PREVALENCE AND RISK FACTORS OF ENDOCRINE DISORDER IN CHILDHOOD BRAIN TUMOR SURVIVORS: A SINGLE- CENTRE STUDY

DR NURUL WAHIDAH BINTI RAMEZAN

DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE DEGREE OF MASTER IN MEDICINE (PAEDIATRICS)

UNIVERSITI SAINS MALAYSIA

2023

Principal Investigator:

Dr. Nurul Wahidah RAMEZAN

Department Paediatric, School of Medical Sciences,

Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan

Main supervisor:

Dr. Suhaimi HUSSAIN

Consultant Paediatric Endocrinologist,

Department of Paediatric, School of Medicine Sciences,

Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan

Co-supervisor:

Assoc Prof.Dr.Norsarwany MOHAMAD

Consultant Paediatric Haemato-oncologist,

Department of Paediatric, School of Medicine Sciences,

Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan

Dr.Najib Majdi YAACOB

Medical Lecturer/ Public Health Specialist

Department of Biostatistics and Research Methodology, School of Medical Science,

Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan

ACKNOWLEDGEMENT

Of the utmost importance, praises and thanks are due to Allah, the Almighty, for showering me with blessings to go through my research work and to complete the research successfully.

I would like to express my heartfelt thanks to my research supervisor,Dr. Suhaimi bin Hussain (Lecturer and research supervisor, Pediatric Department, Hospital Universiti Sains Malaysia) for providing endless guidance throughout this research. His expertise greatly assisted this research. I was deeply inspired by his vision, sincerity and motivation. It was an enormous privilege to work and study under his guidance. I am also extending my undying gratitude to my co-supervisor,Assoc Prof.Dr.Norsarwany Mohamad (Associate professor and research co-supervisor, Pediatric Department, Hospital Universiti Sains Malaysia) for her advice and guidance.

The expertise of Dr Najib Majdi B Yaacob, Biostatistician and Lecturer in Biostatistics and Research Methodology Department, School of Medical Sciences, Universiti Sains Malaysia have hugely helped me in completing this study.

The assistance from the staff of the Record Department, Hospital Universiti Sains Malaysia has been such a blessing in completing my data collection.

I am forever indebted to my parents for their love, prayers, caring and sacrifices in raising me and their continuous support to complete this research. Finally, thank you to all the people who have supported me to complete this research.

TABLE OF CONTENTS

CHAPTER III: THE REFERENCE MATERIALS

LIST OF TABLES AND FIGURES

LIST OF ABBREVIATION AND NOMENCLATURE

USM	:	Universiti Sains Malaysia
IDF	:	International Diabetes Federation
ICD-10	:	International Classification of Diseases 10th Revision
DOSM	:	Department of Statistics
HIS/BA	:	Household Income and Basic Amenities
CBTRUS	:	Central Brain Tumor Registry of the United States
IQR	:	Interquartile range
OR	:	Odd ratio
CNS	:	Central nervous system
BNP	:	Brain natriuretic peptide
HPA	:	Hypothalamic pituitary axis
GH	:	Growth hormone
TSH	:	Thyroid-stimulating hormone
ACTH	:	Adrenocorticotropic hormone
LH	:	Luteinizing hormone
FSH	:	Follicle- stimulating hormone
CBTS	:	Childhood brain tumor survivors
DNET	:	Dysembryoplastic neuroepithelial tumor
PNET	:	Primitive neuroectodermal tumor
sPNET	:	Supratentorial primitive neuroectodermal tumor
RT	:	Radiotherapy
CSI	:	Craniospinal irradiation

SIADH : Syndrome of inappropriate antidiuretic hormone secretion

CSW : Cerebral salt wasting

DI : Diabetes insipidus

MPHD : Multiple pituitary hormone deficiency

GHD : Growth hormone deficiency

ACTHD : Adrenocorticotropic hormone deficiency

MetS : Metabolic syndrome

SD : Standard deviation

ABSTRAK

Kelaziman dan Faktor – Faktor Risiko berkaitan Masalah Endokrin dalam kalangan Survivor Kanser Otak Kanak- Kanak; Kajian Setempat.

Objektif: Tujuan kajian adalah untuk menilai kelaziman dan faktor-faktor risiko masalah endokrin dalam kalangan survivor kanser otak kanak- kanak.

