



(REVIEW ARTICLE)



## Pituitary microadenoma in children and adolescents: Minireview of literature and symptomatic case series

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### Abstract

Pituitary microadenomas in children and adolescents represent a rare yet clinically significant entity, with a prevalence of up to 1 per million children and constituting only a small fraction of pediatric intracranial neoplasms. This minireview synthesizes current literature to provide an insightful overview of the epidemiology, clinical presentation, management, and outcomes of these tumors. Pituitary microadenomas are categorized as either functioning or nonfunctioning, with the former being less common in children than adults. Functioning microadenomas, such as prolactinomas, growth hormone-secreting adenomas, and ACTH-secreting adenomas, present with symptoms linked to hormonal overproduction, while nonfunctioning adenomas are often asymptomatic.

Clinical presentations vary with tumor type, with common symptoms including amenorrhea, galactorrhea, gynecomastia, and headaches. Diagnosis relies heavily on hormonal assessments and MRI, with stable courses often observed in non-functioning microadenomas. We report 6 cases which were presented with variable endocrine abnormalities. Management strategies are tailored based on the tumor's functionality and size. Medical therapy, primarily dopamine agonists, is preferred for functioning adenomas, while transsphenoidal surgery is reserved for symptomatic or non-responsive cases. Radiotherapy is considered as a third-line option.

Outcomes are generally favorable, with high response rates to medical therapy and successful surgical resections. However, recurrence and long-term hormonal imbalances pose challenges, necessitating vigilant long-term follow-up. Current research is oriented towards enhancing diagnostic accuracy, understanding genetic contributions, and optimizing treatment to minimize long-term developmental impacts. This review underscores the necessity for a nuanced approach in the diagnosis and management of pediatric pituitary microadenomas, highlighting the importance of ongoing research and follow-up for optimal patient care.

**Keywords:** Pituitary; Microadenoma; Children; Adolescents; Presentation; Diagnosis; Management.

### 1. Introduction

Pituitary tumors are rare in childhood and adolescence, with a reported prevalence of up to 1 per million children. Only 2 - 6% of surgically treated pituitary tumors occur in children. Although pituitary tumors in children are almost never malignant and hormonal secretion is uncommon, these tumors may result in significant morbidity. Pituitary microadenomas, while rare, present unique challenges due to their potential hormonal activity and growth within a critical developmental period. Those smaller than 10 mm were known as microadenoma and the rest as macroadenoma. (1-4)

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## *Objective*

This review synthesizes the current literature, incorporating statistical data, diagnostic criteria, and recent medical and surgical trials, to provide a comprehensive overview. As well we present 6 children/ adolescents with microadenoma who presented with hormonal derangement.

### **1.1. Existing Knowledge**

Pituitary microadenomas are rare in children, representing a small fraction of intracranial neoplasms with an incidence of about 1 per million. They are less common compared to adults, and only a small percentage are functioning microadenomas.

The manifestations in children can vary based on the type of microadenoma. Functioning adenomas present symptoms due to hormone overproduction like prolactinomas, growth hormone-secreting adenomas, and ACTH-secreting adenomas.

Nonfunctioning adenomas are usually asymptomatic and discovered incidentally. Diagnosis: Relies heavily on hormonal assessments and MRI. Nonfunctioning microadenomas generally show a stable course.

Treatment strategies depend on the tumor's functionality and size. Functioning adenomas are usually treated with medical therapy while surgery is reserved for symptomatic or non-responsive cases.

The outcomes are generally favorable with high response rates to medical therapy and successful surgical interventions. However, there are challenges like recurrence and long-term hormonal imbalances.

### **1.2. What does this study add?**

This case series analysis provides detailed insights from 6 cases of pediatric pituitary microadenomas, highlighting the variability in clinical presentation and hormonal abnormalities. This real-world data enriches the understanding of how these tumors manifest in children.

It offers specific information on the management strategies employed in these cases and the outcomes observed, which is crucial for guiding future treatment approaches.

The study underscores the necessity of vigilant long-term monitoring to manage potential recurrences and hormonal imbalances, which is crucial for patient care.

It highlights current research focused on improving diagnostic accuracy, understanding genetic contributions, and refining treatments to minimize long-term developmental impacts.

In summary, this mini review provides a comprehensive overview of pediatric pituitary microadenomas, combining existing literature with new findings from a case series. It emphasizes the importance of individualized management approaches, long-term follow-up, and ongoing research to optimize patient outcomes.

