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Short-Term Endocrinological Complications Following Treatment of Paediatric Brain Tumors

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Keyword: Brain tumor, Craniopharyngioma, hypopituitarism, Pilocytic astrocytoma, radiotherapy.

Abstract

Objective: To determine the frequency of post-treatment endocrine complications in patients with pediatric brain tumors within one year after treatment.

Study design: A cross-sectional study.

Place and duration: Outpatient department of Paediatric Endocrinology at the National Institute of Child Health (NICH), from May 2022 to August 2023.

Material and methods: Children of either gender, aged between 1-18 years, diagnosed with brain tumour who received any treatment (radiotherapy, chemotherapy, surgical treatment) for brain tumour within the last one year were analyzed. Data regarding age, gender, laboratory and radiology evaluation of the patients were noted. Combined pituitary hormone deficiency (CPHD) was defined as a deficiency in 2 or more pituitary hormone. Hypopituitarism (HP) was defined as diminished production of 1 or more pituitary hormones.

Results: In a total of 45 patients, 32 (71.1%) were boys. The mean age was 11.61±3.32 year (ranging between 3 to 17 years).The most common tumor types consisted of craniopharyngioma, and pilocytic astrocytoma, noted in 35 (77.8%) and 5 (11.1%) cases respectively. The mean tumor size was 2.08±0.88 x 1.83±0.71 x 1.71±1.00 cm. The mode of treatment were surgery, radiotherapy, and combination of surgery and radiotherapy documented in 31 (68.9%), 6 (13.3%), and 8 (17.8%) children, respectively. The mean duration of time elapsed since treatment was 11.02±1.45 months. CPHD and HP were reported in 23 (51.1%) and 15 (33.3%) children respectively.

Conclusion: Notable proportion of children following treatment of brain tumors have endocrinological complications. Comprehensive follow-up and continuous monitoring of endocrine parameters are crucial for paediatric brain tumor survivors, aiming detection and addressing complications promptly, ultimately enhancing post-treatment care and outcomes.

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Introduction

In the United States, 1 in 285 children are diagnosed with cancer before their 20th birthday.[1] The most common types of tumors are leukemias, central nervous system tumors and lymphomas.[2] Among adolescents (ages 15 to 19 years), the most common types of cancer are brain and other central nervous system tumors and lymphomas, followed by leukemias and gonadal germ cell tumors.[2] The estimates show that there may be 13·7 million new cases of childhood cancer globally between 2020 and 2050 among which 6·1 million (44·9%) may remain undiagnosed.[3] *There is paucity of information regarding pattern of distribution of pediatric cancers from Asian countries. Recent regional data from India evaluating 247 registered pediatric cancers patients revealed central nervous system malignancies among the least common solid tumor cancers with a prevalence of 3%.*[4]

Primary brain tumors in children present some of the most challenging cases. These are also the 2nd most common neoplasms, and the most common solid neoplasms.[5] *Clinical manifestations of tumors like pituitary adenomas reflect oversecretion of involved hormone, most commonly growth hormone, prolactin, corticotropin, or thyrotropin.*[5] Another study showed that among 1058 patients treated after being diagnosed with pituitary tumors in a span of 7 years, 37.1% had at least 1 endocrine disorder. The commonest endocrine disorders being hypopituitarism (17.4%) and hypothyroidism (6.1%). Female gender, patients with age <10 years and patients who received radiotherapy were more likely to have endocrine disorders compared to those who did not.[6]

The literature highlights measures which can be used to emphasize the need of endocrine surveillance, regular assessment of endocrine function and timely interventions in paediatric patients treated for brain tumors.[7] Also, there is no data available in Pakistani pediatric population to determine frequency of endocrinological complications after treating brain tumors. Hence, our study can help achieve the ultimate goal of a well functioning pediatric population treated for brain tumors and may help in provision of optimal healthcare. The objective of this study was to determine the frequency of post-treatment endocrine complications in patients with pediatric brain tumors within one year after treatment.