Kaedah: Kajian telah dijalankan di Hospital Universiti Sains Malaysia (USM), Kelantan, Malaysia dan melibatkan 124 survivor kanser otak kanak- kanak dari Januari 2002 sehingga Disember 2017. Subjek adalah survivor kanser otak kanak- kanak yang berumur 18 tahun dan ke bawah dan mempunyai kanser otak yang berada dalam keadaan stabil atau dalam "remission" dan hidup sekurang-kurangnya 2 tahun selepas diagnosis. Data demografik (umur ketika diagnosis,jantina, kaum, status sosioekonomi), data antropometri (berat, tinggi, ukur tinggi ibu bapa), tahap akil baligh menurut "Tanner staging", karakter tumor, pilihan rawatan dan penyiasatan endokrin pada waktu diagnosis dan semasa rawatan susulan. . Kaedah "Logistic Regression" telah digunakan untuk menaksir faktor- faktor risiko berkaitan masalah endokrin dalam kalangan survivor kanser otak kanak-kanak.

Keputusan: Kelaziman masalah endokrin dalam kalangan survivor kanser otak kanak-kanak adalah 62.1%. Faktor-faktor risiko adalah BMI yang tinggi [adjusted odds ratio (OR) 1.29 , 95% CI: 1.12 to 1.5] , lokasi berisiko tinggi [adjusted odds ratio (OR) 7.15, 95% CI: 1.41 to 36.3] dan kemoterapi [adjusted odds ratio (OR) 0.18 , 95% CI: 0.05 to 0.62].

Kesimpulan: Kelaziman masalah endokrin dalam kalangan survivor kanser otak kanak-kanak di center kami adalah 62.1%. Faktor-faktor risiko adalah BMI yang tinggi, lokasi berisiko tinggi (suprasellar dan intrasellar) dan kemoterapi.

Kata Kunci: Masalah endokrin, Survivor Kanser Otak Kanak-Kanak ,faktor-faktor risiko

ABSTRACT

Prevalence and risk factors of endocrine disorder in childhood brain tumor survivors : A single-centre study.

Objective: We aimed to study the prevalence and risk factors of endocrine disorder in childhood brain tumor survivors.

Methodology: This study took place at Hospital USM and recruited 124 childhood brain tumor survivors from January 2002 till December 2017. We included brain tumor survivors, 18 years old or younger with either stable disease or in remission and survived for at least 2 years after diagnosis. Demographic data (age at diagnosis, gender, ethnicity, socioeconomic status), clinical clues for endocrine disorders, anthropometrics (weight, height, midparental height), pubertal stage according to Tanner staging, tumor-related characteristics, treatment modalities and endocrine laboratory measurements at diagnosis and during follow up. Logistic regression was applied to evaluate risk factors of endocrine disorder in childhood brain tumor survivors.

Results: The prevalence of endocrine disorders in childhood brain tumor survivors was 62.1%. The risk factors were high BMI [adjusted odds ratio (OR) 1.29 , 95% CI: 1.12 to 1.5] , high risk site [adjusted odds ratio (OR) 7.15, 95% CI: 1.41 to 36.3] dan chemotherapy [adjusted odds ratio (OR) 0.18 , 95% CI: 0.05 to 0.62].

Conclusion: The prevalence of endocrine disorders in childhood brain tumor survivors in our centre was 62.1%. The significant risk factors were high BMI, tumor location (suprasellar and intrasellar) and chemotherapy.

Keywords : Endocrine disorder, Childhood Brain Tumor Survivors, Risk Factors.

CHAPTER II

THE TEXT

2.1

SECTION A

INTRODUCTION

INTRODUCTION

Brain tumors are the most common type of paediatric solid organ tumor[4] and the second most common childhood malignancies after leukaemia, in which it contributes to 21% of all paediatric malignancies[2]. The prevalence of paediatric brain tumors varies among different countries, with the highest rates reported in the United States[4]. The average annual incidence of primary CNS tumors for children and adolescents ≤19 years old in the United States from 2011 to 2015 was 5.95 cases per 100,000 population[4].Approximately 60 percent of cases were malignant and 40 percent non-malignant. According to the Malaysian National Cancer Registry Report 2007–2011, the national incidence of childhood brain and central nervous system (CNS) tumors is 2 per 100,000 children[5]. There were lower incidence rates that have been reported in other parts of the world, such as Japan (estimated incidence 3.61 per 100,000 children)[6] and Italy (3.46 per 100,000 children)[7].

The mortality of childhood brain tumors exceeds the mortality rate of acute lymphoblastic leukaemia, making it the leading cause of childhood cancer-related deaths[4]. Their prognosis and survival rates depend on multiple factors including the histological type, size, and location of the tumor. The survival outcomes in childhood brain tumors have improved significantly due to the advances in diagnosis and treatment, as well as the understanding of the disease aetiology.