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## **2. Methods**

-Case series: we did a chart review for the cases who were presented to Pediatric Endocrine service at Hamad General Hospital in the last 3 years and found to have pediatric onset of microadenoma (younger than 14 years of age).

- Literature Search: We conducted a search of the medical literature using Pubmed, Google Scholar, and Scopus, focusing on research articles about pituitary microadenomas in children and adolescents. A total of 33 articles met our search criteria and were analyzed for this mini review.

The paper focusing on a case series and review of literature regarding pediatric pituitary microadenomas, the statistical analysis used would likely include the following:

### **2.1. Case Series Analysis**

Descriptive Statistics: The emphasis in our paper is on the detailed description of cases and qualitative synthesis of the review. These include:

Patient Demographics: Age, sex, and other relevant characteristics reported using means, medians, standard deviations, and ranges. Case Series data presentations are summarized in a table to succinctly present the data from the six cases, including clinical presentations, diagnostic findings, treatments, and outcomes.

## 2.2. Narrative Synthesis:

Summarization of findings from the reviewed literature, focusing on prevalence, clinical presentations, management strategies, and outcomes of pediatric pituitary microadenomas.

Integration of Literature Findings: Discussion section comparing and contrasting the case series findings with those reported in the literature, highlighting similarities, differences, and new insights gained.

In summary, this paper utilizes basic descriptive statistics to characterize the case series and a narrative, thematic approach to synthesize findings from the literature.

The ethical committee of the Research Center of Hamad Medical Center has approved the research proposal (Retrospective study) of the study (MRC-01-19-053). The study was conducted according to the ethical principles of the Declaration of Helsinki (1964) and its later amendments.

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## 3. Case series

Our case series includes 6 children with pituitary microadenoma who had variable presentation. (Table 1)

### 3.1. Case 1

S, a 12-year-old, presented for short stature. She was a term baby with a birth weight of 3.4 kg, with no abdominal symptoms, chronic illnesses, or medications. Initial Weight SDS (WtSDS) was -2.22, height SDS (HtSDS) was -2.6, and she had a slow GV of 4 cm/year. Midparental height SDS (MPHSDS) was -1.28. The examination showed a healthy adolescent, Tanner stage 3, with no dysmorphism. Investigations showed equal bone age, normal TFT, negative celiac screen, and IGF1 SDS of -1.81. GHST peaked at 5.2 mcg/L. MRI revealed a slightly smaller pituitary and a small right-sided lesion suggestive of a microadenoma. Treatment with somatropin started and continued until age 15, when HtSDS improved to -1.3 SDS (153 cm) with no significant change in microadenoma size (3.3 mm).

### 3.2. Case 2

I, a 12.4-year-old girl, presented at 9.5 years with headaches and fatigability. Her mother has been treated with hypothyroidism. The examination showed no dysmorphism, normal growth (HtSDS = -0.5, MPHSDS = 0), euthyroid, and Tanner stage 2. Workup indicated central hypothyroidism (low free T4 and normal TSH). MRI showed a globular pituitary with a hypo-enhancing lesion, suggestive of a microadenoma. Levothyroxine treatment resolved headaches and fatigability. Follow-up revealed growth deceleration (GV = 2.6 cm/year), an advanced bone age, and an IGF1 SDS of -1.28. Despite a GH peak of 6.7 mcg/L, growth hormone therapy was not pursued. Levothyroxine was briefly stopped but resumed due to persistently low FT4 and slow GV. The last assessment showed HtSDS of -1 at Tanner stage 5.

### 3.3. Case 3

J, at 7 years and 10 months old, presented with premature thelarche, associated with rapid growth and premature pubarche. No menarche or axillary hair was reported. Her GV was 12.2, HtSDS was +1.72, MPHSDS was -0.82, and BMISD was 0.6. Advanced bone age and elevated LH, FSH, and estradiol levels were noted. Pelvic ultrasound showed normal reproductive organ development, and MRI head revealed a lesion suggestive of a microadenoma. GnRH analogue therapy was initiated.

### 3.4. Case 4

M, a 12-year-old, had recurrent headaches accompanied by vomiting, dizziness, and blurred vision. She had a history of obesity and early menarche followed by secondary amenorrhea. Examination showed no dysmorphism and advanced bone age. MRI detected a hypointense pituitary lesion. Her labs showed high-normal morning ACTH and normal cortisol, with elevated IGF1 SDS and basal GH. She is planned for further endocrine evaluation and imaging.

