

## Midline brain abnormalities and associated endocrine dysfunctions: a clinical and MRI-based study

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### ABSTRACT

**Background:** This study aimed to assess the spectrum and prevalence of endocrine disorders in pediatric patients with midline brain abnormalities (MBA).

**Methods:** This retrospective observational study was conducted at a tertiary pediatric endocrinology center and included patients younger than 18 years of age with MBA. Clinical data were obtained from medical records.

**Results:** The study included 17 patients (52.9% male) with a median age of 11.1 (8.9–15.7) years. The median age at first admission was 5.3 (1.5–9.9) years, and the median follow-up period was 6.8 (2.1–7.9) years. The most common clinical finding at admission was short stature (29.5%). Brain magnetic resonance imaging most frequently revealed corpus callosum abnormalities (52.9%), followed by septo-optic dysplasia (17.6%). Endocrine disorders were present in 82.3% of patients with MBA. The most frequently observed endocrine disorder was multiple pituitary hormone deficiency (41.2%). In addition, isolated endocrine disorders such as central hypothyroidism (17.6%), growth hormone deficiency (11.8%), diabetes insipidus (5.9%), and hypogonadotropic hypogonadism (5.9%) were observed. When each endocrine disorder was evaluated individually, central hypothyroidism emerged as the most frequently identified condition (58.8%). Three patients had no detectable endocrine dysfunction.

**Conclusions:** Endocrine disorders were observed in 82.3% of patients with MBA, with central hypothyroidism being the most common when considered individually. The high prevalence of endocrine disorders in children with MBA underscores the importance of routine endocrine screening in this population.

**Keywords:** children, endocrine disorders, hypopituitarism, midline brain abnormalities

### INTRODUCTION

The hypothalamus, pituitary gland, and other endocrine organs play a crucial role in regulating growth, reproduction, metabolism, and fluid balance.<sup>1</sup> The pituitary gland originates from the Rathke's pouch and the neuroectoderm

of the diencephalon, with its development occurring around the sixth to seventh week of embryogenesis. Congenital and developmental abnormalities of the hypothalamic-pituitary axis include pituitary hypoplasia or agenesis, ectopic posterior pituitary, absence of the pituitary bright spot, duplication of the pituitary gland or stalk, empty



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sella syndrome, and various midline congenital anomalies. Additionally, midline structural defects such as optic nerve hypoplasia, absence of the septum pellucidum, and corpus callosum abnormalities may coexist with these conditions.<sup>2</sup>

Children with midline brain abnormalities (MBA) often present with neurological impairments, including developmental delay and hydrocephalus.<sup>3</sup> Given the potential risk of morbidity and mortality associated with undiagnosed endocrinopathies, recognizing the clinical manifestations of hormone deficiencies in these patients is essential. Hypopituitarism, if left undiagnosed, may lead to severe complications such as hypoglycemia, adrenal crisis, and increased mortality.<sup>4</sup> Reports in the literature suggest that the prevalence of endocrinopathies in children with neuroanatomical anomalies can be as high as 82%.<sup>4-8</sup>

Pediatric endocrinologists frequently evaluate children and adolescents with MBA to assess potential endocrine dysfunction. In addition to clinical symptoms, anthropometric measurements and laboratory investigations aid in diagnosing various pituitary endocrinopathies.<sup>9</sup> Furthermore, brain magnetic resonance imaging (MRI) of the hypothalamic-pituitary region is a key diagnostic tool for identifying structural abnormalities associated with endocrine dysfunction.<sup>9,10</sup>

This study aimed to evaluate the prevalence and spectrum of endocrine disorders in pediatric patients with MBA.

## MATERIAL AND METHODS

This retrospective study included 17 patients diagnosed with MBA. Patients younger than 18 years of age who were followed at a tertiary pediatric endocrinology center for endocrine evaluation due to MBA between January 2011 and January 2021 were enrolled. In some cases, MBA was incidentally detected during neuroimaging performed for non-endocrine indications, while in others, it was identified during evaluation for suspected endocrine dysfunction. Patients diagnosed with an endocrinopathy after the detection of MBA underwent additional hormonal assessments as part of routine endocrine follow-up. Data on patient demographics, including age, sex, age at presentation, auxological measurements, endocrine laboratory findings, and MRI results, were retrieved from medical records. Anthropometric percentiles and standard deviation scores (SDS) were calculated using the Child Metrics online calculator (<http://www.childmetrics.com>), based on the national child growth reference data for Turkey.<sup>11</sup>