With improved survival rate, there has been a rising concern regarding the late sequelae of childhood brain tumor survivors, especially when craniospinal radiation therapy (RT) is used in young children. Their long-term complications such as neurological impairments, cognitive dysfunction and growth, and endocrine disturbances have increased[13]. Many survivors will face numerous lifelong health-related challenges after curative treatment of a childhood brain tumor[13].

There are few studies done regarding prevalence of endocrine disease among patients with childhood brain tumors survivors. The prevalence was 49% in the United States and Canada, and 40% of those had multiple endocrine deficits [13]. In South Korea , the prevalence was lower, estimated at about 37.1%[16]. Locally the prevalence was 61%[17] from a study in UMMC. Hypothalamic pituitary axis (HPA) dysfunction is usually associated with brain tumors located near the hypothalamic-pituitary area . Common endocrine complications consist of growth hormone (GH) deficiency and deficiency of thyrotropic and adrenocorticotropic hormones[19].Several studies suggest that the lack of appropriate and timely follow-ups could result in late referrals, hence adversely influencing the outcome related to endocrine dysfunctions [26].

Age at cancer diagnosis, tumor histology, tumor location and radiation exposure are identified to be the potential risks for developing these complications[13]. Cranial radiotherapy is the main cause of hypothalamic and pituitary injury and hormonal deficiency in children with brain tumors[19]. A recent analysis of the St Jude Lifetime Cohort revealed that there was at least one anterior pituitary disorder in 51.4% of childhood cancer survivors who received cranial radiotherapy[24].

Sufficient amounts of circulating hormones are crucial for ample recovery and for maintaining optimal growth and development into adolescence and ensuring good quality of life.This highlights the importance of on-time surveillance of a functioning endocrine system. Even in children with a brain tumor that has no mass effect on the pituitary region, endocrine dysfunction may present in the first 5 years after diagnosis[24]. Timely recognition and treatment of an endocrine deficiency can improve general well being of patients and better quality of life.

Our findings would contribute to the lack of data regarding prevalence and risk factors of brain tumor survivors not only locally but also worldwide and this clinical information would aid in improving the management of patients who are at risk of endocrine disorders.

2.2

SECTION B

STUDY PROTOCOL

2.2.1

DOCUMENTS

SUBMITTED FOR

ETHICAL APPROVAL

Dissertation proposal

School of Medical Science

University Science Malaysia

Prepared in partial requirement fulfilment

For the Degree of Master of Medicine (Paediatric)

2019/2023

Prevalence and risk factors of endocrine disorder in childhood brain tumor survivors : A single-centre study

Dr Nurul Wahidah Binti Ramezan

P-UM0316/19

Supervisor:

Dr Suhaimi Hussain

Co Supervisor:

Assoc Prof.Dr.Norsarwany Mohamad

Dr Najib Majdi Yaacob

Research title: Prevalence and risk factors of endocrine disorder in childhood brain tumor survivors : A single-centre study

Principal investigator : Dr Nurul Wahidah Binti Ramezan

Supervisor : Dr Suhaimi Hussain

Co-researchers : Assoc Prof.Dr.Norsarwany Mohamad Dr Najib Majdi Yaacob

Introduction

Primary malignant central nervous system (CNS) tumors are the second commonest childhood malignancies, where it accounts for 21% of all paediatric cancers[1] and are the most common paediatric solid organ tumor[18] . The mortality rate childhood brain tumor surpasses the mortality rate of acute lymphoblastic leukemia,making it the leading cause of death from childhood cancer[19] .

The Malaysian National Cancer Registry Report 2007–2011 enunciates that brain and nervous system tumors are the second most common childhood cancers among Malaysian children aged between 0 and 14 years old. The national incidence of childhood brain and central nervous system (CNS) tumors is 2 per 100,000 children[25] . In the United States from 2011 to 2015, the average annual incidence of primary non-malignant and malignant CNS tumors for children and adolescents ≤19 years of age was 5.95 cases per 100,000 population[19] . Approximately 60 percent of cases were malignant and 40 percent non-malignant. Somewhat lower incidence rates have been reported in other parts of the world, including Japan (estimated incidence 3.61 per 100,000 children)[20] , Italy (3.46 per 100,000 children)[21], Germany (2.6 per

100,000 children) [22], Australia (3 per 100,000 children)[23] , and Taiwan (1.7 per 100,000 children)[24] .

