RESEARCH ARTICLE

A Brief Report on the Prevalence of Vitamin D3 Deficiency in Children with Brain Tumors

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Abstract

Introduction: For both benign and malignant brain tumors, the outcome continues to remain dismal despite the progress made in the last half a century. The picture is gloomier in the pediatric age-group. As for any disease with limited survival and high morbidity, it is imperative to study the disease etiology to have meaningful interventions. Apart from genetics that cannot be modified, environmental and dietary factors play a role in oncogenesis, and these are potentially modifiable. A lesser-studied aspect is the role of micronutrients in the causation of brain tumors, especially in early childhood. We analyzed the association of vitamin D3 (Vit D3) in children with brain tumors.

Methods and materials: A prospective study of 50 children diagnosed with brain tumors in early childhood (<5 years old) was carried out. Vit D3 levels were measured in the blood samples of these patients and their mothers. A correlation was established between levels of Vit D3 and brain tumors.

Results: Around 26 children (52%) with pediatric brain tumors (PBTs) had Vit D3 deficiency. Of the 50 patients whose mothers were also analyzed, 22 (44%) mothers had Vit D3 deficiency. Interestingly, out of 26 children with Vit D3 deficiency, 17 were those whose mothers were also having hypovitaminosis D3. If the mother is deficient in Vit D3, the odds ratio for a child to be deficient in Vit D3 is 7.2

Conclusion: Large majority of children with brain tumors and their mothers were found to have a deficiency of Vit D3. Further large studies are required before any meaningful prevention strategy can be formulated.

Keywords: Brain tumors, Deficiency, Vitamin D.

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Introduction

The availability of advanced diagnostics, better surgical techniques, and adjuvant therapy has definitely improved survival in PBT, but the overall scenario remains dismal. The future strategy has to focus on disease etiology and therapeutic interventions in relation to these. Various carcinogens have been described in the literature. These include radiation (ionizing and nonionizing), N-nitroso compounds, and viral infections (John Cunningham virus, cytomegalovirus, human immunodeficiency virus, simian virus 40, varicella zoster, and chicken pox).[1–5] Since many micronutrients like Vit B9, Vit B12, and Vit D3 play an important role in deoxyribonucleic acid (DNA) metabolism; it is logical to conclude that insufficiency of these nutrients could potentially lead to DNA damage or incorrect methylation leading to tumorigenesis.[4,6,7]

There has been a recent interest in the role of Vit D3 in tumorigenesis. Various mechanisms, which may be Vit D receptors (VDR) dependent or independent, have been suggested. Vit D 3 seems to affect every stage of tumorigenesis from initiation to spread.[8–12] However, the journey from lab to actual clinical benefit is still not fully established. Furthermore, elaborate studies which can conclusively comment on the role of such micronutrients in PBT are lacking.

Since a deficiency of micronutrients is a potentially correctable risk factor, an understanding of its role in PBT etiology could be of value in prevention strategies. We studied the levels of Vit D3 in children with brain tumors.

Materials and Methods

A prospective observational study of children <5 years of age suffering from brain tumors was carried out. Patients suspected of having brain tumors on the basis of clinical diagnosis underwent contrast-enhanced magnetic resonance imaging of the brain to have a provisional diagnosis. After obtaining informed consent, these patients underwent surgery for tumor removal as per department protocol. The tumor specimen was subjected to histopathology, and a final diagnosis was established. Those with recurrent brain tumor or on nutritional supplements were excluded. Ethical approval was obtained from the institutional ethical committee. Consent for participation in the study was obtained from parents. Blood samples of children and their mothers were collected at admission. These samples were analyzed for serum levels of cholecalciferol (Vit D3) by using direct chemiluminescence acridinium ester technology in the ADVIA Centaur® Siemens machine.

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The normal value in our laboratory is 11–43 ng/mL. A deficiency of vitamins was considered if the measured value was less than the lower limit. The results from children and mothers were analyzed with respect to brain tumors and the incidence of hypovitaminosis D3.

Results

The study group included 50 children and their mothers. Age of the children ranged from 4 to 56 months (mean 32 months). There were 28 males and 22 females. The age of mothers ranged from 23 to 46 years (mean 29 years).

The range of brain tumors found was—medulloblastoma in 16 children, pilocytic astrocytoma in four, primitive neuroectodermal tumor in two, craniopharyngioma in six, brainstem glioma in six children, and other tumors in rest.

A total of 26 (out of 50) and 22 mothers (out of 50) had Vit D3 deficiency (Table 1).

Interestingly, we found that of the 26 children with VitD3 deficiency, 17 were the ones whose mothers also had hypovitaminosis D3. If the mothers were deficient in Vit D3, the odds ratio for a child to be having hypovitaminosis Vit D3 was 7.2.

