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ORIGINAL ARTICLE

Endocrine Disorders in Childhood Brain Tumour Survivors: A Single-Centre Study

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Abstract

Objective. The study aims to determine the prevalence and risk factors for endocrine disorders in childhood brain tumour survivors.

Methodology. Included in the study were 124 childhood brain tumour survivors aged 18 years old or younger with either stable disease or in remission, and had 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 staging, tumour-related characteristics, treatment modalities and endocrine laboratory measurements at diagnosis and during follow up were obtained. Logistic regression was applied to evaluate risk factors for endocrine disorders in childhood brain tumour survivors.

Results. The prevalence of endocrine disorders in childhood brain tumour 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] and chemotherapy [adjusted odds ratio (OR) 0.18, 95% CI: 0.05 to 0.62].

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

Key words: endocrine disorder, childhood brain tumor survivors, risk factors

INTRODUCTION

Brain tumours are the commonest type of paediatric solid organ tumours, and it is the second most common childhood malignancy after leukaemia which contributes to 21% of all paediatric malignancies.[1] Its prevalence varies among different countries, with the highest rates reported in the United States.[2] The average annual incidence of primary CNS tumours for children and adolescents ≤19 years old in the United States from 2011 to 2015 was 5.95 cases per 100,000 population.[2] Approximately 60 percent of cases were malignant and 40 percent were non-malignant. According to the Malaysian National Cancer Registry Report 2007–2011, the national incidence of childhood brain and central nervous system (CNS) tumours was 2 per 100,000 children.[3] 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) and Italy (3.46 per 100,000 children).[4]

The mortality of childhood brain tumour 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 tumour. The survival outcomes in childhood brain tumours have improved significantly due to the advances in diagnosis and treatment, as well as the understanding of the disease aetiology.[5]

With improved survival rate, there has been a rising concern regarding the late sequelae of childhood brain tumour survivors, particularly associated with the use of craniospinal radiation therapy (RT) in young children. Their long-term complications such as neurological impairments, cognitive dysfunction, growth and endocrine disturbances have increased. Many survivors will face numerous lifelong health-related challenges after curative treatment of a childhood brain tumour.[5]

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Some of the potential risks for developing endocrine complications are age at cancer diagnosis, tumour histology, location and radiation exposure. Cranial radiotherapy is the main cause of hypothalamic and pituitary injury resulting in hormonal deficiency in children with brain tumours.[6] A recent analysis of the St. Jude Lifetime Cohort revealed that there was at least one anterior pituitary hormone deficiency in 51.4% of childhood cancer survivors who received cranial radiotherapy.[7]

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

METHODOLOGY

Study design and setting

We conducted a cross-sectional study at the Hospital Universiti Sains Malaysia (HUSM). The subjects were patients with brain tumours who were diagnosed from January 2002 till December 2017. It was approved by the Human Research Ethics Committee USM (reference: USM/JEPeM/21010039).

Subjects and procedures

We included all patients aged 18 years old and who survived for 2 years or more after diagnosis; had stable residual disease or no evidence of disease progression at the time of follow-up. We excluded patients who were syndromic, patients with incomplete data, had pre-existing endocrine disorders which were diagnosed before the tumour and congenital causes of endocrine disorders such as septo-optic dysplasia.

Records were traced from the medical record unit. Demographic data (age at diagnosis, gender, ethnicity and socioeconomic status), tumour-related characteristics and treatment modalities were extracted from medical records. We also collected clinical data (clues for endocrine disorders), anthropometrics (weight, height, midparental height), pubertal stage according to Tanner staging, endocrine laboratory measurements at diagnosis and during follow-up. All data collected were recorded in the data collection sheet.