Low-grade astrocytomas are the largest group of CNS tumors in children, where pilocytic astrocytoma is the most common, with an incidence of approximately 1 per 100,000 population[19]. Medulloblastoma accounts for approximately 6 to 7 percent of all pediatric CNS tumors (malignant and nonmalignant)[19]. Paediatric sellar and suprasellar tumors contribute approximately 10% of all primary brain tumors in children [2]. More than 90% of purely intrasellar lesions comprises pituitary adenoma. Suprasellar tumors consist of craniopharyngiomas, germinomas, dermoid/epidermoid cysts, lipomas, teratomas, and hamartomas. Other sellar tumors such as meningiomas or gliomas are commonly asymptomatic during childhood and adolescence.

Despite of differences in tumor type and age at diagnosis, overall survival in children with a primary malignant or benign brain tumor has improved significantly, with a current expected 5-year overall survival rate of 73%[3] .However, their quality of life are usually impaired because of treatment-related side-effect[4].The mass effect of the brain tumor and the treatment modality—neurosurgery, cranial radiotherapy (RT), and/or chemotherapy—can cause serious adverse effects on the developing brain. Many survivors will experience various lifelong health-related challenges after curative treatment of a childhood brain tumor [4,7,8]. Neuroendocrine disorders can significantly affect the long-term health and wellbeing of childhood.

Childhood brain tumors located near the hypothalamic-pituitary area are especially associated with an increased risk of hypothalamic pituitary axis (HPA) dysfunction [9]. Common endocrine complications consist of growth hormone (GH) deficiency and deficiency of thyrotropic and adrenocorticotropic hormones [10]. On top of that, the prevalence of endocrine

disease among patients with childhood brain tumors is 49%, and that of more than one endocrine deficiency is estimated to be 40%[4]. Studies suggest that the lack of an appropriate and timely follow-up could lead to late referrals, adversely influencing the hormone balance of these patients[11].

Risk for developing these complications has been associated with age at cancer diagnosis, tumor histology, tumor location and radiation exposure.[4,11,12]. Cranial radiotherapy is a leading cause of hypothalamic and pituitary injury and hormone deficiency in children with brain tumors[13,14]. A recent analysis of the St Jude Lifetime Cohort revealed at least one anterior pituitary disorder after 27.3 years of follow-up in 51.4% of adult survivors of any type of childhood cancer was treated with cranial RT.

Adequate concentrations of circulating hormones are important for adequate recovery and for growth and development into adolescence and optimal daily activities, which emphasize the importance of on-time surveillance of an intact endocrine system. Even in children with a brain tumor that is without mass effect on the pituitary region, dysfunction of the hypothalamic-pituitary system may be present in the first 5 years after diagnosis[15-17].Timely recognition and treatment of an endocrine deficiency can improve daily energy and health and thus improve quality of life.

For these reasons, the primary objective of this retrospective study is to assess the prevalence and risk factors of endocrine disorder in childhood brain tumour survivors in Hospital Universiti Sains Malaysia (Hospital USM).

Problem statement & Study rationale

Reports on the number of childhood brain tumours in Malaysia are scarce. Direct damage to or compression of normal structures can result in various endocrine abnormalities. These

endocrine disorders can also be exacerbated by curative treatment of the tumours. Commonly observed complications are diabetes insipidus and deficiencies of growth hormone, gonadotropin, thyroid-stimulating hormone, and adrenocorticotropic hormone. The most common presentation in children is growth failure, which is caused by either hypothyroidism or growth hormone deficiency.

Hypothalamic dysfunction can cause disabling obesity, disorders of temperature regulation, sleep disorders, or diabetes insipidus. Other morbidity can reflect complications of obesity, including metabolic syndrome, type 2 diabetes mellitus, and non-alcoholic liver disease

The associated morbidity may adversely affect the quality of life because of interference with normal growth and development and psychological adjustment. However, many of these problems can be prevented with early detection and appropriate intervention.

The objectives of this study are to describe prevalence of endocrine disorder in childhood brain tumour survivors and its associated risk factors.

Research Question(s)

What is the prevalence of endocrine disorder in childhood brain tumor survivors in Hospital USM and its associated risk factors?

Objective

General:

1-To identify the prevalence and risk factors of endocrine disorder in childhood brain tumor survivors

Specific:

1. To determine the demographic data of childhood brain tumor survivors in Hospital USM.
2. To determine prevalence of endocrine disorder in childhood brain tumor survivors in Hospital USM.
3. To explore the associated risk factors related to endocrine disorder in brain tumor survivors in Hospital USM.