## Exclusion criteria

Patients with acquired brain abnormalities due to trauma, infection, or malignancy were excluded. Additionally, cases with septum pellucidum variation and empty sella, considered normal anatomical variants due to their high prevalence in the general population, were not included in the study.<sup>12,13</sup>

## Endocrine assessments

Clinical findings, baseline laboratory tests, and dynamic endocrine function tests were evaluated by a pediatric endocrinologist. The diagnosis of hypopituitarism was established according to current clinical guidelines.<sup>14-18</sup> Growth hormone deficiency (GHD) was defined as an insufficient response to two different stimulation tests, after excluding chronic diseases, in patients with a mean height of less than  $-2$  SDS for sex or a low growth velocity.<sup>14</sup> Central hypothyroidism was diagnosed in cases with low or normal thyrotropin (TSH) levels and reduced free thyroxine (FT4) concentrations.<sup>15</sup> Central adrenal insufficiency was identified based on morning cortisol levels and confirmed with adrenocorticotrophic hormone (ACTH) stimulation tests.<sup>16</sup> Central diabetes insipidus was diagnosed using serum and urine osmolality measurements, supplemented by a water deprivation test when necessary.<sup>17</sup> Hypogonadism was assessed through luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels, as well as responses to a gonadotropin-releasing hormone (GnRH) stimulation test.<sup>18</sup> Multiple pituitary hormone deficiencies (MPHD) were defined as the presence of at least two deficiencies among growth hormone (GH), TSH, ACTH, and gonadotropins.<sup>4</sup> MRI scans were reviewed by an experienced neuroradiologist to assess structural abnormalities. All clinical evaluations, endocrine laboratory tests, and imaging assessments were performed as part of routine patient care.

## Ethical approval

This retrospective study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the Clinical Research Ethical Committee of Istanbul University-Cerrahpasa Cerrahpasa Medical Faculty (Approval number: 83045809-604.01.01-370476). Due to the retrospective nature of the study, informed consent was not required.

## Statistical analysis

All statistical analyses were conducted using SPSS 21.0 (IBM Corp., Armonk, NY, USA). Categorical variables were expressed as numbers and percentages, while continuous variables were presented as means and standard deviations for normally distributed data. For non-normally distributed continuous variables, the median and interquartile range (25th–75th percentiles) were reported.

## RESULTS

The study included 17 patients, of whom 52.9% (n=9) were male, with a median age of 11.1 (8.9–15.7) years. The median age at admission was 5.3 (1.5–9.9) years, and the median follow-up duration was 6.8 (2.1–7.9) years. Demographic, clinical, and laboratory findings of the patients are presented in Table 1. The median SDS for weight, height, and body mass index were -1.51 [(-2.10)–0.3], -2.19 (-3.0–0.66), and -0.15 (-1.85–1.5), respectively. The height SDS values among all patients ranged from -7.26 to +2.75. Tall stature (height SDS: +2.75) was observed in one patient, which is atypical for pituitary hormone deficiencies. The patient was diagnosed with Sotos syndrome, a condition associated with excessive childhood growth. No endocrine abnormalities were detected, and cranial MRI demonstrated corpus callosum hypoplasia.

The most frequently observed clinical finding at admission was short stature (29.5%). Additional presenting features included cleft lip/palate, neuromotor delay, optic nerve hypoplasia, electrolyte imbalances, autism, undescended testis, and tall stature (Table 1).

Brain MRI revealed corpus callosum abnormalities as the most common MBA (52.9%). Other malformations

included septo-optic dysplasia (SOD), polymicrogyria with pituitary hypoplasia, pituitary stalk interruption syndrome, ectopic neurohypophysis, holoprosencephaly, and Chiari malformation type 1 (Table 2).

