

# Comprehensive Insights Into Pediatric Craniopharyngioma: Endocrine and Metabolic Profiles, Treatment Challenges, and Long-term Outcomes from a Multicenter Study

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## What is already known on this topic?

Craniopharyngiomas (CPG) are challenging to treat due to their proximity to vital structures, and the tendency for recurrence. The pituitary axis is frequently affected during the presentation of CPG.

## What this study adds?

Recurrence of CPG was predominantly related to incomplete resection and the low rate of postoperative radiotherapy. The study revealed hesitancy among physicians regarding use of recombinant growth hormone, highlighting a need for further exploration and understanding.

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## Abstract

**Objective:** Craniopharyngiomas (CPG) have complex treatment challenges due to their proximity to vital structures, surgical and radiotherapeutic complexities, and the tendency for recurrence. The aim of this study was to identify the prevalence of endocrine and metabolic comorbidities observed during initial diagnosis and long-term follow-up in a nationwide cohort of pediatric CPG patients. A further aim was to highlight the difficulties associated with CPG management.

**Methods:** Sixteen centers entered CPG patients into the ÇEDD NET data system. The clinical and laboratory characteristics at presentation, administered treatments, accompanying endocrine, metabolic, and other system involvements, and the patient's follow-up features were evaluated.

**Results:** Of the 152 evaluated patients, 64 (42.1%) were female. At presentation, the mean age was  $9.1 \pm 3.67$ , ranging from 1.46 to 16.92 years. The most common complaints at presentation were headache (68.4%), vision problems (42%), short stature (15%), and nausea and vomiting (7%). The surgical procedures were gross total resection (GTR) in 97 (63.8%) and subtotal resection in 55 (36.2%). Radiotherapy (RT) was initiated in 11.8% of the patients. Histopathological examination reported 92% were adamantinomatous type and 8% were papillary type. Postoperatively, hormone abnormalities consisted of thyroid-stimulating hormone (92.1%), adrenocorticotrophic hormone (81%), antidiuretic hormone (79%), growth hormone (65.1%), and gonadotropin (43.4%) deficiencies. Recombinant growth hormone treatment (rhGH) was initiated in 27 (17.8%). The study showed hesitancy among physicians regarding rhGH. The median survival without relapse was 2.2 years. Median (range) time of relapse was 1.82 (0.13-10.35) years. Relapse was related to longer follow-ups and reduced GTR rates. The median follow-up time was 3.13 years. Among the last follow-up visits, the prevalence of obesity was 38%, but of these, 46.5% were already obese at diagnosis. However, 20% who were not obese at baseline became obese on follow-up. Permanent visual impairment was observed in 26 (17.1%), neurological deficits in 13 (8.5%) and diabetes mellitus in 5 (3.3%) patients.

**Conclusion:** Recurrence was predominantly due to incomplete resection and the low rate of postoperative RT. Challenges emerged for multidisciplinary regular follow ups. It is suggested that early interventions, such as dietary restrictions and increased exercise to prevent obesity, be implemented.

**Keywords:** Craniopharyngioma, pituitary, dysfunction

## Introduction

One of the most difficult brain tumors to treat is a craniopharyngioma (CPG), which is characterized by benign histology but has the potential to cause serious functional and clinical problems because of where the CPG is usually located in the central nervous system, frequently involving the sellar and suprasellar regions, compressing nearby tissues (1,2,3,4,5). The complex nature of the surgical management of CPG, compounded by its complicated anatomical positioning, has encouraged the exploration of novel treatment strategies. In contrast to treatment techniques, follow-up data show no appreciable differences in long-term effects (1,6,7). CPG constitutes 1.2-10% of all pediatric brain tumors, with an incidence of 0.5-2.5 cases per 1,000,000 individuals, making it particularly prevalent in the pediatric population (1,2) and CPG is most commonly diagnosed in children. It exhibits a two-peak age distribution, with the highest occurrences observed in individuals aged 5 to 15 years during childhood and another peak in individuals aged 45 to 60 years in adulthood (2,3).