Literature review

Jaesung Heo and et al.[26] conducted a study regarding Prevalence of Endocrine Disorders in Childhood Brain Tumor survivors in South Korea. It was published in the International Journal of Experimental and Clinical Pathophysiology and Drug Research in 2019. The study aimed to analyze the prevalence of endocrine disorders in childhood brain tumor survivors in South Korea using nationwide Korean National Health Insurance claims database. Patients under 18 years of age who were diagnosed with paediatric brain tumors between January 2007 and December 2016 were identified from the data of the nationwide Korean National Health Insurance claims database. The Korean Classification of Disease, sixth edition, which is based on the International Classification of Diseases 10th Revision (ICD-10) was used. Brain tumors cases were distinguished with the code C71 (malignant neoplasms of brain). Those who did not need oncology consultations for any type of cancer during the 2-year period (2-year washout period) since 2007 were considered to be cancer-free. From a nationwide cohort of patients, they identified in 1,058 patients diagnosed with brain tumors between January 1st 2009 to March 29th 2016. The prevalence of endocrine disorder in brain tumor survivors is 37.1%. The median duration of follow-up from the diagnosis of the primary brain tumor to the diagnosis of the first endocrine disorder was 26.3 (range=0.1-96.7) months. Among the 393 survivors, 333 were

diagnosed with endocrine disorders within 5 years of diagnosis of childhood brain tumors. They evaluate associations between clinical factors and endocrine disorders using multivariable logistic regression. Most endocrine disorders were identified at a median duration of 26.3 (range=0.1-96.7) months of follow-up, with the peak occurring soon after the diagnosis of the tumors. On top of that, they found that: i) a relatively younger age at the time of cancer diagnosis, ii) female gender, and iii) previous history of radiation therapy were independent risk factors for endocrine disorders. After a median follow-up of 60.0 months, 393 (37.1%) patients had at least 1 endocrine disorder. The commonest endocrine disorders were hypopituitarism (17.4%) and hypothyroidism (6.1%). Female gender (odds ratio (OR)=1.45, p=0.005) and age <10 years (OR=1.65, p=0.001) conferred a higher risk. Patients who received radiotherapy were more likely to have endocrine disorders compared to those who did not (OR=1.79, p<0.001). They concluded that for childhood brain tumor survivors with a risk of endocrine disorders, regular assessment of endocrine function and timely interventions are necessary.

Sarah C. Clement and et al.[10] published a journal entitled Prevalence and Risk Factors of Early Endocrine Disorders in Childhood Brain Tumor Survivors: A Nationwide,Multicenter Study. It was published in the Journal of Clinical Oncology in 2016. The study's purpose is to evaluate the prevalence of, and risk factors for, early endocrine disorders in childhood brain tumor survivors (CBTS). This nationwide study cohort consisted of 718 CBTS who were diagnosed between 2002 and 2012, aged 18 years and below at diagnosis, and survived 2 years after diagnosis. Patients with craniopharyngioma or a pituitary gland tumor were excluded. Results of all endocrine investigations, which were executed at diagnosis and during follow-up, were obtained from patient charts. Multivariable logistic regression was used to determine associations between demographic and tumor- and treatment-related variables and the prevalence

of early endocrine disorders. A total of 178 CBTS (24.8%) were diagnosed with an endocrine disorder after a median follow-up of 6.6 years. Furthermore, a number of 159 CBTS (22.1%) presented with at least one endocrine disorder within the first 5 years after diagnosis. On top of that, most endocrine disorders emerged already at a median follow-up time of only 2.2 years. They found that GH deficiency is the earliest and most common pituitary disorder and affects 12.5% of patients after a median follow-up of 6.6 years. The other endocrine disorders were precocious puberty (12.2%), thyroid-stimulating hormone deficiency (9.2%), and thyroidal hypothyroidism (5.8%). The risk of hypothalamic-pituitary dysfunction (n = 138) was associated with radiotherapy (odds ratio [OR], 15.74; 95% CI, 8.72 to 28.42), younger age at diagnosis (OR, 1.09; 95% CI, 1.04 to 1.14), advanced follow-up time (OR, 1.10; 95% CI, 1.02 to 1.18), hydrocephalus at diagnosis (OR, 1.77; 95% CI, 1.09 to 2.88), and suprasellar (OR, 34.18; 95% CI, 14.74 to 79.29) and infratentorial (OR, 2.65; 95% CI, 1.48 to 4.74) tumor site. Their conclusion is that the prevalence of early endocrine disorders among CBTS is high. The observation that 22.1% of CBTS developed at least one endocrine disorder within the first 5 years after diagnosis stresses the importance of early and regular assessment of endocrine function in CBTS who are at risk for endocrine damage.