Anthropometric measurements were plotted using World Health Organization growth chart for children less than 5 years old and National Centre for Health Statistics chart for children who are more than 5 years old. We included weight and height reviewed by the managing team before starting any treatment such as growth hormone in our analysis. BMI was calculated using the latest weight and height. The tumour location was classified as high-risk and low-risk. We analysed endocrine abnormalities detected even years after the diagnosis of brain tumour and had persisted beyond 2 years.

Sample size estimation

The sample size requirement for the estimation of the prevalence of endocrine disorders was determined using the sample size formula for estimation of proportion, $n = (Z_\alpha/\Delta)^2 P(1-p)$, where P is the observed prevalence reported from the previous study, Δ is the margin of error and Z_α is the Z-value corresponding to the level of confidence. For an estimation with a 95% confidence level, 10% margin of error and prevalence of 61%, as Ng et al., reported, the required sample size is 92 patients.

The sample size required to determine factors associated with endocrine disorders was calculated using the calculation for logistic regression analysis in G*power software version 3.1.9.7 (Test family: Z-test; Statistical test: Logistic regression). Sex was a significant predictor of endocrine disorders from a previous study, with females having a higher risk of developing endocrine disorders. It has been reported that the percentage of male patients with endocrine disorders was 36.5%. To achieve 80% study power with type I error of 5% (two-tailed), odds ratio (OR) of 3, R^2 contributed by other factors of 0.02, and equal ratio between sex, the required sample size was 113 patients. Considering a 10% possibility of missing data, the corrected sample size was 126 patients.

Statistical analysis

Data analysis was done using Statistical Package for Social Science (SPSS) IBM version 26.0. All data were checked for their distribution with histogram and probability plots. Numerical variables with normal distribution were presented as mean and standard deviation (SD). Non-normally distributed numerical variables were presented as median and interquartile range (IQR). Categorical data were presented as frequency (percentage).

Logistic regression analysis was used to determine factors associated with endocrine disorders in brain tumour survivors. Simple logistic regression analysis was used to identify factors to be included in the multiple regression analysis. Cut-off was set at $p<0.25$ in determining variables to be included in the final model. For multiple logistic regression we used backward stepwise regression. The selection starts with all independent variables in the model and then remove those with the largest p-value, one at a time. Criteria to retain the variable was set at $p<0.05$. All the assumptions of the test were examined. The fitness of the model was assessed using Hosmer-Lemeshow test. Outlier and influential observations were examined using Cook's influential statistics, while linearity was examined using the Box-Tidwell procedure. The area under the curve was 0.812. The factors that remained in the final model were presented using a table with its corresponding adjusted odds ratio, 95% CI, and p-value.

RESULTS

Demographic, clinical and hormonal characteristics are summarized in Table 1. The majority were female at 54% compared to male at 46%. The predominant race was Malay (96%). The majority of the subjects were in the low socioeconomic group (83.9%). The subject's mean age at diagnosis of brain tumour was 8.6 years (SD 8). The median body weight of the patients was 32 kg (IQR 19-45) and their median height was 135 cm (IQR 112-152). The median BMI was 17 kg/m^2 (IQR 11-41). For age distribution and BMI percentile, (refer to Appendix), 66.7% had 95th BMI percentile for the age range 12-18 years old, 33.3% had >97th BMI percentile for age 6-12 years old, while 22.2% of age 12-18 years old had >97th BMI percentile. There were 20.2% subjects with tumours at high-risk sites. Most of the subjects underwent intracranial surgery (91.9%). Other treatments received by patients were radiotherapy 38.7%, chemotherapy 16.9% and chemoradiation 11.3%.

