the definition of the "nerve-cancer circuit," where nerves directly stimulate tumor growth through the release of neuropeptides.[18] The importance of innervation in hepatoblastoma is less well understood.

CEREBRAL PALSY CAUSES EXCESSIVE INFLAMMATION

A number of single nucleotide polymorphisms (SNPs) in different genes have been associated with CP. In particular, the rs1042714 SNP in the β-2 adrenergic receptor (ADRB2) gene is associated with the development of CP after preterm birth.[19] ADRB2 is involved in the regulation of cerebral blood flow and inflammation,[20] but can also modify responses to environmental factors such as oxygen radicals from oxygen ventilators through a variety of mechanisms, such as the secretion of C-reactive protein (CRP).[19] There was an 8-fold, higher level of CRP in the plasma of children with CP in comparison with CP and healthy adults;[21] however, this study did not measure CRP abundance in the serum of non-CP children. In another study, to understand how chronic inflammation is associated with CP compared with cytokine levels in healthy children, the investigators measured serum levels of TNFα as a marker for systemic inflammation. They

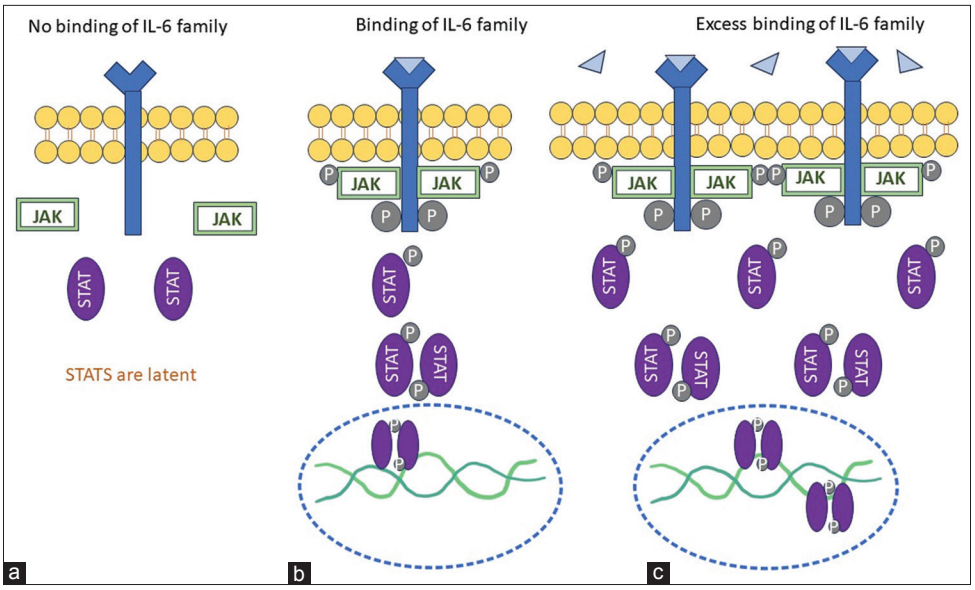

Figure 1: STAT transcription factors are located in the cytoplasm (a). The binding of interleukin (IL)-6 family members to their target receptor promotes JAK phosphorylation and the recruitment of STAT transcription factors. Phosphorylated STATs translocate to the nucleus and promote cytokine expression (b). Chronic IL-6 production causes dysregulation of downstream inflammatory cytokines (c). IL – Interleukin

found that healthy children had TNFα levels of 3.80 pg/ml and children with CP had TNFα levels of 11.15 pg/ml.[6] After age-adjustment of the data, there was a reduction in significance; however, there was a trend of two-fold higher levels of circulating TNFα in children with CP. This study also identified a 1.5-fold higher level of IL-6 in children with CP, similar to previous studies. However, CRP concentrations greater than 1 mg/L indicative of systemic inflammation was recorded in only 2 of 23 CP patients.[6] Consequently, children with CP only have moderate activation of their innate immune system, despite the proinflammatory cytokine background.[22] These data suggest that the innate immune system (which is the main defense system in infants) is moderately weak in patients with CP and may possibly not be able to identify and challenge malignant cells.