**3.5. Case 5**

A 2.8-year-old girl presented with premature thelarche, with no pubic or axillary hair development but reported vaginal discharge. There was no previous height to document GV, but current HtSDS was 2.4 and BMISD was 0.44. Hormone tests showed high LH and FSH after stimulation, high estradiol, and IGF1 SDS. MRI suggested a microadenoma. She started on triptorelin and will be monitored.

**3.6. Case 6**

A 7-year-5-month-old girl showed signs of precocious puberty and had excessive body hair. Advanced bone age and a pituitary lesion on MRI were noted. Treatment with a GnRH analogue was started. Later reassessment showed abnormal growth and pubertal development, high IGF1, and increased GH, indicating GH hypersecretion.

In the six pediatric cases presented, the growth anomalies ranged from short stature with slow growth velocity (GV) to signs of precocious puberty with accelerated linear growth and advanced bone age. Endocrine anomalies varied, including growth hormone (GH) deficiency with subnormal GH peak levels in cases 1 and 2, central hypothyroidism in case 2, and central precocious puberty with elevated luteinizing hormone (LH), follicle-stimulating hormone (FSH), and estradiol levels in cases 3, 5, and 6. Additionally, case 4 showed high-normal adrenocorticotropic hormone (ACTH) and high insulin-like growth factor 1 standard deviation score (IGF1 SDS), while case 6 exhibited hypersecretion of GH and ACTH. Imaging findings across the cases commonly pointed to pituitary microadenomas with various degrees of pituitary gland abnormalities.

**Table 1** Main data for six children with pituitary microadenomas

| Case | Age at Presentation | Presenting Complaints                                       | Main Findings                                                                                       | Hormonal Abnormalities                          | Imaging Findings                                                   | Treatment/Follow-up                                                       |
|------|---------------------|-------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|-------------------------------------------------|--------------------------------------------------------------------|---------------------------------------------------------------------------|
| 1    | 12 years            | Short stature                                               | WtSDS=-2.22, HtSDS=-2.6, GV=4 cm/year, MPHSDS=-1.28, IGF1 SDS=-1.81, GH peak 5.2 mcg/L              | GH deficiency                                   | Slightly smaller pituitary, small right-sided lesion               | Started somatropin, no significant change in microadenoma size            |
| 2    | 12.4 years          | Headaches and fatigability                                  | HtSDS=-0.5, MPHSDS=0, GV=2.6 cm/year, IGF1 SDS=-1.28, GH peak 6.7 mcg/L, low FT4, advanced bone age | Central hypothyroidism, GH deficiency           | Globular pituitary with convex upper margin, hypo-enhancing lesion | Started on levothyroxine, slow GV, continued levothyroxine after stopping |
| 3    | 7 years 10 months   | Premature thelarche, accelerated growth, premature pubarche | GV=12.2 cm/year, HtSDS=+1.72, MPHSDS=-0.82, advanced bone age, high basal LH and FSH                | Central precocious puberty                      | Small, rounded hypo-enhanced lesion in left posterior aspect       | Started on GnRH analogue, will be reevaluated                             |
| 4    | 12 years            | Recurrent headaches, secondary amenorrhea                   | BMISDS=2.5, HtSDS=+0.8, GV=2.2 cm/year, high morning ACTH, normal cortisol, prolactin, LH and FSH   | ACTH hypersecretion, central precocious puberty | Well-demarcated hypointense lesion on T1 and T2W sequences         | Planned for GH suppression test, pelvic US, and salivary cortisol         |

|   |                  |                                                              |                                                                                           |                                                        |                                               |                                                                      |
|---|------------------|--------------------------------------------------------------|-------------------------------------------------------------------------------------------|--------------------------------------------------------|-----------------------------------------------|----------------------------------------------------------------------|
| 5 | 2.8 years        | Premature thelarche, family concern about accelerated growth | HtSDS=2.4, BMISD=0.44, high basal and stimulated LH and FSH, high estradiol, IGF1SDS=+3.1 | Central precocious puberty                             | Hypo-enhanced lesion in left posterior aspect | Started on triptorelin, will be followed for growth and MRI          |
| 6 | 7 years 5 months | Excessive body hair, symptoms of precocious puberty          | Advanced bone age, high IGF1, paradoxical increase in GH during suppression test          | Central precocious puberty, GH and ACTH hypersecretion | microadenoma                                  | Treatment with GnRH analogue, reassessment indicated abnormal growth |