There were 62.1% patients with endocrine disorders (Table 1). The age distribution of involved patients was highest at age 6-12 years old (45.5%); followed by those aged 2-5-years-old (31.2%); 13-18 years old (20.8%) and <2 years (2.6%). The proportion of hypopituitarism was 6.5%, panhypopituitarism was 18.5% while isolated central hormonal deficiency was 4.8%. The most common hormonal deficiency was hypothyroidism (26.6%) followed by growth hormone deficiency (GHD) (21%), gonadotropin deficiency (21%) and ACTH deficiency (20%). Most of the specific endocrine disorders (refer to Appendix) occurred in those aged 6-12 years old, namely hypothyroidism (51.5%), growth hormone deficiency (57.7%), ACTH deficiency (64.4%), gonadotropin deficiency (57.7%), delayed puberty (56.1%), short stature (54.4%), obesity with metabolic syndrome (38.1%0, SIADH (75%) and cranial diabetes insipidus (55.6%). For cerebral salt wasting, it was predominantly seen in those 2-5 years old (43.8%).

From Table 2, the commonest clinical manifestations of endocrine disorders were short stature (46%) and obesity with metabolic syndrome (33.9%). Other clinical manifestations were delayed puberty (33%), oliguria secondary to syndrome of inappropriate secretion of anti-diuretic hormone (SIADH), (3%), polyuria secondary to cerebral salt wasting (CSW), (12.9%), and polyuria secondary to cranial diabetes insipidus (DI) (14.5%).

Figure 1 summarizes the tumour histology of our subjects. The commonest tumour was medulloblastoma (26.6%), followed by astrocytoma (25%) and glioblastoma (11.3%). The proportion of ependymoma was 7% while the proportion of pituitary adenoma and primitive neuroectodermal tumour (PNET) were both 6%. Regarding medulloblastoma and age category (refer to Appendix), 63.6% affected those 6 to 12 years old, 21.2% affected those 2 to 5 years old, 9.1% among 12 to18 years old and 6.1% in those less than 2 years old.

From simple logistic regression analysis, BMI, weight, household income, site of brain tumour, hydrocephalus at diagnosis, chemotherapy and chemoradiation were

Table 1. Demographic, clinical and hormonal characteristics

Variables	n (%)
Age at diagnosis (years)	8.6 (5.0)[c]
Weight (kg)	32.0 (19-45)[a]
Height (cm)	135.0 (112-152)[a]
BMI (kg/m^2)	17.0 (11-41)[a]
Sex	
Boy	57 (46)[b]
Girl	67 (54)[b]
Race	
Malay	119 (96)[b]
Others	5 (4)[b]
Income	
B40	104 (83.9)[b]
Non-B40	20 (16.1)[b]
High-risk site	25 (20.2)[b]
Surgery	114 (91.9)[b]
Radiotherapy	48 (38.7)[b]
Chemotherapy	21 (16.9)[b]
Chemoradiation	14 (11.3)[b]
Endocrine disorders	77 (62.1)[b]
Hypopituitarism	8 (6.5)[b]
Panhypopituitarism	23 (18.5)[b]
Isolated hormone deficiency	6 (4.8)[b]
Growth hormone deficiency	26 (21)[b]
ACTH deficiency	25(20.2)[b]
Gonadotropin deficiency	26 (21)[b]
Hypothyroidism	33 (26.6)[b]

[a] Height, Weight, Body mass index (BMI) are not-normally distributed and presented as median [interquartile range (IQR)]
[b] Frequency and percentages for categorical variables
[c] Age is normally distributed and presented as mean [standard deviation (SD)]
B40: total household income < RM4850, Non-B40: total household income other than B40, High-risk site: intrasellar and suprasellar region, Low-risk site: other locations, ACTH: Adrenocorticotropic hormone.