Inflammation is associated with a variety of different chronic diseases including arthritis, diabetes, heart disease, and obesity.[23] This chronic state of inflammation increases the likelihood of developing cancer by impairing the growth of healthy cells, impairing immune function, and promoting survival signals in malignant cells. The potentially elevated inflammation in individuals with CP identified as having abnormally elevated IL-6, CRP, and TNFα may put that individual at an increased risk of hepatoblastoma development.[24]

METABOLIC IMPACT OF CEREBRAL PALSY

In one study, metabolic imbalance was identified in all children with CP ($n = 23$).[6] Liver dysfunction and associated metabolic problems can be a precursor to hepatoblastoma development. The FXR ligand-activated transcription factor plays a role in regulating the synthesis of bile acid and modulating the circulation in the enterohepatic system. It can also have an impact on carbohydrate and lipid homeostasis.[25] Since FXR is a transcription factor, it can directly control the expression and activation of tumor suppressors involved in controlling gastrointestinal and hepatic cancers.[25] Metabolic dysregulation that brings about disruption of normal FXR function may contribute to tumor cell survival and cancer development.[25] The chronic inflammatory state associated with obesity and metabolic syndrome in adults is an established risk factor in adult malignancies; however, this contribution to risk is believed to evolve over many years. Whether metabolic problems that exist prenatally will contribute to the development of malignancies such as hepatoblastoma in early childhood is unclear. There is little evidence linking altered metabolism with malignancy in children. However, it has been proposed that children with CP have increased metabolic needs because of hypertonia or developmental problems compared with other children.[26] Elevated metabolic needs can lead to poor weight gain and immune dysfunction, which can leave the body weakened and susceptible to cancer. A study of patient tissue samples and pre-clinical modeling showed that there was some element of metabolic disruption across multiple pediatric cancer types.[15]

CEREBRAL PALSY AND INFANT GROWTH

The well-being and general health of an infant can be determined by physical growth, thus abnormal growth can indicate a disruption in child's nutrition and health.[27] Children with CP experience growth at a slower rate even under seemingly good conditions (a suitable environment and regular medical attention) than children without chronic health conditions. Poor growth in children with CP is due to multiple factors such as poor nutritional intake, abnormal endocrine function with reduced growth hormone production, and decreased mechanical weight bearing that can also have other negative effects on development.[28] Bilateral CP is more strongly associated with poor growth than unilateral CP, suggesting a degree of compensation is possible.[29] The neurological deficiencies associated with CP can have a broad impact on numerous developmental processes.[29] All children with CP, regardless of their degree of motor impairment, are at risk for malnutrition, and children with CP show reduced levels of exploration and attachment behaviors that can have an impact on the development of social-emotional development.[29] Malnutrition, where insufficient micro- and macronutrients are taken into or absorbed by the body to support normal development, itself can have negative effects on motor function, neurological function, and psychological function.[29] In addition, malnutrition in children with CP increases the severity of gastroesophageal reflux. Infants with CP can experience difficulty in getting proper nutrition and gain or maintain weight due to swallowing, sucking, or other feeding problems.[30] Poor oral-motor function is a significant problem for infants with CP which makes it difficult for the child to safely consume the calories and nutrients necessary for growth.[29] CP may affect not only the gross motor function, but also swallowing and feeding function. It was found that swallowing disorders were found in 64.9% of children with CP.[31] Since numerous cancers are linked to dietary deficiencies, particularly vitamin deficiency,[1] infants with CP are likely more vulnerable to malignancy. A meta-analysis has revealed that the risk of liver cancer increases with vitamin D deficiency.[32]

Patterns of abnormal growth in children with CP suggest possible endocrinopathy.[23] Patterns of growth

hormone (GH) secretion in children with CP and growth failure have been investigated. In a study group of 10 children with CP and growth failure, 6 had abnormal GH secretion, both naturally and in response to pharmacological stimulation (Arginine/l-DOPA), consistent with GH deficiency.[23] The authors reached a conclusion that growth failure of children with CP can be caused by abnormalities of GH secretion.[23] GH plays an important role in immune function and contributes to the lymphocyte proliferation, immunoglobulin synthesis, and cytokine release. In combination with other aspects of immune system dysregulation, GH deficiency may suppress immune surveillance in the circulation of children with CP.

Gastrointestinal (GI) symptoms are a prominent facet of CP and 92% of children with CP exhibited clinically significant GI symptoms, most often due to GI motility problems.[33] This can cause poor digestion and malabsorption of nutrients from the diet, which can lead to poor growth. GI motility problems can cause vomiting, which is present in 32% of patients with CP, and which can further suppress nutrients absorption. Abnormal growth can have an impact on the development of many systems in the body, including the immune system[29] which is crucial in controlling cancer development.