Endocrine disorders in patients with CPG significantly affect their quality of life (4,5,6,7,8,9,10,11,12). The pituitary axis is frequently affected during the presentation (2,3,13,14). Furthermore, radiotherapy (RT) impacts hypothalamic-pituitary function (3,6,15,16,17,18). Compared to the pituitary gland, the hypothalamus is more susceptible to damage by radiation (16,17). As hypothalamic function

is often impaired, 40-50% of patients are affected by hypothalamic obesity (7,14,19,20,21). Moreover, the degree of hypothalamic involvement before surgical intervention is a significant factor in determining the persistent outcomes after the surgical procedure (21,22,23).

Interventions and treatments for endocrine and metabolic problems also present challenges. Although replacement therapy for pituitary hormones is stated not to cause a risk for CPG recurrence, it remains controversial (24,25,26,27). The effect of recombinant human growth hormone (rhGH) on the psychosocial status and quality of life has been investigated, and it has been shown that individuals who take rhGH during the growth period have better height growth; however, this did not lead to weight loss in adult patients, only in the pediatric group (27,28,29).

Managing pediatric CPG is challenging due to the complex diagnostic process, the distinctiveness of the anatomical position of the CPG, the extent of involvement in surrounding tissues, the secondary harm induced by treatments, the weight of endocrine and metabolic complications, and the adverse impacts on sustained quality of life. The aims of this research was twofold: first, to determine the prevalence of endocrine and metabolic comorbidities during the diagnostic phase and long-term follow-up in a national cohort of pediatric patients diagnosed with CPG; and second, to determine the problems involved in successfully treating the endocrine abnormalities in these patients.

## Methods

### Clinical and Laboratory Enrollment Criteria

This aim of this investigation was to comprehensively assess individuals under follow-up at pediatric endocrinology centers with experience in CPG management. The study involved the active participation of 16 different endocrinology departments. Patients' data entry into the ÇEDD NET database was uploaded through cooperative efforts of participating centers to enhance data gathering. The investigation of several aspects, such as the age at which the disease first manifested, clinical manifestation, length of symptoms, demographic traits, cranial magnetic resonance imaging (MRI) results at diagnosis, surgical and/or RT treatments used, and tumor histology, was covered by the study protocol.

Comprehensive datasets capturing concurrent endocrine, metabolic, ophthalmological, and neurological profiles were systematically collected. Physical evaluation included height standard deviation (SD) score (SDS), visual acuity (VA) assessment, body mass index (BMI), and Tanner's puberty stage. In addition, laboratory investigations, including thyroid function tests [thyroid-stimulating hormone (TSH), fT4], adrenal function (ACTH, cortisol), prolactin (PRL) levels, gonadotropins, testosterone/estradiol levels, and, in instances of growth hormone (GH) deficiency, insulin-like growth factor 1 (IGF-1) and insulin-like growth factor binding protein 3 (IGFBP3) levels, were assessed. The occurrence of central diabetes insipidus (CDI) and treatments were also evaluated. Quantitative measures of fasting insulin levels, lipid profiles, aspartate aminotransferase and alanine transaminase levels, and uric acid concentrations were required to evaluate metabolic health.

The patients underwent a thorough ophthalmological and neurological examination and assessments of any associated social and psychiatric issues, cardiovascular symptoms, obstructive sleep apnea, and further symptomatic presentations. The complexities of post-diagnostic monitoring were investigated, including the typical follow-up time, the resulting MRI findings, and disparities observed in the endocrine, metabolic, ophthalmological and neurological systems. Reoperations that followed tumor recurrences were documented.

Inclusion criteria required participants to have received a definitive diagnosis before 18 years, substantiated by unequivocal histopathological confirmation of CPG. Conversely, candidates were excluded if their diagnosis rested solely on clinical and radiological grounds and lacked histopathological confirmation.

The study was approved by the Ankara University Faculty of Medicine of Human Research Ethics Committee (protocol number: 12-130-21, date: 16.02.2021).

### Statistical Analysis

All statistical calculations were performed using Statistical Package for the Social Sciences for Windows, version 22.0 (IBM Inc., Armonk, NY, USA). The conformity of the variables to the normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Shapiro-Wilk test). Differences between dependent groups were analyzed using Student's t-test and independent groups were analyzed using the Mann-Whitney U test. A  $p < 0.05$  was considered statistically significant.