Table 2. Clinical manifestation of endocrine disorders

Variables	n (%)
Short stature	57 (46)[b]
Polyuria secondary to CSW	16 (12.9)[b]
Obesity with metabolic syndrome	42 (33.9)[b]
Delayed puberty	41 (33.1) [b]
Oliguria secondary to SIADH	4 (3.2)[b]
Polyuria secondary to Cranial DI	18 (14.5)[b]

CSW: Cerebral salt wasting, SIADH: Syndrome of inappropriate secretion of antidiuretic hormones, DI: Diabetes Insipidus

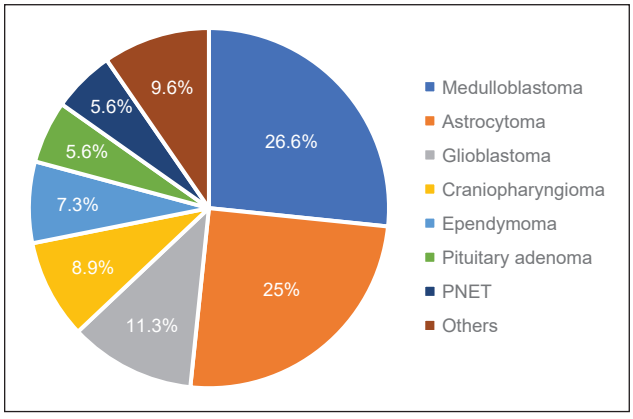

Figure 1. Histology.

[a] Others (%): oligodendroglioma: (1.6%), meningioma: (1.6%), Schwannoma: (0.8%), germ cell tumour: (2.4%), germinoma:(3.2%)

Table 3. Factors associated with endocrine disorders in childhood brain tumour survivors

Variable		Crude OR[a] (95% CI)	Adjusted OR[b] (95% CI)	Wald stat[b] (odd)	P value[b]
Body Mass Index (BMI)		1.28 (1.13, 1.45)	1.29 (1.12, 1.50)	12.06 (1)	0.001
High risk site	Yes	9.58 (2.14,42.87)	7.15 (1.41, 36.25)	5.64 (1)	0.018
	No	1.00	1.00		
Chemotherapy	Yes	1.00	1.00	7.27(1)	0.007
	No	0.33 (0.10, 1.05)	0.18 (0.05, 0.62)		

[a] Simple logistic regression
[b] Multiple logistic regression
OR: Odd ratio, CI: Confidence interval
The model reasonably fits well. Model assumptions are met. There are no interactions and multicollinearity problems.

important variables with $p<0.25$. Statistically significant variables from multiple logistic regression analysis (Table 3) were high BMI (adjusted OR 1.29, 95% *CI*: 1.12 to 1.5, p =0.001), high-risk site (adjusted OR 7.15, 95% *CI*: 1.41 to 36.3, p=0.018) and no chemotherapy (adjusted OR 0.18, 95% *CI*: 0.05 to 0.62, p=0.007). Brain tumour survivors with high BMI have an increased odds of having endocrine disorders by 1.2 times. Those survivors with brain tumours at high-risk sites have increased odds of having endocrine disorders by 7.2 times than those at lower risk sites. Brain tumour survivors that received no chemotherapy have decreased odds of having endocrine disorders by 83% than those who received chemotherapy.

DISCUSSION

The prevalence of endocrine disorders among childhood brain tumour survivors (CBTS) in our centre was 62% which was almost similar to a local study conducted in Klang valley by Ng et al, 61%.[8] Our prevalence was higher compared to other studies done in South Korea (37.1%), Netherlands (22.1%) and United States (49%).[2,9,10] Studies by Clement et al., in the Netherlands excluded patients with craniopharyngioma or a pituitary gland tumour while our study not only included all childhood brain tumour survivors, but also all types of endocrine complications such as obesity, growth, pubertal disorders and water/salt disturbances.[11] A study by Heo et al., only included patients based on insurance claim with limited coding for endocrine disorders and therefore explains the lower prevalence in South Korea.[10] The lower prevalence in other centres was also explained by a lack of standard guidelines for surveillance of endocrine disorders, inconsistent follow up, delayed referral to paediatric endocrinologist and lack of awareness among doctors in managing CBTS.[12,13]

Most endocrine disorders occur 2 to 3 years after diagnosis of the brain tumour.[14] Based on the age categories for our centre majority affected those 6 to 12 years old, followed by those 2 to 5 years old (31.2%), 13 to 18 years old (20.8%), and lastly, those less than 2 years old (2.6%). The median age of our patients diagnosed to have primary brain tumour with or without endocrine disorders was 8.6 years compared to Ng et al., which was 5.6 years and Clement et al., at 8.5 years old.[10,11] We were unable to compare the age categories of patients with endocrine disorders with other centres due to lack of data.

