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RESEARCH

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The pattern and clinical outcomes of non-diabetic pediatric endocrine disorders, Al-Baha, Saudi Arabia: a retrospective study

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Abstract

Purpose Pediatric endocrine disorders (PED) are a common component of medical health challenges in Saudi Arabia. We aimed to describe the pattern and clinical outcomes of different non-diabetic pediatric endocrine disorders in Al-Baha Region, Saudi Arabia, aiming for early diagnosis and management.

Methods The clinical and laboratory data of 744 children and adolescents who presented with non-diabetic endocrine disorders and received medical care at the pediatric endocrine clinic et al.-Baha during the period from 2018 to 2022 were retrospectively analyzed based on the records.

Results A total of 744 patients were recruited, 377 were females and 361 were males with a female/male ratio of 1.04/1. The patients' ages ranged from 2 months to 17 years, with a mean age of 9.87 ± 4.59 years. The commonest endocrine disorders were thyroid disorders 234 (31.5%), short stature 176 (23.7%), obesity 123 (16.5%), and calcium phosphate metabolism disorders 117 (15.7%). Other disorders seen were pubertal disorders 27 (3.6%), adrenal gland disorders 22 (3%), syndromes with endocrine features 14 (1.9%), sex development and gender disorders 6 (0.8%), pituitary and hypothalamic disorders 4 (0.5%), and mixed endocrine disorders 4 (0.5%). PED is a substantial source of morbidity in 26 cases and mortality in 2 cases.

Conclusions Thyroid, growth, and obesity disorders were the most common PED. Pediatric endocrine disorders have a substantial source of morbidity and mortality among Saudi children and adolescents. This baseline data is useful for planning PED care at institutional and national levels.

Keywords Pediatric, Endocrine disorders, Saudi Arabia, Al-Baha

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Background

Pediatric endocrine disorders (PED) represent a major health issue worldwide. They span a vast range of conditions including short stature, tall stature, thyroid disorders, puberty disorders, glucose, and lipid metabolism disorders, and others according to the International Classification of Pediatric Endocrine Diagnoses [1].

The field of PED is constantly advancing as a result of massive advances in methods of diagnosis over the last few decades, leading to various specializations within the field. Pediatric endocrinology specialists must be aware of the common conditions they will encounter [2, 3].

Type 1 diabetes is the commonest pediatric endocrine disorder encountered in pediatric endocrine clinics and is responsible for morbidities and mortalities among children and adolescents. In addition, non-diabetic PED is a substantial source of morbidity and mortality and most of them are treatable. In Saudi Arabia, care and proper treatment of children with PEDs have improved with the development of the pediatric endocrine sub-specialty and increasing awareness among the Saudi population [4, 5].

Worldwide, including Saudi Arabia sparse data is available on the prevalence of non-diabetic PED among children and adolescents and there is a lack of previous literature assessing and explaining the prevalence and clinical outcomes of non-diabetic PED among children and adolescents in different regions of Saudi Arabia [6].

To our knowledge, this is the first study that has analyzed the pattern and clinical outcomes of non-diabetic PED in Al-Baha, Saudi Arabia, over 5 years. Therefore, we aimed to evaluate the pattern and clinical outcomes of non-diabetic pediatric endocrine disorders in the pediatric endocrine clinic in Al-Baha Region, Saudi Arabia, to give baseline data, serve as a single source of knowledge concerning these conditions and raise awareness among pediatric endocrinologists in planning priorities for research and prevention.

Methods

Study design

Between April 2018 and April 2022, a retrospective single-center study was conducted in the Pediatric endocrine clinic at King Fahad Hospital, Al-Baha, Saudi Arabia. The pediatric endocrine clinic is the main pediatric endocrine clinic in the region. It receives referrals from all public and private Hospitals in the surrounding areas. Al-Baha Region is located in Saudi Arabia's southwestern region, with an area of 9921 km^2. The Saudi population aged 0 to 19 years residing Al-Baha Region of 132,712 (35.3%), with the age category 0 to 4 being the largest [7].

Patients

The data of all recruited cases were reviewed. Data were obtained from patients' records of the endocrinology clinic register. Diagnosis of the various endocrine disorders was from clinical features, relevant laboratory/radiological, and genetic studies. The genetic studies were referred to CENTOGENE-The Rare Disease Company, Germany (centogene.com). Diagnoses were further classified according to the International Classification of Pediatric Endocrine Diagnoses-ICPED [1]. Short stature is defined as height below − 2.0 SDS (2.3rd percentile) for a given age, sex, and population. Obesity is defined as a BMI at or above the 95th percentile for children and teens of the same age and sex using the Saudi growth chart.

Inclusion criteria

All Saudi children, and adolescents attending the endocrine clinic with suspected endocrine disorders.

Exclusion criteria

Missing files, incomplete data, diabetes mellitus without the associated endocrine disorder, none Saudi, and age above 18 years were excluded from the analysis.

Data collection

A predesigned questionnaire was used for data collection. It is composed of two main sections. "Background" section includes the socio-demographic characteristics of the participants (age, gender, and residency). The second section assessed the diagnosis, cause, and outcomes of the case.