## Results

### Study Participants and Clinical Presentation

One hundred fifty-two patients (64 females; 42.1%) were enrolled in the study. At the time of diagnosis, the mean age was 9.1 years. The height SDS was  $-1.09 \pm 1.5$ , and the BMI SDS was  $0.7 \pm 1.6$ . The study included 110 prepubertal and 42 pubertal patients. Notably, 39 (25%) patients had short stature ( $< -2.0$  SDS) at diagnosis. Distribution was as follows: 19 girls had a height SDS of  $-2.9 \pm 0.14$  and 20 boys had a height SDS of  $-3.1 \pm 0.20$ . In addition, at the point of diagnosis, 35 (23%) patients were classified as obese, including 10 girls (BMI SD:  $2.6 \pm 0.16$  SD) and 25 boys (BMI SD:  $2.7 \pm 0.15$  SD) (Table 1).

Of the 152 patients, the foremost initial complaint was headache (68.4%). Sixty-five patients (42%) had vision problems including 52 patients with reduced VA, seven with restricted field of vision, two presented with diplopia, and two had nystagmus. Other presenting complaints included obesity in 38 patients (25%), impaired growth in 23 patients (15%), nausea and vomiting in 11 patients (7%), neurological symptoms (seizure, drowsiness, ataxia, tremor) in 14 patients (9%) and pubertal problems in 4 patients (3%) (Table 1).

In the first evaluation, hormone deficiencies in descending order of frequency were: TSH deficiency in 121 patients (79%); ACTH deficiency in 106 patients (69%); CDI in 95 patients (62.5%); GH deficiency in 83 patients (54.6%); and gonadotropin deficiency in 63 patients (41%). In total 137 patients had PRL measurements and of these, 48 had elevated PRL levels, 68 patients had normal and 23 patients had low PRL levels (Table 1).

**Table 1. Demographic characteristics, clinical and laboratory evaluation of patients with craniopharyngioma at presentation**

Demographic characteristics	
Patients (n)	152
Age at the time of diagnosis (year)	9.1 ± 3.6
Sex	
Female (n)	64 (42%)
Male (n)	88 (58%)
Height SDS	-1.9 ± 1.5
Short stature at diagnosis	
Female (n)	19 (height SD: -2.9 ± 0.14)
Male (n)	20 (height SD: -3.1 ± 0.20)
BMI SDS	0.7 ± 1.6
Obesity at diagnosis	
Female (n)	10 (BMI SD: 2.6 ± 0.16)
Male (n)	25 (BMI SD: 2.7 ± 0.15)
Pubertal status	
Prepubertal (n)	110 (72%)
Pubertal (n)	42 (28%)
Symptoms at diagnosis	
Headache	104 (68%)
Had vision problems	
Reduced visual acuity	52 (34%)
Restricted vision	7 (5%)
Diplopia	2 (1%)
Nystagmus	2 (1%)
Impaired growth	23 (15%)
Nausea and vomiting	11 (7%)
Neurological symptoms	14 (9%)
Pubertal problems	4 (3%)
Hormone deficiencies in patients	
TSH deficiency	121 (79%)
ACTH deficiency	106 (69%)
Central diabetes insipidus	95 (62.5%)
GH deficiency	83 (54.6%)
Gonadotropin deficiency	63 (41%)
Prolactin level (n = 137)	
- Elevated	48 (35%)
- Normal	68 (49.6%)
- Low	23 (16.7%)

BMI SDS: body mass index standard deviation (SD) score, ACTH: adrenocorticotrophic hormone deficiency, TSH: thyroid-stimulating hormone, GH: growth hormone

## Cranial Imaging and Extension Patterns

Cranial imaging showed that extension into a single area was observed in 64 patients, with 55 involving the suprasellar region, five the third ventricle, four the anterior fossa (one each for infundibulum, optic chiasm, and other parts). Extension into multiple areas was noted in 43 patients. Thirteen patients showed no extension, while 32 patients had unspecified extension patterns.

## Treatment Approaches and Outcomes

Transnasal interventions were performed in 76 patients (50%), endoscopic procedures in 73 patients (48%), and gamma knife treatment in two patients (1.3%). The type of operation was not specified in one patient. Notably, 73 patients (48%) underwent triple-phase interventions, which consisted of the first stage of transient CDI, second stage of an antidiuretic phase, and the permanent CDI phase (30,31). RT was initiated in 11.8% of the patients.