The most frequent type of brain tumour confirmed by histopathological examination in our centre was medulloblastoma (26%), which is similar to many other publications, accounting for 25 to 30% of childhood brain tumours.[15] For the age distribution in our centre, 63.6% affected those aged 6 to 12 years old and tended to affect the posterior fossa. Most present with signs of increased intracranial pressure, altered mental state, cerebellar ataxia and focal neurological deficits.[16] Other types of brain tumour based on biopsy findings varied between centres and this may reflect different studied populations, ethnicities and possibly genetic heterogenicity.

Regarding specific pattern of hormonal deficiency in our centre, hypothyroidism was the commonest (26.6%) followed by GHD (21%), gonadotropin deficiency (21%) and ACTH deficiency (20%). Ng et al., reported ACTH deficiency was the most prevalent (37%) followed by hypothyroidism (35%) and CDI (21%).[8] In other parts of the world, the commonest hormonal deficiency was GHD that ranged from 12 to 58% and this pattern was seen more consistently compared to other hormonal deficiencies,[17-19]

Short stature (46%) was the most common clinical presentation seen in our centre and the causes could be multifactorial, such as specific hormonal deficiency secondary to GHD, hypothyroidism, ACTH deficiency, poor nutrition, familial short stature or constitutional delay in growth and puberty (CDGP).[19] This finding was also reported by Gurney et al, and Pasqualini et al.[20,21] Despite it being the most common manifestation, not all the CBTS were referred to endocrine unit for screening of the specific hormonal deficiency which might be due to poor awareness among the primary doctors.

The majority of the salt and water disturbances occur in the immediate post-operative period such as cranial diabetes insipidus (CDI), cerebral salt wasting (CSW) and SIADH.[22] Most are transient and resolved around 4 to 6 weeks post-operation.[23] However, some of the water/salt disturbances persist years after the insult particularly those with residual tumour, and in our centre, persistent CSW and CDI contributed about 12.9% and 14.5%, respectively.

There are many risk factors for the development of endocrine complications in CBTS. One of the potential risks is the site of brain tumour. The high-risk sites are the hypothalamus and pituitary regions.[19] Any insults due to

surgery, radiotherapy and the primary tumour itself may cause damage to the hypothalamus/pituitary and result in a hormonal deficiency. The radiation dose of at least 18 Gy from TBI is associated with GHD as somatotroph cells are very sensitive to ionising radiation. A dose of radiation above 50 Gy may result in multiple pituitary hormonal deficiency or hypopituitarism.[6] Our finding was consistent with Clement et.al., and Lawson et. al., but the tumour location was not found to be a significant factor in a study by Ng et al.

The hypothalamic form of obesity is an important endocrine complication commonly encountered in CBTS.[24] Hypothalamic arcuate and paraventricular nuclei are the appetite centres that regulate satiety and hunger, and they form a complex pathway for food intake and energy expenditure.[25] The main mechanism of hypothalamic obesity is damage to hypothalamic nuclei secondary to surgery, radiotherapy or primary brain tumour which results in interference of afferent sensory input and energy regulation leading to hypothalamic hyperphagia and obesity.[24] Other associations were excessive consumption of unhealthy food and sedentary lifestyle related to neurological/motor dysfunction a few years after surgery/radiotherapy.[24] Our finding was consistent to Lutsig et al., and Cooksey et al., that concluded obesity was a known complication in CBTS.[26,27]