Discussion

Carcinogenesis is a complex multifactorial process. These factors include genetic and environmental or what is known as—"Nature or Nurture." An individual cannot change his/her genetic makeup, and therefore, the genetic factors influencing carcinogenesis remain largely unmodifiable. Since environmental factors can potentially be tweaked to our advantage, a major thrust of cancer research is focused on these factors.

Children <5 years of age, in the growing phase, have a high nutrient demand. Nutrient deficiency during intrauterine life or in early childhood can potentially lead to faulty DNA production and hence predispose them to tumor formation.

The role of certain vitamins is paramount in DNA methylation, cell division, and differentiation. Deficiency of Vit B9, Vit B12, and Vit D3 plays a role in the development of certain childhood brain tumors like medulloblastoma, primitive neuroectodermal tumors, and glioma.[6,13]

In the present study, we found that majority (56%) of children with brain tumors had Vit D3 deficiency. Of these, 65% were the ones whose mothers also had Vit D3 deficiency. It appears feasible that during a crucial stage of organogenesis, *in utero*, when cells are rapidly dividing, micronutrient deficiency can lead to faulty DNA production leading to tumorigenesis.

Vitamin D3 (Vit D3) deficiency has been implicated in the causation of as many as 18 different types of cancers. Breast cancer exhibits antiproliferative effects through both VDR and independent pathways.[10] In malignant pleural mesothelioma, calcitriol decreases cell viability and also decreases proliferation. It also augments the effect of chemotherapy.[11]

Various hypothesis has been suggested explaining the role of Vit D3 as an antitumorigenic agent during the initiation and progression of the tumor. During the initiation phase, Vit D3 exhibits anti-inflammatory properties by inhibiting prostaglandin production. Vit D3 has an antiproliferative effect that causes cell cycle inhibition at different levels by inducing cyclin-dependent kinase 1 (CDK1), CDK 2, and downregulation of CDK1, leading to arrest in the growth 2 (G_2) phase.[14] Vit D3 can suppress vascular endothelial growth factor expression leading to antiangiogenesis with consequent growth inhibitory effect on endothelial cells. It can induce p21 expression and G_1 phase cell cycle arrest in a mutant p53, which is VDR dependent. In addition, it limits reactive oxygen species-induced cell damage. During the tumor progression stage, it exhibits antiproliferative and differentiation action and also induces apoptosis through a mitochondrial-dependent pathway by the release of cytochrome c and protein of the B-cell lymphoma 2 families. It can induce differentiation in cancer cells through repression of Wnt/β-catenin signaling. Further, Vit D3 induces autophagic cell death.[8,9,12]

Further, Vit D3 inhibits the signaling of the Hedgehog pathway.[13] Hedgehog pathway is an essential developmental signaling pathway in maintaining tissue polarity and stem cell population.[15] Hedgehog signaling pathway has been especially implicated in the causation of medulloblastoma. The mitogenic nature of the sonic hedgehog (Shh) ligand leads to massive granule neuron progenitors in the developing cerebellum. If the Shh pathway is constitutively activated, proliferation persists beyond the normal development period leading to medulloblastoma.[16] Shh pathway stimulation promotes secretion of angiogenic factors such as activin A, angiogenin, angiopoietin 1, granulocyte-macrophage colony-stimulating factor, matrix metallometallopeptidase-9, and urokinase-type plasminogen activator.[17]

Since adequate levels of Vit D3 appear to be so important as an anticancer agent, it is imperative to have a look at the reasons for its deficiency. These include poor sunlight exposure due to fewer outdoor activities. Increasing urbanization with small dwelling units and lifestyle changes are potential reasons. Children, instead of playing outdoors, prefer to spend their free time in front of the television, computers, smartphones, etc. In addition, certain diseases like pneumonia/diarrhea/mucositis, etc., can cause loss of appetite leading consequently to poor oral intake of dietary Vit D3. Infants and very young children might inherit Vit D3 deficiency from their mothers. Maternal dietary modifications at the level of the community have the potential to not only prevent commonly associated benign diseases linked with vitamin D deficiency (rickets) but may also prevent dreaded diseases like brain tumors in future progeny.

Table 1: Distribution of Vit D3 levels among children with brain tumors and their mothers

		Maternal Vit D3 levels			
		Hypovitaminosis	*Normal*	*Hypervitaminosis*	*Total*
Vit D3 levels in children	Hypovitaminosis	17	6	3	26
	Normal	4	13	0	17
	Hypervitaminosis	1	6	0	7
	Total	22	25	3	50

Limitations of the study include (1) the small size of the study group, (2) the lack of a control group of age-matched children to establish the causal relation, and (3) vitamin levels were measured at diagnosis, which after the phase of pathogenesis. We suggest a high-volume, multicentric prospective population study with a focus on the antenatal and immediate postnatal periods.