Eglė Ramanauskienė and et al.[26] did a study regarding Early Development Of Endocrine And Metabolic Consequences After Treatment Of Central Nervous System Tumors In Children. They published the journal in Medicina in 2014. The objective of this study was to characterize endocrine and metabolic late effects after treatment of brain tumors in children. Late complications were studied in 51 children treated for brain tumors at the Hospital of Lithuanian University of Health Sciences during 2000–2011. Data on late endocrine and metabolic effects were gathered from medical records. Most frequently patients suffered from

low-grade glioma (n = 17, 33.3%) and medulloblastoma (n = 13, 25.5%). The majority (n = 42, 82.4%) of the patients underwent surgery;29 (56.9%) received radiotherapy (RT); 26 (51.0%), chemotherapy; and 17 (33.4%), combined treatment. The median follow-up was 21 months (range 0.25–10.6 years). Most common endocrine consequence was low serum insulin-like growth factor (IGF-I) levels (58.3%), found on average in 30.7 months after cancer treatment. Short stature was observed in 34.6% (mean time to development, 47.7 months), and hypothyroidism in 40.7% of patients (mean time to development, 63.6 months). Low bone mineral density was found in 50.0% of the cases after 44.5 months and overweight in 30.0% after 49.9 months of follow-up. The conclusion of this study is that survivors of brain tumors suffer from numerous endocrine and metabolic consequences, the majority of them developing within the first 5 years after brain tumor therapy. An active follow-up aiming for early diagnosis and therapy is essential for improvement of quality of life in these patients.

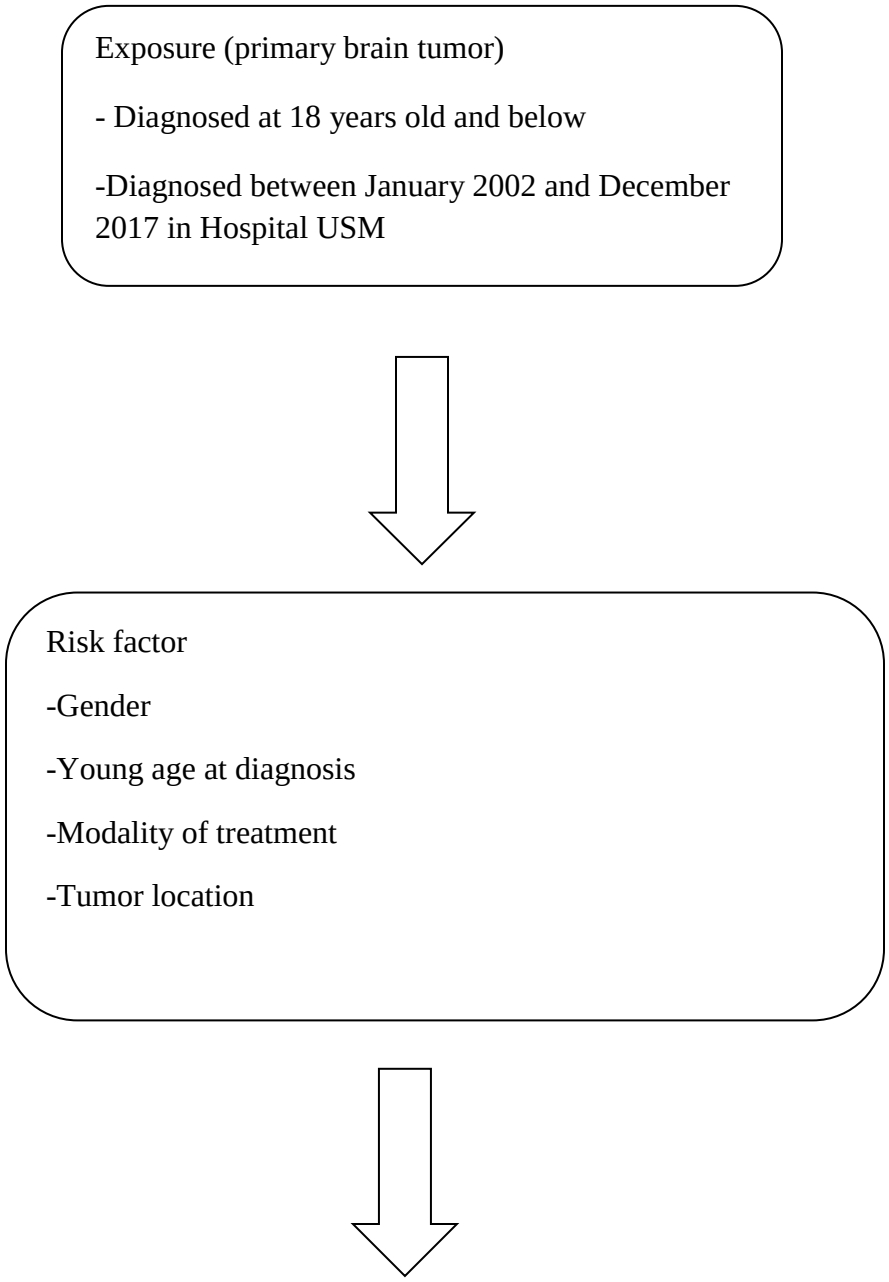
Ralph E. Vatner and et al.[27] performed a study about Endocrine Deficiency As A Function Of Radiation Dose To The Hypothalamus And Pituitary In Pediatric And Young Adult Patients With Brain Tumors. They analysed the correlation between radiotherapy (RT) dose to these structures and development of endocrine dysfunction in this population. Dosimetric and clinical data were collected from children and young adults (<26 years of age) with brain tumors treated with proton RT on three prospective studies from 2003 to 2016. Results Of 222 patients in the study, 189 were evaluable by actuarial analysis, with a median follow-up of 4.4 years (range, 0.1 to 13.3 years), with 31 patients (14%) excluded from actuarial analysis for having baseline hormone deficiency and two patients (0.9%) because of lack of follow-up. One hundred thirty patients (68.8%) with medulloblastoma were treated with craniospinal irradiation (CSI) and boost; most of the remaining patients (n = 56) received involved field RT, most commonly