Endocrine disorders were identified in 14 patients (82.3%), while no endocrine pathology was detected in three cases. MPH were observed in 41.2% of the cases, as detailed in Table 3. Additionally, isolated endocrine disorders—including central hypothyroidism, GHD, diabetes insipidus, and hypogonadotropic hypogonadism—were also observed. When each endocrine disorder was evaluated individually, central hypothyroidism was the most frequently identified condition (58.8%, n=10). Among the three cases without endocrine abnormalities, all had corpus callosum abnormalities. One patient presented with hydrocephalus and GHD, along with cavum septum pellucidum et vergae variation, which is considered a normal anatomical variant (Table 3).

## DISCUSSION

This study investigated the relationship between neuroanatomical abnormalities and endocrine dysfunction in patients with MBA. Endocrine disorders were detected in 82.3% of children referred to our tertiary pediatric endocrinology center with MBA. Previous studies have reported the prevalence of endocrinopathies in similar populations to range between 37% and 82%.<sup>4-8</sup> Variability in reported prevalence rates may stem from differences in study design and patient selection criteria. Since endocrine dysfunction may develop progressively over time, an initially normal pituitary function does not exclude the possibility of future endocrinopathy. In particular, patients with SOD and hypothalamic-pituitary dysfunction are frequently diagnosed within the first two years of life.<sup>19,20</sup> Furthermore, Cerbone et al.<sup>6</sup> demonstrated that individuals with SOD may continue to develop hormone deficiencies

**Table 1.** Admission findings of cases

Clinical Finding	n	%
Short stature	5	29.5
Neuromotor retardation	3	17.6
Cleft lip/palate	2	11.8
Optic nerve hypoplasia	1	5.9
Optic nerve hypoplasia + short stature	1	5.9
Electrolyte imbalance	1	5.9
Electrolyte imbalance + cleft lip/palate	1	5.9
Autism	1	5.9
Cryptorchidism	1	5.9
Tall stature	1	5.9

**Table 2.** Brain abnormalities of cases on MRI

Brain Malformation	n	%
Corpus callosum abnormality (agenesis, dysgenesis, hypoplasia)	9	52.9
Septo-optic dysplasia	3	17.6
Polymicrogyria and pituitary hypoplasia	1	5.9
Pituitary stalk interruption syndrome	1	5.9
Ectopic posterior pituitary	1	5.9
Holoprosencephaly	1	5.9
Chiari malformation type 1	1	5.9

<b>Table 3. Endocrine status of cases</b>		
<b>Endocrine Disorder</b>	<b>n</b>	<b>%</b>
Multiple pituitary hormone deficiency	7	41.2
Central hypothyroidism + growth hormone deficiency + adrenal insufficiency	2	
Central hypothyroidism + adrenal insufficiency	1	
Central hypothyroidism + diabetes insipidus	1	
Central hypothyroidism + hypogonadotropic hypogonadism	1	
Central hypothyroidism + growth hormone deficiency	1	
Adrenal insufficiency + diabetes insipidus	1	
Central Hypothyroidism	3	17.6
No detected endocrine disorder	3	17.6
Growth hormone deficiency	2	11.8
Diabetes insipidus	1	5.9
Hypogonadotropic hypogonadism	1	5.9

throughout adolescence. Delayed or missed diagnoses can lead to irreversible complications, increasing both morbidity and mortality risks.<sup>5,7,9</sup> Therefore, children with midline cerebral and intracranial malformations require thorough endocrine evaluation and long-term follow-up to monitor potential hormonal dysfunction.<sup>5,21</sup>

Not all congenital MBA are necessarily associated with hypopituitarism.<sup>5,6,22</sup> In our study, corpus callosum anomalies were identified in the three patients without any endocrine dysfunction. Corpus callosum abnormalities are among the most frequently detected MBA during routine prenatal ultrasonography and are associated with more than 200 syndromes.<sup>22,23</sup> However, their relationship with endocrine dysfunction remains unclear. While some cases remain asymptomatic, others present with neuromotor impairment, intellectual disability, seizures, and endocrine disorders.<sup>3,24</sup> Additionally, associated structural abnormalities, such as gyrus dysplasia and cortical heterotopia, may influence prognosis when combined with corpus callosum anomalies.<sup>25</sup> Endocrine dysfunction is particularly common in holoprosencephaly and SOD, as these conditions significantly impact hypothalamic and pituitary development.<sup>19,26</sup> In such cases, hormonal deficiencies are more likely to result from hypothalamic dysfunction rather than direct pituitary anomalies.<sup>21</sup>