## Pathology and Tumor Characteristics

The histopathological evaluation was not reported in 46 (30.3%) of patients. Among the 106 patients with histopathological reports available, 92% were classified as the adamantinomatous type, while 8% exhibited the papillary type. The mean tumor diameter measured was 3.7 ± 1.5 cm.

## Postoperative Complications and Findings

The mean follow-up duration was 4.5 ± 3.9 years. At the last follow-up, the mean age was 13.7 ± 4.9 years, with the height SDS documented as -1.1 ± 1.62. Among the patients, 36 (23.6%) had a height SDS below -2 SD (Table 2). Relapse was observed in 56 patients (38%), with a median (range) time to relapse (from the first surgery) of 1.82 (0.13-10.35) years. No significant differences in age, gender, or tumor size were observed between patients with and without relapse (p > 0.05). The follow-up duration was 5.4 ± 3.6 years for patients with relapse and 3.8 ± 3.6 years for those without. Complete resection was achieved in 57% of patients with relapse and 71% in those without (p < 0.05). The significant factors contributing to the development of relapses were the inability to achieve complete resection and the low rate of adding postoperative RT.

## Hormone Deficiencies and Outcomes

Hormone deficiencies were prevalent at the final assessment. These included TSH deficiency in 140 patients (92.1%), ACTH deficiency in 123 patients (81%), permanent CDI in 120 patients (78.1%), GH deficiency in 99 patients (65.1%), and gonadotropin deficiency in 66 patients (43.4%) (Table 2).

**Table 2. Postoperative follow-up and outcomes in patients with craniopharyngioma**

Postoperative findings - follow-up	
Follow-up duration (years)	4.5 ± 3.9 [0.08; 20]
Age at last follow-up (years)	13.7 ± 4.9 [2.9; 29]
Height SDS	-1.1 ± 1.6 [-6.4; 2.6]
BMI SDS	1.4 ± 1.4 [-2.35; 5.08]
Relapse (n)	58 (38.2%)
Remission (n)	92 (60.5%)
Type of surgery	
GTR (n)	97 (63.8%)
Subtotal (n)	54 (35.5%)
Transnasal (n)	76 (50%)
Endoscopic (n)	73 (48%)
Gamma knife (n)	2 (1.3%)
Radiotherapy (n)	18 (11.8%)
Postoperative hormone deficiencies in patients	
Growth hormone deficiency	99 (65.1%)
Gonadotropin deficiency (total 109 pubertal status)	66 (43.4%)
TSH deficiency	140 (92.1%)
ACTH deficiency	123 (81%)
Central diabetes insipidus	120 (78.9%)
BMI SDS: body mass index standard deviation (SD) score, ACTH: adrenocorticotropic hormone deficiency, TSH: thyroid-stimulating hormone, GTR: gross total resection	

Among the preoperative patients, 35 individuals (23%) were obese, and 58 individuals (38%) were obese in the postoperative period. However, 20% who were not obese at baseline became obese on follow-up. In the postoperative period, 31 newly obese patients were evident. However, eight of 35 patients, that were preoperatively obese, had normal BMI in the postoperative follow-up.

Among the patients, 12/42 (28%) had a metabolic status indicating prediabetes and 4/120 (3%) had diabetes mellitus. On follow-up, neurological deficits were observed in 8 (6%) patients. Among these, five patients had epilepsy, while three had motor deficits.

There was no apparent difference in survival between relapse and nonrelapse groups. However, due to the limited number of patients, statistical significance could not be demonstrated.

## Discussion

CPG constitutes a significant portion of childhood central nervous system tumors (1,2). Our patients had a mean age at diagnosis of around 9.2 years. According to Beckhaus et

al. (21), CPG patients with a younger age at diagnosis (less than 12 years old) had a worse event-free survival rate. Our contribution could modify this interpretation, particularly considering the long-term follow-up encompassing adult age. The literature suggests that the most common initial clinical manifestations include headaches, visual impairment, and endocrine issues, such as growth retardation, obesity, delayed puberty, and CDI (5,13,22,23,32,33,34). Approximately 60-75% of patients primarily report headaches and in keeping with this, headaches were the most common presenting complaint (68.4%) (32). During initial evaluations, 70-80% of patients may have visual impairments (32). A notable 42% of our patients experienced visual disturbances as their first symptom. However, this rate might differ, based on the location of the tumor in the chiasm (anterior or posterior) and asymmetric extension of the tumor in our study. Among patients afflicted by suprasellar CPGs, 50% exhibited decreased VA and visual field impairment at diagnosis. Interestingly, previously published studies indicated a prevalence of 38% during the diagnostic phase, which further diminished to 15% postoperatively (35).