Chemotherapy is another factor associated with endocrine complications such as delayed puberty and infertility.[28] Most often it is associated with the use of cyclophosphamide, ifosfamide, and busulfan.[28]

We found that 33% of CBTS had delayed puberty. The prevalence of pubertal delay varies between studies with a range of 4 to 11%.[8,11] It is most often underrepresented due to missing pubertal assessment or short duration of follow up because the median age of diagnosis was at prepubertal age. Alkylating agents cause gonadal toxicity and results in a hypergonadotropic form of hypogonadism or primary hypogonadism.[29] Affected subjects would have absence or poor progression of puberty and may be infertile later on. Other factors that may contribute to delayed puberty and infertility are radiotherapy, poor nutrition and abnormal body composition.[30]

Limitations of the study

Our study had a few limitations as it was retrospective in nature. We managed to trace 290 records using keywords of brain tumour. One hundred sixty-six were excluded since 98 of them were adults, 50 already died and 24 had missing records. A few years before the endocrine service was started, hormonal levels were not regularly checked during follow-up which may be the reason for missed diagnosis of specific endocrine disorders. There was no screening for osteoporosis in the studied subjects which is a known complication among CBTS. Subjects selected were limited to our hospital, which might not truly represent the childhood brain tumour survivors in our state. Lastly, all CBTS need a longer follow-up as endocrine complications may occur as long as 20 years following initial diagnosis of brain tumour.

CONCLUSION

The prevalence of endocrine disorders in childhood brain tumour survivors in our centre was 62%. The risk factors were high BMI, tumour location (suprasellar and intrasellar) and chemotherapy.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

Credit Author Statement
NWR: Conceptualization, Methodology, Software, Validation, Investigation, Resources, Data Curation, Writing - original draft preparation, Visualization, Project administration, Finding acquisition; **SH:** Software, Validation, Formal analysis, Resources, Data Curation, Writing - review and editing, Visualization, Supervision; **NM:** Validation, Supervision; **NMY:** Software, Validation, Formal analysis, Supervision

Author Disclosure
The authors declared no conflict of interest.

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References
1. Nandagopal R, Laverdière C, Mulrooney D, Hudson MM, Meacham L. Endocrine late effects of childhood cancer therapy: A report from the children's oncology group. Horm Res. 2008;69(2):65-74. PMID: 18059086. https://doi.org/10.1159/000111809.
2. Ostrom QT, De Blank PM, Kruchko C, et al. Alex's Lemonade Stand Foundation infant and childhood primary brain and central nervous system tumour diagnosed in the United States in 2007-2011. Neuro Oncol. 2015;16(Suppl 10):x1-36. PMID: 25542864. PMCID: PMC4277295. https://doi.org/10.1093/neuonc/nou327.
3. Azizah Am, Hashimah B, Nirmal K, et al. Malaysia National Cancer Registry Report (MCNR) 2013-2016;2019. https://www.moh.gov.my/moh/resources/Penerbitan/Laporan/Umum/2012-2016%20(MNCRR)/MNCR_2012-2016_FINAL_(PUBLISHED_2019).pdf
4. Takada A, Ii N, HIrayama M, et al. Long-term follow-up of intensive chemotherapy followed by reduced-dose and reduced-field irradiation for intracranial germ cell tumor. J Neurosurg Pediatr. 2018;23(3):317-24. PMID: 30497152. https://doi.org/10.3171/2018.9.PEDS18181.
5. Chemaitilly W, Cohen LE, Mostoufi-Moab S, et al. Endocrine late effects in childhood cancer survivors. J Clin Oncol. 2018;36(21):2153-9. PMID: 29874130. https://doi.org/10.1200/JCO.2017.76.3268.
6. Merchant TE, Conklin HM, Wu S, Lustig RH, Xiong X. Late effects of conformal radiation therapy for pediatric patients with low-grade glioma: Prospective evaluation of cognitive, endocrine, and hearing deficits. J Clin Oncol. 2009;27(22):3691-7. PMID: 19581535. PMCID: PMC2799064. https://doi.org/10.1200/JCO.2008.21.2738.
7. Chemaitilly W, Li Z, Huang S, et al. Anterior hypopituitarism in adult survivors of childhood cancers treated with cranial radiotherapy: A report from St Jude Lifetime Cohort. J Clin Oncol. 2015;33(5):492-500. PMID: 25559807. PMCID: PMC4314596. https:///doi.org/10.1200/JCO.2014.56.7933.
8. Ng YJ, Jalaludin MY, Foo JC, Qaddoumi I, Rajagopal R. Prevalence and risk factors for endocrine disorders in childhood brain tumors from a single tertiary center in Malaysia. J Pediatr Hematol Oncol. 2022;44(4):159-66. PMID: 35446802. https://doi.org/10.1097/MPH.0000000000002447.
9. Clement SC, Schouten-van Meeteren AYN, Kremer LCM, van Trotsenburg ASP, Caron HN, van Santen HM. High prevalence of early hypothalamic-pituitary damage in childhood brain tumor survivors: Need for standardized follow-up programs. Pediatr Blood Cancer. 2014;61(12):2285-9. PMID: 25131941. https://doi.org/10.1002/pbc.25176.