Material and methods

This cross-sectional study was conducted in the outpatient department of paediatric endocrinology at the National Institute of Child Health (NICH), from May 2022 to August 2023. A sample size of 45 cases was calculated by WHO sample size calculator using proportion of the frequency of central nervous system tumors among children as 3%,[4] keeping the confidence level at 95% with margin of error as 5%. Children of either gender, aged between 1-18 years, diagnosed with brain tumour, and registered at endocrine or oncology clinic at NICH were analyzed. Children were included who received any treatment (radiotherapy, chemotherapy, surgical treatment) for brain tumour within the last one year. Parents/patients withdrawing consent to participate in the study were excluded. Children diagnosed previously with any kind of endocrine disorder or having recurrent brain tumor were also not included. Non-probability, consecutive sampling technique was used. Approval from Institutional Review Board was acquired. Written and informed consents were taken from children/parents/guardians for the enrolled cases. Primary brain tumor was diagnosed throught relevant radiological examinations and labeled as sellar and supra-sellar lesions including craniopharyngiomas, pituitary adenomas, medulloblastomas, gliomas, germinomas, ependymomas, meningiomas, chordomas, cysts (rathke's cleft cyst, dermoid cyst, arachnoid cyst). Data regarding age, gender, laboratory and radiology evaluation (hormonal level assessment and CT/MRI) of patients. For endocrinological complications, hormonal profile were sent according to symptoms of patients. If post-treatment complications were found, those were treated accordingly and patients were asked to remain in regular follow-up at paediatric endocrine clinic. Combined pituitary hormone deficiency (CPHD) was defined as a deficiency in 2 or more pituitary hormone. Hypopituitarism (HP) was defined as diminished production of 1 or more pituitary hormones.[8] Normal values are shown in table-1.

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Table-1: Normal values of Endocrine Laboratory Parameters (n=45)

Parameters	Normal values
TSH (uUI/ml)	**21 weeks-20 years** 0.7-6.4
Serum FT4 (ng/dl)	0.93-1.7
FT3 (ng/ml)	0.32-2.15
Serum Cortisol (ug/dL)	8AM <8.0
Prolactin levels (ng/ml)	3-14.7
Plasma ACTH (pg/ml)	>45.0
Serum LH (mIU/ml)	Both MALE and FEMALE 1.0-3.5
Serum FSH (mIU/ml)	**MALE 1-9 years** 0.0-5.0 **10-11 years** 0.0-6.0 **12-18 years** 0.0-10.0 **FEMALE 1-2 years** 0.0-8.0 **3-8 years** 0.0-5.0 **9-11 years** 0.0-10.0 **12-18 years** 0.0-15.0
Serum Testosterone (ng/dl)	**BOYS 1-5 years** 2-25 **6-9 years** 3-30 **GIRLS 1-5 years** 2-10 **6-9 years** 2-20
Serum IGF-1 (ng/mL)	85.2-248
Serum growth hormone (ng/mL)	<5 (basal)
Urine osmolality (mosm/kg)	50-1400
Serum Osmolality (mosm/kg)	275-300

Data analysis was done using IBM-SPSS Statistics, version 26.0. Mean and standard deviation (SD) were computed for quantitative variables (age, height, weight, BMI). Frequency and percentage were computed for qualitative variables such as gender, symptoms (headache, vomiting, weight loss/gain, growth arrest, convulsions, behavioral changes, increased thirst and urination, constipation, somnolence), hormonal profile and outcome (satisfactory surgical outcome). Effect modifiers were controlled through the stratification of age, gender and symptoms. Chi-square test was applied to see the effect of categorical data on outcome variables. T test was applied for quantitative variables. $P<0.05$ was considered as statistically significant.

Results

In a total of 45 patients, 32 (71.1%) were boys, representing a boys to girls ratio of 2.5:1. The mean age was 11.61±3.32 year (ranging between 3 to 17 years). The mean height and weight were 130.09±16.96 cm and 36.94±15.83 kg respectively. The mean SD height and weight scores were -2.81±1.75 and -1.96±2.21. The most common tumor types consisted of craniopharyngioma, and pilocytic astrocytoma, noted in 35 (77.8%) and 5 (11.1%) cases respectively. The mean tumor size was

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2.08±0.88 x 1.83±0.71 x 1.71±1.00 cm. The mode of treatment were surgery, radiotherapy, and combination of surgery and radiotherapy documented in 31 (68.9%), 6 (13.3%), and 8 (17.8%) children respectively. The most frequent presenting symptoms were headache, visual problems and vomiting, noted in 42 (93.3%), 23 (51.1%) and 19 (42.2%) patients respectively (figure-1). The mean duration of time elapsed since treatment was 11.02±1.45 months (ranging between 8 to 12 months). Table-2 is showing the mean and SD of endocrinological laboratory parameters.