The diagnostic utility of brain MRI for detecting endocrinopathies has been debated. Sensitivity and specificity have been reported as 67.9% and 83.3%, respectively, indicating that abnormal MRI findings alone may not reliably predict endocrine dysfunction, nor does a normal MRI exclude the possibility of hormonal

abnormalities.<sup>7</sup> Nonetheless, MRI remains a valuable tool for identifying structural lesions. Given the lack of standardized guidelines for the endocrinological management of patients with MBA, follow-up and treatment should be individualized.<sup>9</sup> Specific MRI abnormalities have been linked to an increased risk of early-onset hypopituitarism, emphasizing the need for lifelong endocrine monitoring in these patients.<sup>5,6</sup> Furthermore, the severity of MBA does not always correlate with the degree of endocrine dysfunction.<sup>5</sup>

The prevalence and distribution of endocrine disorders in children with neuroanatomical abnormalities vary widely. While growth hormone deficiency is frequently cited as the most common endocrinopathy in this population, followed by hypothyroidism, ACTH insufficiency, and diabetes insipidus,<sup>8,21</sup> our study identified central hypothyroidism as the most prevalent disorder (52.9%). Qian et al.<sup>7</sup> reported that ACTH insufficiency was the most frequently observed endocrine disorder in these cases. Previous research has indicated that patients with MPHD often present with GH and TSH deficiencies as the most common hormonal deficits.<sup>27</sup> Pituitary hypoplasia can cause endocrine deficiencies in the spectrum ranging from isolated GHD to panhypopituitarism in patients with SOD. The most common endocrine findings reported in patients with SOD are central hypothyroidism, GHD, and adrenal insufficiency.<sup>19,20,28</sup> In our study, patients with SOD exhibited a range of endocrine abnormalities, including hypothyroidism, GHD, and adrenal insufficiency. In holoprosencephaly, endocrine dysfunction—particularly adrenal insufficiency, diabetes insipidus, GHD, and hypogonadism—is frequently observed due to severe midline defects affecting hypothalamic and

pituitary development.<sup>26</sup> In our study, the patient with holoprosencephaly had both adrenal insufficiency and diabetes insipidus.

Additionally, hypothyroidism has been linked to developmental delay in patients with corpus callosum abnormalities.<sup>25</sup> In a study by Qian et al.,<sup>7</sup> 20.9% of children with developmental delay were diagnosed with hypothyroidism. Congenital central hypothyroidism, characterized by low thyroxine and inappropriately low or normal TSH levels, is often missed in neonatal screening programs that rely solely on TSH measurements. In countries where neonatal screening does not include direct T4 assessment, early detection and treatment may be delayed. Given the high prevalence of endocrine disorders in children with MBA, early diagnosis and timely intervention for central hypothyroidism are critical to minimizing neurological complications and improving long-term outcomes.<sup>29</sup>

A key limitation of this study is the small sample size, which may limit the generalizability of the findings. Additionally, the retrospective study design did not allow for long-term follow-up, restricting our ability to assess the progression of endocrinopathies over time. Future prospective studies with larger cohorts are needed to better characterize the natural history of endocrine dysfunction in children with MBA.

## CONCLUSION

Endocrine disorders were identified in 82.3% of children with MBA, with central hypothyroidism being the most frequently observed endocrinopathy. Given the high prevalence of hormonal dysfunction in this population, routine endocrine assessment should be conducted regardless of the presence or absence of clinical symptoms. Early diagnosis and appropriate management are essential to mitigating morbidity and preventing further neurological impairment. A multidisciplinary approach involving pediatric endocrinologists, neurologists, and radiologists is crucial for optimizing the care of these patients.

## Ethical approval

This study has been approved by the Ethics Committee of Istanbul University-Cerrahpaşa (approval date 26.04.2022, number 83045809-604.01.01-370476). Due to the retrospective nature of the study, informed consent was not required.

## Author contribution

The authors declare contribution to the paper as follows: Study conception and design: YÖ, OE; data collection: YÖ, BD, HT, DT, DAB, OE, SS, OE; analysis and interpretation of results: YÖ, OE; draft manuscript preparation: YÖ, OE. All authors reviewed the results and approved the final version of the article.

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## Conflict of interest

The authors declare that there is no conflict of interest.

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