Statistical analysis

SPSS version 21 for Windows (SPSS, Chicago, IL) was used to analyze the data. For quantitative variables mean with standard deviation (SD) was used and the number of cases (percentage) for categorical variables.

Results

During the study period, 744 Saudi individuals with different non-diabetic endocrine disorders were included in this study. Twenty-nine cases were excluded because they did not meet the inclusion criteria. There were 377 females (50.7%), 361 males (48.5%), and six (0.8%) cases that could not be gender-assigned at the time of present, with a female/male ratio of 1.04/1. The patients' ages ranged from 2 months to 17 years, with a mean age of 9.87 ± 4.59 years.

Pattern of PED

During the study period, the spectrum of the reported PED were thyroid disorders 234 (31.5%), short stature

176 (23.7%), obesity 123 (16.5%), calcium phosphate metabolism disorders 117 (15.7%), pubertal disorders 27 (3.6%), adrenal gland disorders 22 (3%), syndromes with endocrine features 14 (1.9%), sex development and gender disorders 6 (0.8%), pituitary and hypothalamic disorders 4 (0.5%), and mixed endocrine disorders 4 (0.5%) (Table 1).

Thyroid disorders

Thyroid disorders were the most frequent endocrine disorders in our region, accounting for 234 (31.5%) of all cases. Most of them were females (61%). The patients' ages ranged from 1 month to 16 years, with a mean age of 8.13 ± 3.19 years. Hypothyroidism cases accounted for 219 (29.4%) cases. The majority of hypothyroidism cases had congenital hypothyroidism in 156 (71.2%), Hashimoto's hypothyroidism in 32 (14.6%), followed by subclinical hypothyroidism in 18 (8.2%), non-Hashimoto's hypothyroidism in 11 (5%), and secondary hypothyroidism in 2 cases. Most of the hypothyroidism cases were detected by the national screening program (Table 1, Fig. 1A–C).

Hyperthyroidism cases were seen in 12 cases, 8 of them were Graves' disease and 4 cases of non-defined hyperthyroidism. In addition to 2 cases of euthyroid goiter and 1 case of papillary thyroid carcinoma. The case of papillary thyroid carcinoma was seen in a 9-year-old female

Table 1 Pattern of pediatric endocrine disorders in the studied population

Parameter	Endocrine disorder	Number (%)
Short stature		176 (23.7%)
Tall stature		2 (0.3%)
Puberty disorders		27 (3.6%)
	Precocious puberty	18
	Delayed puberty	6
	Premature thelarche	3
Sex development and gender disorders		6 (0.8%)
Obesity		123 (16.5%)
The pituitary gland and hypothalamus		4 (0.5%)
Thyroid gland		234 (31.5%)
	Hypothyroidism	219
	hyperthyroidism	12
	Goiter	2
	Thyroid tumors	1
Adrenal glands disorders		22 (3%)
	Adrenal insufficiency	18
	Cushing syndrome	2
	Premature adrenarche	2
Tests and male reproductive tracts		3 (0.4%)
Ovaries and female reproductive tracts		3 (0.4%)
Glucose and lipid metabolism		7 (0.9%)
Calcium and phosphate metabolism		117 (15.7%)
	Hypocalcemia	26
	Hypercalcemia	2
	Rickets	89
	Conditions associated with altered bone mass	0
Salt and water regulation		2 (0.3%)
Syndromes with endocrine features		14 (1.9%)
	Down syndrome	6
	Turner syndrome	3
	Dysmorphic syndromes	3
	Non-dysmorphic syndromes	2
Mixed endocrine disorders		4 (0.5%)