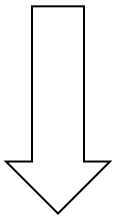
for ependymoma (13.8%; n = 26) and low-grade glioma (7.4%; n = 14). GH deficiency was the commonest endocrinopathy (cumulative incidence, 33.3%), followed by hypothyroidism (20.1%, with 91% central TSH deficiency), ACTH (7.4%), and gonadotropins (4.2%). They observed a clear dose response to all hormones tested, with GH deficiency being the most sensitive to radiation. At doses of less than 20 GyRBE, there was only a 9% actuarial incidence at 5 years compared with 40% after 20 to 40 GyRBE and 79% after more than 40 GyRBE. The 4-year actuarial rate of any hormone deficiency, growth hormone, thyroid hormone, adrenocorticotropic hormone, and gonadotropin deficiencies were 48.8%, 37.4%, 20.5%, 6.9%, and 4.1%, respectively. When stratified by age, patients treated between 6 and 10 years of age had a higher rate of endocrinopathy than patients treated less than 6 years old. Patients more than 10 years of age at the time of treatment had the lowest incidence of hormone deficiency. Age at start of RT, time interval since treatment, and median dose to the combined hypothalamus and pituitary were correlated with increased incidence of deficiency. They concluded that median hypothalamic and pituitary radiation dose, younger age, and longer follow-up time were associated with increased rates of endocrinopathy in children and young adults treated with radiotherapy for brain tumors.

Raven Cooksey and et al.[28] conducted a research entitled Metabolic Syndrome Is A Sequela Of Radiation Exposure In Hypothalamic Obesity Among Survivors Of Childhood Brain Tumors. This study explores the effects of radiation exposure to hypothalamus-pituitary-adrenal axis (HPA) on metabolic risk among survivors of childhood brain tumors. Inclusion criteria were age <18 years at the time of cancer diagnosis, had at least 1 year after completion of treatment, which could have included any combination of surgery, chemotherapy or radiation, if they were aged between 5 and 21 years at the time of study. The rationale for inclusion of subjects >1 year after completing therapy for their tumor was to allow sufficient time for the neuroendocrine and