## 4. Review

### 4.1. Prevalence

Pituitary adenomas represent approximately 3% of all intracranial neoplasms in children and 5% of pituitary adenomas in general. A study of pediatric pituitary adenomas over a 60-year period found that only a small percentage of these were microadenomas, indicating their rarity. (5)

The exact prevalence of pituitary microadenomas in children is not well-documented due to their often-asymptomatic nature. Functioning microadenomas, which secrete hormones, are less common in children compared to adults. Nonfunctioning microadenomas, which don't secrete hormones, tend to be discovered incidentally during imaging for other conditions. (6) In adults, microadenoma represents 41% to 58.7 % of the pituitary adenomas. (7)

Little is known about the genetic causes of sporadic lesions, which comprise the majority of pituitary tumors, but in children, more frequently than in adults, pituitary tumors may be a manifestation of genetic conditions such as multiple endocrine neoplasia type 1 (MEN 1), Carney complex, familial isolated pituitary adenoma (FIPA), and McCune-Albright syndrome. (8)

### 4.2. Clinical Presentations and manifestations

In a study of 20 microadenomas, 75% occurred in girls, with the average age at diagnosis being 14.4 years. Common symptoms included amenorrhea (53.3%) and galactorrhea (42.8%) in girls, and gynecomastia in all boys. (9,10) In 76 children with non-functioning microadenoma (median age 15 years), the most common presentation was headache (n = 16, 36%). No significant increase in the size of the microadenoma or worsening of pituitary function was seen over the average clinical follow-up of 4.5 ± 2.6 years. (11)

Presentation differs according to the pathological types which include:

- Prolactinomas: These are the most common type of functioning pituitary adenomas in children. They secrete prolactin, leading to symptoms such as galactorrhea, menstrual irregularities in girls, and delayed puberty.
- Growth Hormone-Secreting Adenomas: These lead to gigantism in children, characterized by excessive growth due to increased levels of growth hormone.
- ACTH-Secreting Adenomas: While rare in children, these can cause Cushing's disease, characterized by weight gain, growth failure, and other metabolic disturbances due to excess cortisol. (12,13)

A study showed that among 42 pituitary adenomas, 33% were macroadenomas, and 21% were microadenomas, with prolactin-secreting and ACTH-secreting adenomas being the most common. (12)

Nonfunctioning adenomas do not secrete hormones and can be asymptomatic, but they can potentially compress the surrounding areas of the anterior pituitary leading to hormonal deficiencies. (14,15)

The symptoms in children largely depend on the type of hormone secreted. For instance, prolactinomas can cause delayed puberty and menstrual irregularities, while growth hormone-secreting adenomas result in accelerated growth and gigantism. ACTH-secreting adenomas present with features of Cushing's syndrome, including obesity, hypertension,

and growth retardation. Diagnosis predominantly relies on hormonal assessments (table 1) and MRI. A significant study involving 74 children found that none of the non-functioning microadenomas increased significantly in size during follow-up, suggesting a stable course for these tumors. Accurate MRI measurements are crucial, as size discrepancies of more than 2mm were considered significant progression. (16,17)

**Table 2** Summary of management of children with pituitary microadenoma.

| Evaluation Aspect                       | Details                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Basal Measurements</b>               | Serum IGF1, cortisol (09:00 am), prolactin, FSH/LH, estradiol (females)/testosterone (males), TSH, and FT4                                                                                                                                                                                                                                                                                                                                                                            |
| <b>Check for hormone hypersecretion</b> | <ol style="list-style-type: none"> <li>1. If IGF1 is elevated, further evaluation for GH excess.</li> <li>2. Screening for glucocorticoid excess can be considered, regardless of clinical suspicion.</li> </ol>                                                                                                                                                                                                                                                                      |
| <b>Check for hypopituitarism</b>        | <ol style="list-style-type: none"> <li>1. Suspected GH deficiency: GH stimulation testing recommended.</li> <li>1. Insulin tolerance test/GHRH + arginine/glucagon tests for GH deficiency.</li> <li>2. Adrenal insufficiency (AI) indicated by basal cortisol &lt; 3 µg/dL, &gt; 15 µg/dL likely excludes AI.</li> <li>3. ACTH stimulation test/ITT/low dose ACTH test for central adrenal insufficiency. Peak cortisol &lt; 18.1 µg/dL at 30 or 60 minutes indicates AI.</li> </ol> |

Pathologic classifications can be done based on immunohistochemical analyses, electron microscopy findings, and the demonstration of various transcription factors and have been also recently introduced. (18)

In our case series, the presentation varied from single hormone abnormality to multiple endocrinopathies, but none was asymptomatic.