CEREBRAL PALSY AND MOBILITY

Deficiencies in movement and posture control are a common feature of CP and symptoms vary considerably from person to person as well as changing over time. A large contributor to the symptom profile is the region(s) of the brain impacted. Many children with CP are unable to engage in sports and other activities at a level of intensity that is sufficient to build strength and maintain fitness.[23] These children often grow up with an increased severity of chronic disease and arrest in development that impacts their overall health and well-being.[30] This is correlated with immune system dysfunction and cancer vulnerability.[34] The World Health Organization's Global Action Plan for the Prevention and Control of Noncommunicable Diseases (NCDs) (including cancer) from 2013 to 2020 aimed to manage and control NCDs and their main risk factors such as obesity, smoking, inactivity, excessive alcohol consumption, and unhealthy diets in adults.[35] The lack of physical activity experienced by children with CP is a major lifetime risk factor for the development of NCDs, particularly cardiovascular problems.[34] The risk of developing any malignancy (relative risk [RR] = 6.51) or metastatic disease (RR = 9.81) was higher for children with CP than for children without CP.[34] There is

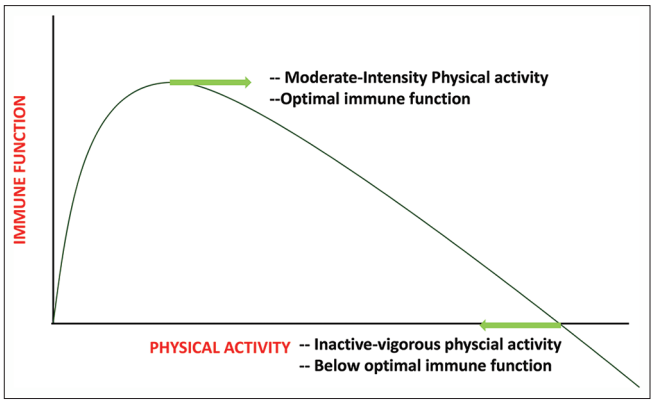

Figure 2: The relationship between physical activity and immune function is an inverted J curve. There is an optimum level of activity to achieve maximum immune function. Excessive strenuous activity and inactivity suppress the immune system

substantial epidemiological evidence that suggests adults who partake in more elevated levels of physical activity have a diminished probability of developing a variety of cancers compared with those who participate in lower levels of physical activity.[24] Studies show mixed results, as to whether exercise interventions result in a reduction in biomarkers linked to physical inactivity such as CRP and IL-6. During exercise, especially during moderate-power oxygen-consuming activities, the T-lymphocyte, NK cell, and neutrophil populations rise and become more active.[24] While this occurs temporarily during an intense bout of exercise, these effects may have a cumulative training effect on the immune system.[24] Chronic periods of physical activity have been linked with an inverted "J-curve" where moderate-intensity physical activity promotes optimal immune-system function, while inactive and vigorous-intensity exercise both result in below optimal immune-system function[24] [Figure 2].

CONCLUSION

Hepatoblastoma is a rare childhood malignancy where one of the major risk factors is a diagnosis of CP. This is because CP may put the individual at risk for a debilitated immune system and stimulate the production of inappropriate proinflammatory cytokines. Two signaling pathways, JAK/STAT and MAPK pathways, can be affected by the abnormal levels of proinflammatory cytokines. These can then have an antagonistic effect on the cancer surveillance system. The immune system loses its capacity to fight malignant cells that arise in response to carcinogens. CP can increase the risk of hepatoblastoma due to the chronic inflammatory state of the immune system and the associated release of growth promoting cytokines. Metabolic defects, which impact on liver function, can arise in CP children, further increasing

the risk of hepatic malignancy. Poor nutrition, GI tract problems, and deficiency in GH release contribute to the poor growth and mobility problems associated with CP that collectively impact immune function and the overall health. In combination, these factors can significantly increase the risk of cancer development for patients with CP in the same way that they can contribute to overall cancer risk in the general population. Poor nutrition results in poor immune function and the loss of immune surveillance capacity. Adults with CP are at greater risk of developing metabolic syndrome, which itself is a risk factor in the development of cancer.[36,37] Whether such metabolic problem can contribute to cancer development in children with CP remains to be established. A better understanding of how the different facets of CP affect the function of the immune system may provide a better understanding of why this neurological condition has an apparent link to hepatoblastoma.

Peer review

This article was peer-reviewed by two independent and anonymous reviewers.

Data availability statement

Data sharing is not applicable for this article, as no new data were created or analyzed.

Author contributions

Conceptualization: N.S.H. and W.T.; Methodology: N.S.H. and W.T.; Writing–original draft preparation: N.S.H.; Writing – review and editing: N.S.H. and W.T.; Supervision: W.T.

Both authors have read and agreed to the published version of the manuscript.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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