Figure-1: Frequency of presenting symptoms

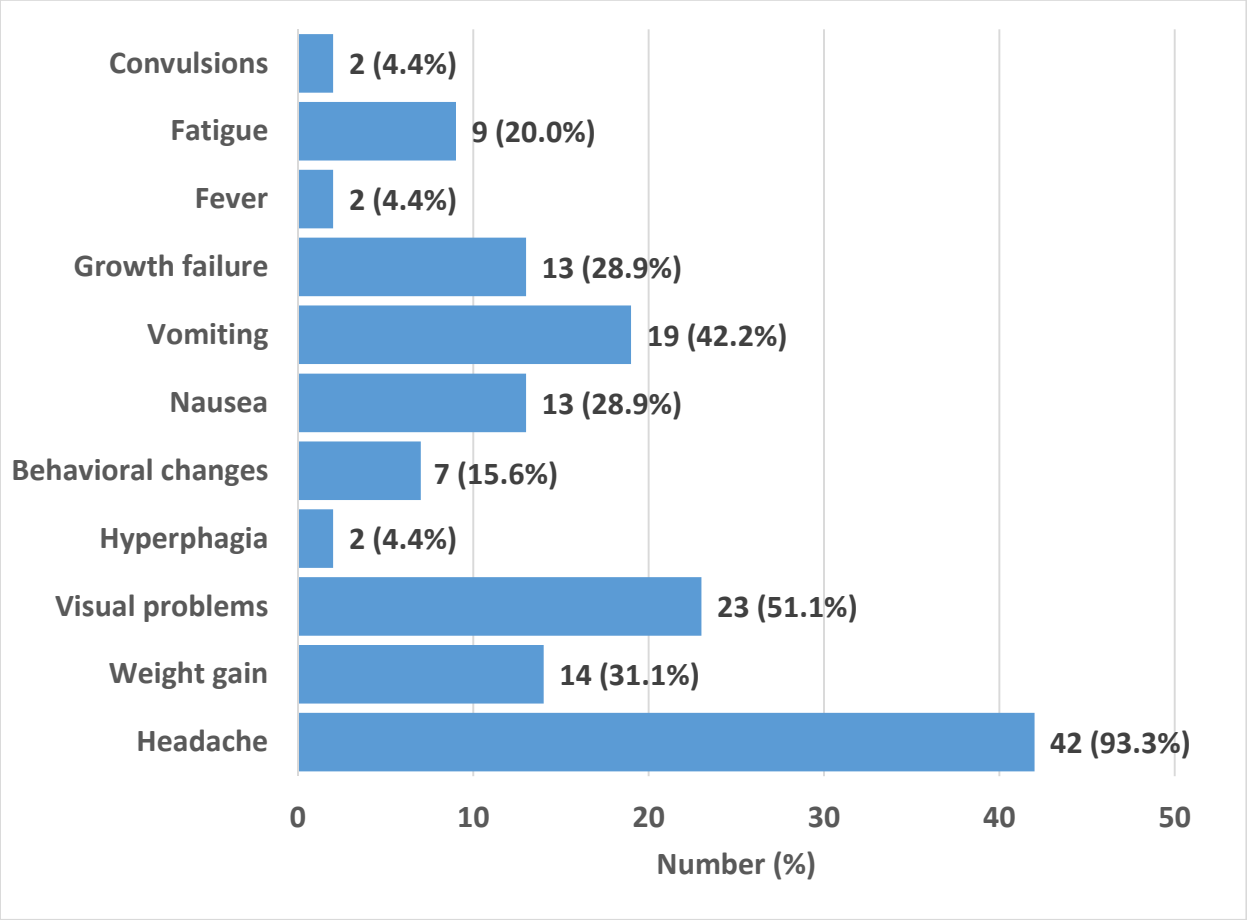

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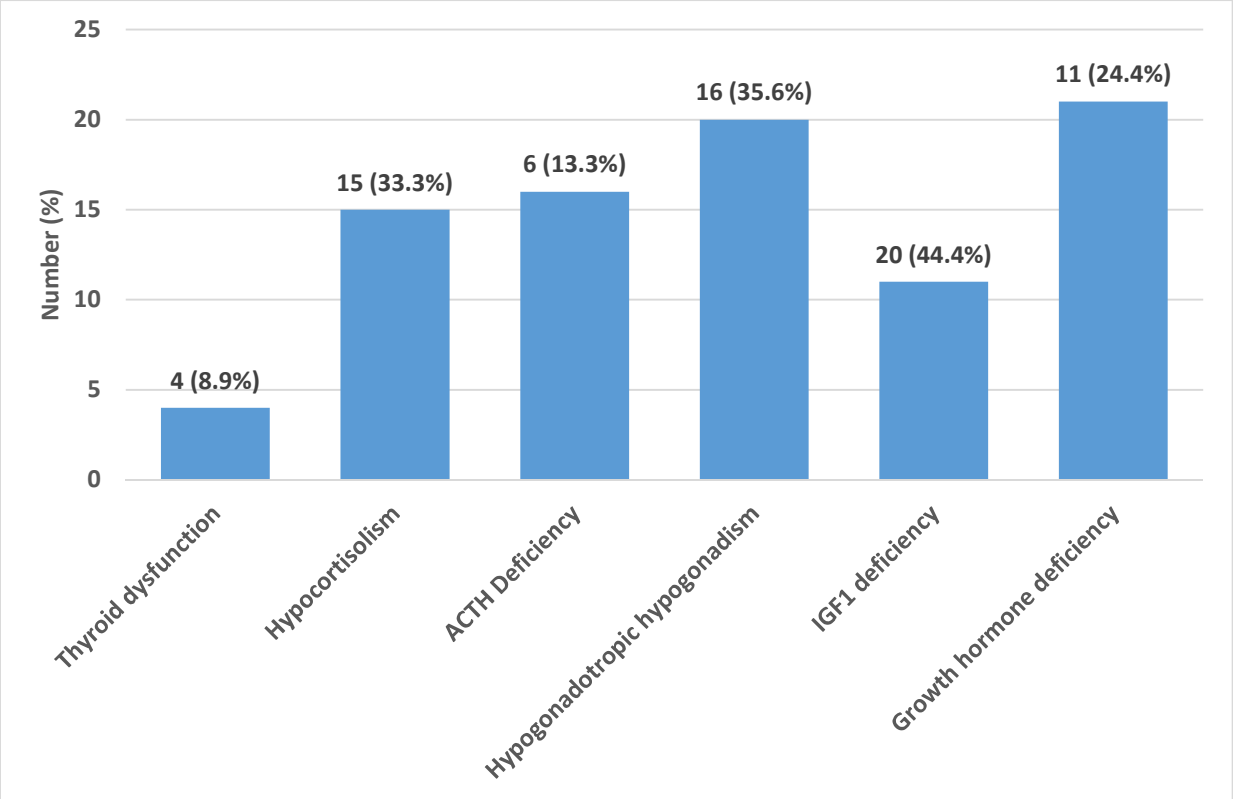
Table-2: Descriptive statistics of Endocrinological laboratory parameters (n=45)

Parameters	Mean±SD
TSH (uUI/ml)	2.74±1.72
Serum FT4 (ng/dl)	2.86±3.22
FT3 (ng/ml)	2.08±0.42
Serum Cortisol (ug/dL)	11.83±7.03
Prolactin levels (ng/ml)	23.90±22.60
Plasma ACTH (pg/ml)	34.28±26.10
Serum LH (mIU/ml)	0.73±0.92
Serum FSH (mIU/ml)	1.21±1.10
Serum Testosterone (ng/dl)	0.84±1.14
Serum IGF-1 (ng/mL)	130.35±107.80
Serum growth hormone (ng/mL)	0.98±1.43
Urine osmolality (mosm/kg)	834.40±627.37
Serum Osmolality (mosm/kg)	288.57±48.82

The most frequent endocrinological complications were growth hormone deficiency, hypogonadotropic hypogonadism and ACTH deficiency, noted in 21 (46.7%), 20 (44.4%), and 16 (35.6%) children respectively, and the details are shown in figure-2.

Figure-2: Frequency of endocrinological complications



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CPHD and HP were reported in 23 (51.1%) and 15 (33.3%) children respectively whereas no endocrinological complications were noted among remaining 7 (15.6%) children. Gender (p=0.674), age (p=0.385), height (p=0.460), weight (p=0.380), tumor types (p=0.202), treatment types (p=0.101), or time elapsed since treatment (p=0.158) were not found to have any significant association with endocrinological complications (table-3).