Conclusion

Children with brain tumors had a high prevalence (52%) of Vit D3 deficiency. Amongst such children, 65% patients' mothers were also deficit in Vit D3. However, further large-scale studies are needed before any meaningful preventive strategy can be formulated.

References

1. Lau SK, Chen YY, Chen WG, et al. Lack of association of cytomegalovirus with human brain tumors. Mod Pathol 2005;18(6):838–843. DOI: 10.1038/modpathol.3800352
2. Moulder JE, Foster KR, Erdreich LS, et al. Mobile phones, mobile phone base stations, and cancer: a review. Int J Radiat Biol 2005;81(3):189–203. DOI: 10.1080/09553000500091097
3. Shirai T, Kawabe M, Ichihara T, et al. Chronic exposure to a 1.439 GHz electromagnetic field used for cellular phones does not promote N-ethylnitrosourea induced central nervous system tumors in F344 rats. Bioelectromagnetics 2005;26(1):59–68. DOI: 10.1002/bem.20079
4. Naveilhan P, Berger F, Haddad K, et al. Induction of glioma cell death by 1,25(OH)2 vitamin D3: towards an endocrine therapy of brain tumors? J Neurosci Res 1994;37(2):271–277. DOI: 10.1002/jnr.490370212
5. Dietrich M, Block G, Pogoda JM, et al. A review: dietary and endogenously formed N-nitroso compounds and risk of childhood brain tumors. Cancer Causes Control 2005;16(6):619–635. DOI: 10.1007/s10552-005-0168-y
6. Milne E, Greenop KR, Bower C, et al. Maternal use of folic acid and other supplements and risk of childhood brain tumors. Cancer Epidemiol Biomark Prev 2012;21(11):1933–1941. DOI: 10.1158/1055-9965.EPI-12-0803
7. Greenop KR, Miller M, de Klerk NH, et al. Maternal dietary intake of folate, and vitamins B6 and B12 during pregnancy and risk of childhood brain tumors. Nutr Cancer 2014;66(5):800–809. DOI: 10.1080/01635581.2014.916326
8. Wu X, Hu W, Lu L, et al. Repurposing vitamin D for treatment of human malignancies *via* targeting tumor microenvironment. Acta Pharm Sin B 2019;9(2):203–219. DOI: 10.1016/J.APSB.2018.09.002
9. Bilani N, Elson L, Szuchan C, et al. Newly-identified pathways relating vitamin D to carcinogenesis: a review. In Vivo 2021;35(3):1345–1354. DOI: 10.21873/invivo.12387
10. Bernhardt SM, Borges VF, Schedin P. Vitamin D as a potential preventive agent for young women's breast cancer. Cancer Prev Res (Phila) 2021;14(9):825–838. DOI: 10.1158/1940-6207.CAPR-21-0114
11. Gesmundo I, Silvagno F, Banfi D, et al. Calcitriol inhibits viability and proliferation in human malignant pleural mesothelioma cells. Front Endocrinol (Lausanne) 2020;11:559586. DOI: 10.3389/fendo.2020.559586
12. Jeon SM, Shin EA. Exploring vitamin D metabolism and function in cancer. Exp Mol Med 2018;50(4):1–14. DOI: 10.1038/s12276-018-0038-9
13. Uhmann A, Niemann H, Lammering B, et al. Calcitriol inhibits hedgehog signaling and induces vitamin d receptor signaling and differentiation in the patched mouse model of embryonal rhabdomyosarcoma. Sarcoma 2012:2012:357040. DOI: 10.1155/2012/357040
14. Eelen G, Gysemans C, Verlinden L, et al. Mechanism and potential of the growth-inhibitory actions of vitamin D and analogs. Curr Med Chem 2007:14(17):1893–1910. DOI: 10.2174/092986707781058823
15. Ingham PW, McMahon AP. Hedgehog signaling in animal development: paradigms and principles. Genes Dev 2001:15(23):3059–3087. DOI: 10.1101/gad.938601
16. Pak E, Segal RA. Hedgehog signal transduction: key players, oncogenic drivers, and cancer therapy. Dev Cell 2016;38(4):333–344. DOI: 10.1016/j.devcel.2016.07.026
17. Zavala G, Prieto CP, Villanueva AA, et al. Sonic hedgehog (SHH) signaling improves the angiogenic potential of Wharton's jelly-derived mesenchymal stem cells (WJ-MSC). Stem Cell Res Ther 2017;8(1):203. DOI: 10.1186/s13287-017-0653-8