10. Heo J, Lee HS, Hwang JS, Noh OK, Kim L, Park JE. Prevalence of endocrine disorders in childhood brain tumor survivors in South Korea. In Vivo. 2019;33(6):2287-91. PMID: 31662569. PMCID: PMC6899123. https://doi.org/10.21873/invivo.11735.
11. Clement, S. C. et al. Prevalence and risk factors of early endocrine disorders in childhood brain tumor survivors: A nationwide, multicenter study. J Clin Oncol. 216;34(36):4362-70. PMID: 27998218. https://doi.org/10.1200/JCO.2016.67.5025.
12. Shaw S. Endocrine late effects in survivors of pediatric brain tumors. J Pediatr Oncol Nurs. 2009;26(5):295-302. PMID: 19837959. https://doi.org/10.1177/1043454209343180.
13. Cohen LE, Gordon JH, Popovsky EY, et al. Late effects in children treated with intensive multimodal therapy for high-risk neuroblastoma: High incidence of endocrine and growth problems. Bone Marrow Transplant. 2014;49(4):502-8. PMID: 24442245. https://doi.org/10.1038/bmt.2013.218.
14. Patterson BC0, Wasilewski-Masker K, Ryerson AB0, Mertens A, Meacham L. Endocrine health problems detected in 519 patients evaluated in a pediatric cancer survivor program. J Clin Endocrinol Metab. 2012;97(3):810-8. PMID: 22188743. https://doi.org/10.1210/jc.2011-2104.
15. Oberfield SE, Allen JC, Pollack J, New MI, Levine LS. Long-term endocrine sequelae after treatment of medulloblastoma. Prospective study of growth and thyroid function. J Paediatr. 1986;108(2):219-23. PMID: 3944706. https://doi.org/10.1016/s0022-3476(86)80986-6.
16. Fang FY, Rosenblum JS, Ho WS, Heiss JD. New developments in the pathogenesis, therapeutic targeting, and treatment of pediatric medulloblastoma. Cancers (Basel). 2022;14(9):2285. PMID: 35565414. PMCID: PMC9100249. https://doi.org/10.3390/cancers14092285.
17. Maciel J, Dias D, Cavaco D, Donato s, Pereira MC, Simões-Pereira MC. Growth hormone deficiency and other endocrinopathies after childhood brain tumors: Results from a close follow-up in a cohort of 242 patients. J Endocrinol Invest.2021;44(11):2367-74. PMID: 33683662. https://doi.org/10.1007/s40618-021-01541-4.
18. Lone DW, Sadak KT, Miller BS, et al. Prevalence of childhood growth hormone deficiency in survivors of pediatric intracranial germ cell tumors. J Clin Oncol. 2022;12(3):79-88. PMID: 36249955. PMCID: PMC9555288. https://doi.org/10.14740/jem807.
19. Lawson SA, Home VE, Golekoh MC, et al. Hypothalamic–pituitary function following childhood brain tumors: Analysis of prospective annual endocrine screening. Pediatr Blood Cancer. 2019;66(5):e27631.
20. Gurney JG, Ness KK, Stovall M, et al. Final height and body mass index among adult survivors of childhood brain cancer: Childhood cancer survivor study. J Clin Endocrinol Metab. 2003;88(10):4731-9. PMID: 14557448. https://doi.org/10.1210/jc.2003-030784.