immune systems to reach steady state. Exclusion criteria were underlying type 1 diabetes mellitus, neurofibromatosis type 1 or diagnosis of craniopharyngioma. Pregnant women were excluded as well as subjects taking steroids. Subjects not willing to comply with all study requirements were not included. One hundred forty-two met inclusion criteria; 60 had tumor surgery plus radiation exposure (>1 Gray (Gy)) to HPA. The second subgroup of 82 subjects had surgery only and were not exposed to radiation. Both subgroups had survived for approximately 5 years at the time of study. This study shows that radiation exposure to the hypothalamus in children is associated with hypothalamic obesity. Survivors also exposed to radiation of the hypothalamic-pituitary-adrenal axis (HPA) were equally obese to those having cranial surgery only. Prevalence of metabolic syndrome among subjects exposed to hypothalamic radiation was 15% and was higher than expected from hypothalamic obesity alone. Prevalence of growth hormone deficiency was higher in subjects exposed to hypothalamic radiation therapy, which was 37.3%. Their conclusion is that radiation exposure may exert untoward endocrinopathies due to HPA exposure that worsens metabolic risk. Early screening for metabolic syndrome in this population is indicated.

Conceptual framework





Outcome:

Growth hormone deficiency

Thyroid stimulating hormone deficiency

Adrenocorticotropic hormone deficiency

Luteinizing hormone/follicle-stimulating hormone deficiency

Cerebral salt wasting

Syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Diabetes insipidus

Thyroidal hypothyroidism

Hypergonadotropic hypogonadism

Central precocious puberty

Delayed puberty

Short stature

Tall stature

Metabolic syndrome

Research design

Cross sectional study

Study area

Hospital USM.

Study population

All pediatric patients in Hospital USM diagnosed with a primary brain tumor between January 2002 and December 2017 (15 years)

Subject criteria

Inclusion criteria:

- All paediatric patients in Hospital USM diagnosed with a primary brain tumor between January 2002 and December 2017
- Age 18 years old and below at diagnosis
- Survived for 2 years and more after diagnosis
- Had stable residual disease or no evidence of disease at the time of follow up

Exclusion Criteria:

- Incomplete data
- Syndromic children
- Existing endocrine disorder which were diagnosed before the tumors

- Congenital causes of endocrine disorders (eg septo-optic dysplasia)

Sample size estimation

Sample size from first objective: To identify the prevalence of endocrine disorder in childhood brain tumor survivors in Hospital USM.

$$n = \frac{z^2 p (1- p)}{\Delta^2}$$

n = minimum required sample

z = value of standard normal distribution = 1.96

Clement SC, Schouten-van Meeteren AYN, Boot AM, Claahsenvan der Grinten HL, Granzen B, Sen Han K, Janssens GO, Michiels EM, van Trotsenburg ASP, Vandertop WP, van Vuurden DG, Kremer LCM, Caron HN and van Santen HM: Prevalence and risk factors of early endocrine disorders in childhood brain tumor survivors: A nationwide, multicenter study. J Clin Oncol 34(36): 4362-4370, 2016. PMID: 27998218. DOI: 10.1200/JCO.2016.67.5025

n = 287

Considering 10% drop out, minimum required sample is + 10% = **315**

Sample size from second objective: To explore the associated risk factors related to endocrine disorder in brain tumor survivors in Hospital USM.

No	Variable	Proportion among patients without outcome, Po (%)	Reference	Estimated proportion among those with outcome (P1)	Ratio between groups (M)	Calculated sample size (n_{total})	Calculated sample size after 10% drop out
1	Gender (Female)	36.5	International Journal of Experimental and Clinical Pathophysiology and Drug Research , 2019, Prevalence of Endocrine Disorders in Childhood Brain Tumor Survivors in South Korea	56.5	3	252	277
2	Age at diagnosis (<10 years old)	45.6	International Journal of Experimental and Clinical Pathophysiology and Drug Research,2019, Prevalence of Endocrine Disorders in Childhood Brain Tumor Survivors in South Korea	65.6	3	248	272
3	Race	No previous study regarding this variable					

4	Socioeconomic status						
5	Radiotherapy	45.6	International Journal of Experimental and Clinical Pathophysiology and Drug Research,2019, Prevalence of Endocrine Disorders in Childhood Brain Tumor Survivors in South Korea	3	65.6	248	272
6	Histology (medulloblastoma)	0	Journal of Clinical Oncology, 2016, Prevalence and Risk Factors of Early Endocrine Disorders in Childhood Brain Tumor Survivors: A Nationwide, Multicenter Study	20	3	84	92
7	Location of primary tumour (suprasellar)	5.8	Journal of Clinical Oncology, 2016, Prevalence and Risk	25.8	3	132	145