SHORT-TERM ENDOCRINOLOGICAL COMPLICATIONS FOLLOWING TREATMENT OF PAEDIATRIC BRAIN TUMORS

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Abstract

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

Methodology: This cross-sectional study was conducted at the outpatient Department of Pediatric Endocrinology at the National Institute of Child Health (NICH), from May 2022 to August 2023. Children of either gender, aged between 1-18 years, diagnosed with brain tumour who received any 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.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 pediatric brain tumor survivors, aiming detection and addressing complications promptly, ultimately enhancing post-treatment care and outcomes.

Keyword: Brain tumor, craniopharyngioma, hypopituitarism, pilocytic astrocytoma, radiotherapy.

Introduction

Data from the developed world has shown that 1 in 285 children are diagnosed with cancer before their 20th birthday which is very alarming.[1] Leukemias, central nervous system related tumors and lymphomas are some of the most frequent types of tumors.[2] During adolescents, the most common types of cancers are related to brain and other central nervous system (CNS) tumors and lymphomas, followed by leukemias and gonadal germ cell tumors.[2] The projected estimates have shown that aroudn 14 million new pediatric cancer cases are expected between 2020-2050 globally while a large proportion of these (around 6 million) are expected to remain un-diagnosed.[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 CNS related malignancies among the least common solid tumor cancers with a prevalence of 3%.[4]

Primary brain tumors in the pediatric age groups are difficult to timely diagnose and treat.[5] Clinical manifestations of tumors like pituitary adenomas reflect oversecretion of related hormone, most frequently growth hormones, 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 abnormality, whereas hypopituitarism (17.4%) and hypothyroidism (6.1%) were the most frequent endocrine disorders. Females, younger age groups and radiotherapy administration were some of the important factors associated with endocrine disorders.[6]

The literature highlights measures which can be used to emphasize the need of endocrine surveillance, regular assessment of endocrine functioning and timely interventions in treated children who had brain tumors.[7] 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. This study aimed to determine the frequency of post-treatment endocrine complications in patients with pediatric brain tumors within one year following treatment.

Patients and Methods

This cross-sectional study was conducted in the outpatient department of pediatric 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.

Approval from "Institutional Ethical Review Board" was acquired (IERB-24/2021, dated: 06-05-2022). 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 pediatric 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.

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

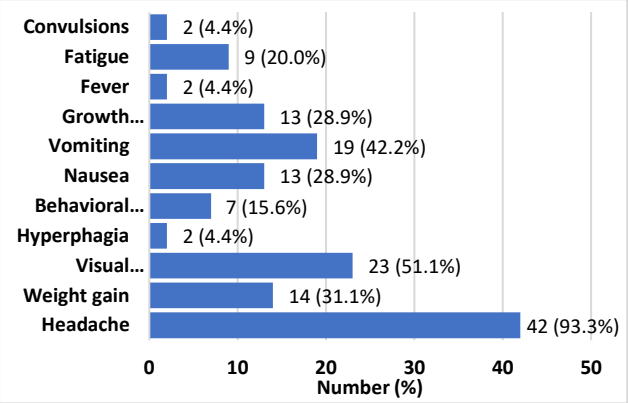
In a total of 45 patients, 32 (71.1%) were boys, representing a boys to girls ratio of 2.5:1. The mean age was 11.61±3.32 year (ranging between 3 to 17 years). The mean height and weight were 130.09±16.96 cm and 36.94±15.83 kg respectively. The mean SD height and weight scores were -2.81±1.75 and -1.96±2.21. 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 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. (Table 1)

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

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).

Figure-1: Frequency of presenting symptoms



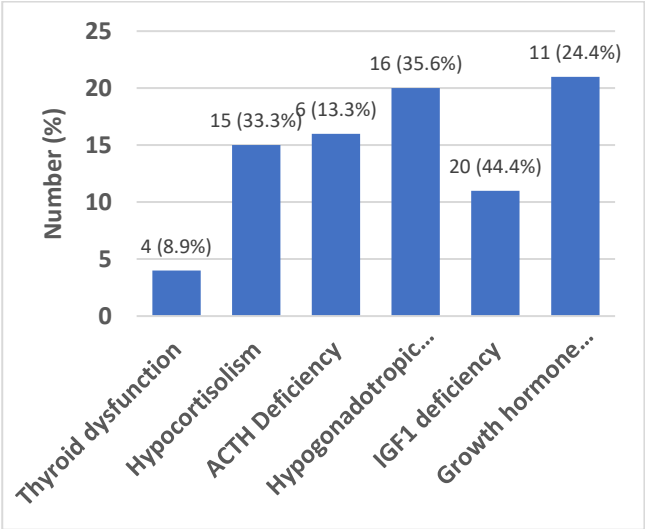
The mean duration of time elapsed since treatment was 11.02±1.45 months (ranging between 8 to 12 months). Table-2 is showing the mean and SD of endocrinological laboratory parameters.

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



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%)	0.2
	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%)	0.1
	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	0.1

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 pediatric brain tumor patients post-treatment in this study. A study examining annual endocrine screenings over a decade revealed that 43% of patients experienced endocrine effects following brain tumor treatment.[12] The highest detection rate for pituitary deficiencies occurred within the first six years post-diagnosis and treatment. Heo et al. reported that 37.1% of brain tumor survivors exhibited at least one endocrine abnormality.[6] Other studies indicated that 40% of children with brain tumors had endocrine disorders.[12,13] Late-onset endocrine sequelae can appear years after initial tumor treatment, thus annual monitoring of growth, puberty, weight, development, and endocrine function is recommended for 10 years following therapy.[14] Endocrine complications often emerge within months to years after completing treatment, with an estimated prevalence of 50%. External beam radiation targeting endocrine organs such as the hypothalamus/pituitary, thyroid, and gonads is a major risk factor.[15] The likelihood of endocrine deficiencies is closely related to the radiation dose received by the hypothalamus and pituitary. Studies have shown that the 4-year actuarial rates for deficiencies in growth hormone, thyroid hormone, adrenocorticotropic hormone, and gonadotropin are 48.8%, 37.4%, 20.5%, 6.9%, and 4.1%, respectively.[16]

We found no significant correlation between the types of brain tumors and endocrine disorders. Previous research has indicated that craniopharyngiomas significantly disrupt the pituitary-hypothalamic axis, necessitating surgical removal of the tumor and associated cysts, as well as irradiation of nearby normal tissues.[17] Post-surgical endocrine complications following pituitary tumor treatment

often present as hypopituitarism, leading to growth hormone deficiency, hypothyroidism, adrenal insufficiency, pubertal disorders, 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 pediatric brain tumor survivors, aiming detection and addressing complications promptly, ultimately enhancing post-treatment care and outcomes.

Disclosure:

Authors declare no conflict (financial or non-financial) interest.

Ethical consideration:

Prior ethical approval was taken from the institutional review board, (IERB-24/2021, dated: 06-05-2022)

The confidentiality of patients was ensured by Primary investigator.

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