21. Pasqualini T, Diez B, Domene H, et al. Long-term endocrine sequelae after surgery, radiotherapy and chemotherapy in children with medulloblastoma. Cancer. 1987;59(4):801-6. PMID: 3802038. https://doi.org/10.1002/1097-0142(19870215)59:4<801::aid-cncr2820590424>3.0.co;2-z.
22. Nyanti L, Samsudin A, Tiong IK. Syndrome of inappropriate antidiuretic hormone secretion and Leser-Trélat syndrome as uncommon paraneoplastic manifestations of renal malignancy - A geriatric experience: A case report. J Med Case Rep. 2019;13(1):188. PMID: 31221202. PMCID: PMC6587240. https://doi.org/10.1186/s13256-019-2122-8.
23. Kumar MM, Foster JR, Sharan S, DeRibaupierre S,McKillop SJ, Kornecki A. Transient blindness as the primary symptom of acute hyponatremia post surgery. J Pediatr Intensive Care. 2013;1(3):169-72. PMID: 31214404. PMCID: PMC6530693. https://doi.org/10.3233/PIC-2012-028.
24. Das UN. Obesity: Genes, brain, gut, and environment. Nutrition. 2010;26(5):459-73. PMID: 20022465. https://doi.org/10.1016/j.nut.2009.09.020.
25. Mediavilla C. Bidirectional gut-brain communication: A role for orexin-A. Neurochem Int. 2020;141:104882. PMID: 33068686. https://doi.org/10.1016/j.neuint.2020.104882.
26. Lutsig RH, Post SR, Merchant T. Risk factors for the development of obesity in children surviving brain tumour. J Clin Endocrinol Metab. 2003;88(2):611-6. PMID: 12574189. https://doi.org/10.1210/jc.2002-021180.
27. Cooksey R, Wu SY, Bowers D, et al. Metabolic syndrome is a sequalae of radiation exposure in hypothalamic obesity among survivors of childhood brain tumours. J Investig Med. 2019;67(2):295-302. PMID: 30530528. https://doi.org/10.1136/jim-2018-000911.
28. Yalçin B, Kremer LCM, van Dalen EC. High-dose chemotherapy and autologous haematopoietic stem cell rescue for children with high-risk neuroblastoma. Cochrane Database Syst Rev.2015;2015(10):CD006301. PMID: 26436598. PMCID: PMC8783746. https://doi.org/10.1002/14651858.CD006301.pub4.
29. Khanal N, Ahmed SS, Kalra M, et al. The effects of hypogonadism on quality of life in survivors of germ cell tumors treated with surgery alone versus surgery plus platinum-based chemotherapy. Support Care Cancer. 2020;28(7):3165-70. PMID: 31707501. https://doi.org/10.1007/s00520-019-05117-0.
30. Zaid MA, Dinh PC, Monahan PO, et al. Adverse health outcomes in relationship to hypogonadism after chemotherapy: A multicenter study of testicular cancer survivors. J Natl Compr Canc Netw. 2019;17(5):459-68. PMID: 31085753. PMCID: PMC6712564. https://doi.org/10.6004/jnccn.2018.7109.