## 5. Management: (table 2)

The treatment approach is influenced by the tumor's functionality and size.

**Medical Management:** Medical treatment is typically preferred for functioning microadenomas, which secrete excess hormones. For instance, prolactinomas are often treated with dopamine agonists like cabergoline or bromocriptine, which can reduce tumor size and prolactin levels. The response rate to medical therapy in children is generally high, with many patients experiencing a reduction in tumor size and normalization of hormone levels. (19,20)

Surgical intervention, primarily transsphenoidal surgery, is indicated for symptomatic or functioning tumors unresponsive to medical therapy. Surgery is considered in cases where the microadenoma is causing significant symptoms, such as vision impairment or if it's not responsive to medical treatment. The most common surgical approach is transsphenoidal surgery, which involves accessing the tumor through the nasal cavity. This method is less invasive and typically has a quicker recovery time compared to traditional brain surgery.

After surgery, micro adenomas remission rate of 80.9% is significantly higher than 51.6% of macroadenoma. (21-24)

Radiotherapy and radiosurgery can be considered in refractory cases or when surgery and medical therapy are not effective. or in cases of tumor recurrence. Radiation therapy is considered a third-line therapy option because of the slow response (up to several years) and the development of new pituitary deficiencies. (25-27)

### 5.1. Outcomes

In our cases who were followed for more than 1 year, none developed any increment in the microadenoma size that required surgical intervention due to difficulty in management of symptoms.

In general, the prognosis for children with pituitary microadenomas is generally favorable.

In the case of medically managed prolactinomas, for example, a significant number of patients achieve normal prolactin levels and tumor shrinkage. For surgically treated cases, success rates vary depending on the type of tumor and the extent of its removal. Complete tumor resection often leads to good outcomes. Recurrence is a concern, particularly in functioning adenomas with a high proliferation index or local invasion. (7,28)

Long-term follow-up is vital to monitor for recurrence and manage hormonal imbalances. A study found that the recurrence rate of Cushing's disease due to ACTH secreting adenoma in children is about 40% over 10 years. Therefore, long-term follow-up is crucial in managing pediatric pituitary microadenomas, regardless of whether the initial treatment was medical or surgical. According to the Endocrine Society guidelines, all patients with radiologically diagnosed pituitary adenomas should undergo clinical and laboratory investigation to evaluate hypersecretion and hyposecretion. (29-32) Monitoring includes detecting the development of any new symptoms, measuring hormone level, and evaluating the growth of the tumor through regular MRI scans. (33)

Research Trends: Current research is focused on improving diagnostic methods, understanding the genetic underpinnings of these tumors, and refining treatment approaches to minimize long-term impacts on growth, development, and quality of life.

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## 6. Conclusion

Pediatric pituitary microadenomas, although rare, necessitate a nuanced approach for diagnosis and management. The integration of advanced diagnostic techniques and evolving treatment protocols has improved outcomes. However, due to the potential for recurrence and long-term endocrine effects, continued research, and vigilant long-term follow-up remain imperative for optimizing patient care and outcomes.

### *Limitations of the study*

In this study on pediatric pituitary microadenomas combining a case series and literature review, the key limitations include a small sample size limiting generalizability, lack of a control group hindering causal inference, potential biases due to its retrospective nature, heterogeneity and potential publication bias in the literature review, absence of long-term follow-up data, and subjectivity in case selection and analysis. These factors challenge the robustness and applicability of the findings across broader populations and clinical settings.

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## Compliance with ethical standards

### *Disclosure of conflict of interest*

Each author declares that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

### *Author contributions*

ATS and FA shared the conception/design and coordination of the review. NA, NH, and HA collected the data. All the Co-authors contributed to the interpretation of data, writing the manuscript, and provided critical comments and suggestions on the manuscript for important intellectual content. VDS performed a critical revision and editing of the manuscript. All authors read the final version of the manuscript and approved it.

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