During the diagnostic phase, hormonal imbalances were described in 93% of the patients. Studies highlighted that hormonal involvement was evident in 40% to 87% of patients during their diagnostic assessment (34). Our findings were at the upper end of the range. This may be attributed to the age at diagnosis and the specific region affected by the tumor.

In the literature, approximately 26% to 75% of CPG patients are reported to have GH deficiency at the time of diagnosis, which increases to 70% to 92% postoperatively. Our study is compatible with these findings, suggesting a correlation with the limited preoperative endocrinological assessment. Without a preoperative multidisciplinary assessment, clinicians involved in the postoperative process may have missed the opportunity for a comprehensive examination at the time of diagnosis. In a study by Müller et al. (36), preoperative GH deficiency was observed in 54% (n=83) patients, while postoperative GH deficiency was noted in 65.1% (n=99) patients. Among them, 28 patients (18%) were started on rhGH. Similar to other studies in the literature, the most frequently reported hormone deficiency in our study was TSH deficiency (4,32).

In the present study, the majority of patients displayed permanent hypopituitarism symptoms. In the literature, postoperative hypopituitarism was reported at a rate of 57-98%. Permanent CDI was reported in 64-80%. Endocrine disorders frequently observed during diagnosis and follow-up in CPG patients significantly contribute to reduced quality of life (4-12).

Sklar (34) reported GH deficiency in 75% of patients, gonadotropin deficiency in 40%, TSH in 25%, and ACTH in 25%. They also indicated CDI in the 9-17% (postoperative: 40-80%) (34). Caldarelli et al. (37) found GH deficiency in 82%, ACTH deficiency in 76%, TSH deficiency in 73%, and gonadotropin deficiency in 67% of patients. In our cohort, tumor extension was predominantly suprasellar, consistent with the literature (38). The impact of the tumor, surgical intervention, and RT are significant factors contributing to hypopituitarism.

Although rarely malignant, CPG presents difficulties in treatment due to its proximity to vital structures, incomplete resection, and tendency to recur. Furthermore, delayed diagnosis is common in children. If complete removal is not possible, subtotal resection with RT for residual tumors is necessary. There is no consensus on the ideal surgical approach (3,4,13,14,21,22,39). Aggressive gross total resection (GTR), previously more commonly practiced, is now associated with higher endocrine problems and decreased quality of life. Subtotal removal with preservation of the pituitary and cranial nerves, followed by radiation, has become more widely used. Long-term quality of life data after endoscopic endonasal surgery is limited (4,5,13,14,21,23,32,39,40). In our study, GTR was achievable in most patients ( $n = 97$ ; 63.8%). Despite the benign nature of CPGs, there is a marked potential for relapse. There are no guidelines on managing pediatric CPGs regarding the ideal surgical approach (3,4,13,14,21,22,39). Surgical procedures might differ based on the use of a personalized approach. Transnasal intervention was the most frequently performed in our patient group. However, due to tumor size, vital organ proximity, and unsuitable location, complete resection was not feasible for all subjects. In the literature, the likelihood of recurrence is more common in pediatric patients than in adults due to the adamantinomatous variant. GTR might not eliminate recurrence risk (22,41,42). It has been suggested that GTR provided variable disease control, with recurrence rates reported at 36.4-40% after GTR (41,43). Despite the prevailing notion that GTR tends to prevent a recurrence, the likelihood of hypothalamic/pituitary damage affects quality of life, and some researchers advocate the benefits of conservative treatments (4).

Following surgery, the number of patients undergoing triphasic response of pituitary stalk injury leading to CDI development reached 48%. In the pediatric age group, a higher number of patients undergo triple-phase interventions compared to adults (2). This seems to be associated with tumor size and the damage inflicted on surrounding tissues by surgery.