Table-3: Association of endocrinological complications with study variables

Study Variables		Endocrinological complications			P-value
		CPHD	HP	Normal	
Gender	Boys	17 (73.9%)	11 (73.3%)	4 (57.1%)	0.674
	Girls	6 (26.1%)	4 (26.7%)	3 (42.9%)	
Age (years)		10.9±3.8	12.5±2.4	12.0±3.0	0.385
Height (cm)		124.9±24.9	133.3±8.1	132.3±13.9	0.460
Weight (kg)		40.6±23.2	37.7±9.4	29.9±9.8	0.380
Tumor types	Craniopharyngioma	19 (82.6%)	10 (66.7%)	6 (85.7%)	0.202
	Pilocytic astrocytoma	2 (8.7%)	2 (13.3%)	1 (14.3%)	
	Pituitary adenoma	-	3 (20.0%)	-	
	Others	2 (8.7%)	-	-	
Treatment	Surgery	12 (52.2%)	12 (80.0%)	7 9100%)	0.101
	Radiotherapy	4 (17.4%)	2 (13.3%)	-	
	Surgery and radiotherapy	7 (30.4%)	1 (6.7%)	-	
Time elapsed since treatment (months)		10.7±1.6	11.6±1.1	10.9±1.6	0.158

Discussion

In the present study, craniopharyngioma and pilocytic astrocytoma were found to be the most common types of brain tumors, noted in 77.8% and 11.1% cases respectively. These findings are somewhat close with the contemporary literature where craniopharyngioma are known to be the most frequent type of brain tumors, contributing 44.6% cases.[9] The literature highlights craniopharyngiomas as the most prevalent suprasellar tumors in childhood, constituting a significant proportion, ranging from 50-80%, of masses within this region. These represent approximately 1.5%-11.6% of all pediatric brain tumors, indicating their substantial prevalence among this specific demographic.[10,11]Brain tumors are frequently diagnosed among children with pituitary deficiencies. Physicians may overlook referring patients to endocrinology in cases of brain tumors not impacting the pituitary region, thus excluding consideration for hypopituitarism.

In this study, CPHD and HP were reported 51.1% and 33.3% children respectively, so, a cumulative proportion of 84.4% children following treatment of brain tumor had endocrinological abnormalities. The combination of tumor location, treatment-related impacts on the pituitary gland, and the particular susceptibility of children's developing endocrine systems may have contributed to the higher proportion of endocrinological complications observed among paediatric brain tumor patients post-treatment in this study. A study analyzing prospective annual endocrine screening showed post-treatment endocrine effects of brain tumors in 43% of patients after 10 years from tumor diagnosis. The highest yield for finding a pituitary deficiency was within the first six years after tumor diagnosis and treatment.[12] Heo et al found that 37.1%brain tumor survivors had at least one endocrine abnormality.[6] Others reported the proportion of endocrine disorders among 40% children with brain tumors.[12,13] Late endocrine sequalae can also manifest years after treating the tumor, hence annual surveillance of growth, puberty, weight, development, and endocrine status is recommended for 10 years after tumor therapy.[14] Endocrine

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complications are frequently observed in patients within months to years after treatment completion, estimated prevalence of endocrine complications being 50%, with external beam radiation of endocrine organs (the hypothalamus/pituitary, thyroid and gonads) being the main risk factor.[15] Endocrine deficiency depends alot on radiation dose to the hypothalamus and pituitary. Correlation between RT dose to brain structures and development of endocrine dysfunction showed 4-year actuarial rate of hormonal deficiencies of growth hormone, thyroid hormone, adrenocorticotropic hormone, and gonadotropin deficiencies as 48.8%, 37.4%, 20.5%, 6.9%, and 4.1%, respectively.[16]

We did not find any significant association of types of brain tumor with endocrine disorders. In the past, it has been shown that craniopharyngiomas result in profound disturbances of pituitary–hypothalamic axis and require surgery to resect the tumor and associated cysts as well as irradiation of adjacent normal tissues.[17] After treating pituitary tumors, post surgical endocrine complications manifest by hypopituitarism, manifesting as growth hormone deficiency, hypothyroidism, adrenal insufficiency, disorders of puberty, diabetes insipidus and hypothalamic obesity.[18]

Relatively small sample size and a single-center study design were some of the limitations of this research. Multi-center studies of prospective designs could provide more robust and comprehensive insights. The study reported findings within a relatively short follow-up period (around 8 to 12 months). Long-term effects and the evolution of endocrinological complications beyond this time frame are not captured in this research. Growth hormone deficiency cannot be commented with assurance just on the basal levels as was done in this study. The study may have lacked some crucial data points or variables related to the patients' treatments, tumor characteristics, or other potential influencing factors that could affect the occurrence of endocrinological complications.

Conclusion

Notable proportion of children following treatment of brain tumors have endocrinological complications. Comprehensive follow-up and continuous monitoring of endocrine parameters are crucial for paediatric brain tumor survivors, aiming detection and addressing complications promptly, ultimately enhancing post-treatment care and outcomes.

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