Pathologically, most of the patients in the present study were diagnosed with adamantinomatous type CPG. It is the most common histological subtype of CPG and exhibits a bimodal age distribution, with the highest incidence occurring in children aged 5-15 years and adults aged 45-60 (2). Pediatric CPG, which predominately manifests as the adamantinomatous subtype, differs in pathology and genetic characteristics from adults. The underlying molecular and cellular mechanisms for the adamantinomatous type involve mutations in the *CTNNB1* gene, responsible for encoding  $\beta$ -catenin. On the other hand, papillary CPGs in adults are associated with *BRAF* V600E mutations. The pathological and genetic characteristics could also affect recurrence outcomes, hormonal imbalances, and survival rates (2,32). While the papillary type is observed at a low frequency, cases occurring during childhood have also been reported in the literature (44,45). This situation is elucidated more clearly through the identification of underlying molecular mechanisms. However, due to the retrospective nature of our study, molecular assessment could not be assessed.

Eighteen patients had received postoperative RT. There was no significant difference in survival compared to other patient groups. However, due to the limited number of patients, statistical analysis would not be reliable. A recent meta-analysis suggested that GTR and STR, along with RT, exhibit similar survival outcomes for CPG (45); due to the small sample size in our study, statistical confirmation was not performed.

On follow-up, neurological deficits were observed in 13 patients, accounting for 8.6% of the patients, including epilepsy and motor deficits. The reported rates of neurological complications in an earlier series ranged from 8% to 36%, aligning well with our findings (10).

In CPG, hypothalamic obesity is challenging, leading to metabolic problems and being unresponsive to lifestyle changes. Hypothalamic findings may be missed during the follow-up. It is known that preoperative hypothalamic engagement and hypothalamic damage during operation lead to preoperative and postoperative obesity (2,46). In individuals affected by hypothalamic damage, there is a decrease in energy expenditure, an increase in daytime sleepiness, and a disrupted response in signals related to leptin, ghrelin, and insulin. As a consequence, hyperinsulinemia develops (47). Obesity developed in 31 patients during follow-up. At diagnosis, 35 patients (23%) were obese. Among the postoperative patients, 58 patients (38%) were obese, of which 27 (18%) were already obese at the time of initial presentation. In the literature, the prevalence of obese patients at diagnosis ranges from

12% to 19%. Furthermore, it has been reported that the frequency of severe obesity after six months postoperatively is approximately 55% (10). Similar to the literature, half of the patients exhibited obesity (48). Notably, lifestyle modifications and other traditional treatments for obesity typically fail to control the condition (2,46). Medical treatment options such as triiodothyronine, octreotide, dextroamphetamine, methylphenidate, sibutramine, and GLP-1 receptor agonists lacked generally applicable scientific evidence and showed side effects (46). Obesity surgery can not achieve permanent weight loss and also causes malabsorption of oral hormone replacement medications (46). Unfortunately, there is no definitive treatment option for hypothalamic obesity. Treatment with rhGH replacement improves growth, weight, and neuropsychology in the pediatric population receiving rhGH treatment (24,25,26,27). In the present study, the use of rhGH appears to be less widespread than recommended to control metabolic parameters (25,46). The study revealed a hesitancy among physicians regarding rhGH therapy. The delay may be due to the risk of side effects. However, rhGH replacement therapy does not adversely affect disease-free survival (25,46,49,50). It is important that rhGH treatment should not be delayed in these patients with CPG.

### Study Limitations

This study has some limitations attributed to the retrospective design of the study and the lack of homogeneity in data collection. Specifically, hypothalamic syndrome data could not be obtained from all participating centers. The onset of obesity could not be assessed for the initial year. Moreover, there is a deficiency in the detailed features of cranial imaging.

### Conclusion

In conclusion, CPG is challenging when it occurs in the pediatric age group, requiring a comprehensive approach. Difficulties with regular multidisciplinary follow-ups have been identified by the present study, and it is suggested that early interventions involving calorie restriction and increased exercise for obesity should be considered. The components of hypothalamic syndrome, including eating disorders, circadian sleep changes, temperature variations, and heart rate variability, should be taken into consideration during patient follow-ups. Recurrence was predominantly due to incomplete resection and the low rate of postoperative RT.

### Ethics

**Ethics Committee Approval:** The study was approved by the Ankara University Faculty of Medicine of Human

Research Ethics Committee (protocol number: I2-130-21, date: 16.02.2021).

**Informed Consent:** Written informed consent was obtained from the patients and parents for publication of this study.

### Authorship Contributions

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