Data presented as numbers and percent

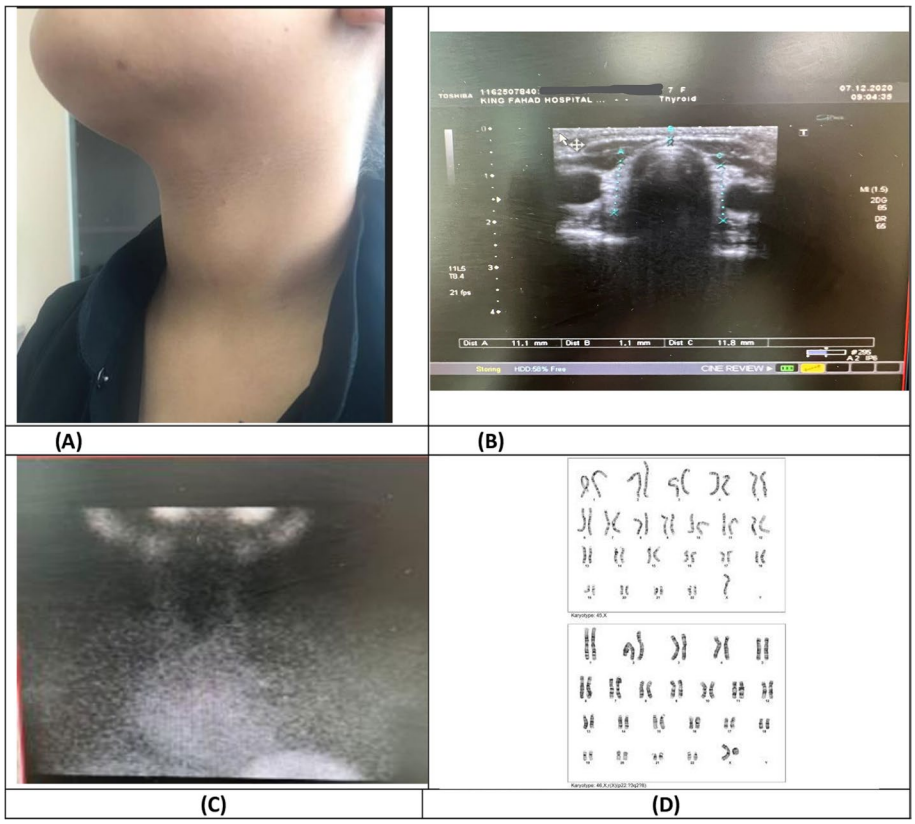

Fig. 1 A 9-year-old girl with goitrous hypothyroidism and the genetic study revealed autosomal recessive thyroid dyshormonogenesis type 3 (**A**); thyroid US showed small heterogenous thyroid gland in a 7-year-old female with hypothyroidism (**B**); the Tc pertechnetate thyroid scintigraphy showing no evidence of functioning thyroid tissue (**C**); Karyotyping of a 7-year-old female presented with short stature showing 45, X (**D**)

with goitrous hypothyroidism with a suspicious nodular lesion on thyroid ultrasound and a fine needle aspiration biopsy to confirm the diagnosis was done. Graves' disease and Hashimoto thyroiditis were associated with type 1 diabetes in seven and with Down syndrome in five cases. Follow-up of hypothyroidism cases revealed proper response to thyroxine therapy with normal intellectual and neurological development with no detected morbidity or mortality.

Short stature

Short stature was the second common endocrine issue in the current study accounting for 176 (23.7%) of all cases. Constitutional short stature is the most common cause accounting for 84 (47.7%), followed by familial short stature in 28 (15.9%), and growth hormone deficiency in 22 (12.5%) (Fig. 2). Most of them were males (79%). The patients' ages ranged from 5 to 16 years, with a mean age of 9.5 ± 4.3 years. There was one case of achondroplasia due to a defect in FGFR3 and one case of acromesomelic dysplasia due to the NPR2 defect. The burden of short stature is mainly physical and psychological.

Obesity

Obesity was reported in 123 (16.5%) cases, 103 of them had simple obesity (nutritional), 9 cases had hypothyroidism, and 4 cases had growth hormone deficiency (Fig. 3). Most of them (51.1%) were male, and the mean age was 9.4 ± 3.5 years. During the study period, 10 cases developed metabolic syndrome, 6 cases had elevated blood pressure or hypertension, 6 cases developed type 2 diabetes, and 2 cases had obstructive sleep apnea (Fig. 4A). All this would eventually lead to an increase in morbidity in children and adolescents.

Calcium and phosphate metabolism disorders

Calcium and phosphate metabolism disorders were reported in 117 (15.7%) of all cases. Rickets was present in 89 (12%) of all cases and nutritional deficiency was the main cause (59%). Hypocalcemia was reported in 26 cases, 6 of them with hypoparathyroidism and the rest with rickets. Thirty-seven (5%) of all cases had vitamin D deficiency, with four cases having vitamin D-dependent rickets type 2 with typical features of rickets and

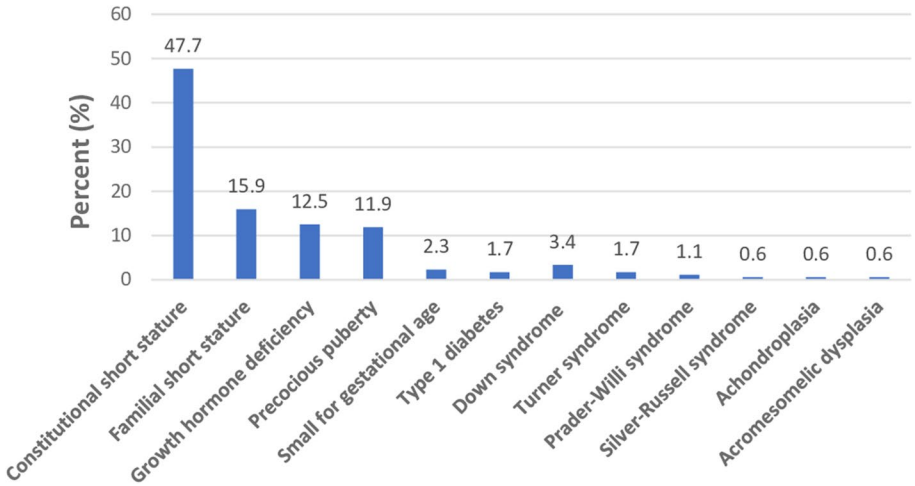

Fig. 2 Constitutional short stature is the most common cause of short stature among studied cases 47.7%, followed by familial short stature 15.9%, and growth hormone deficiency 12.5%

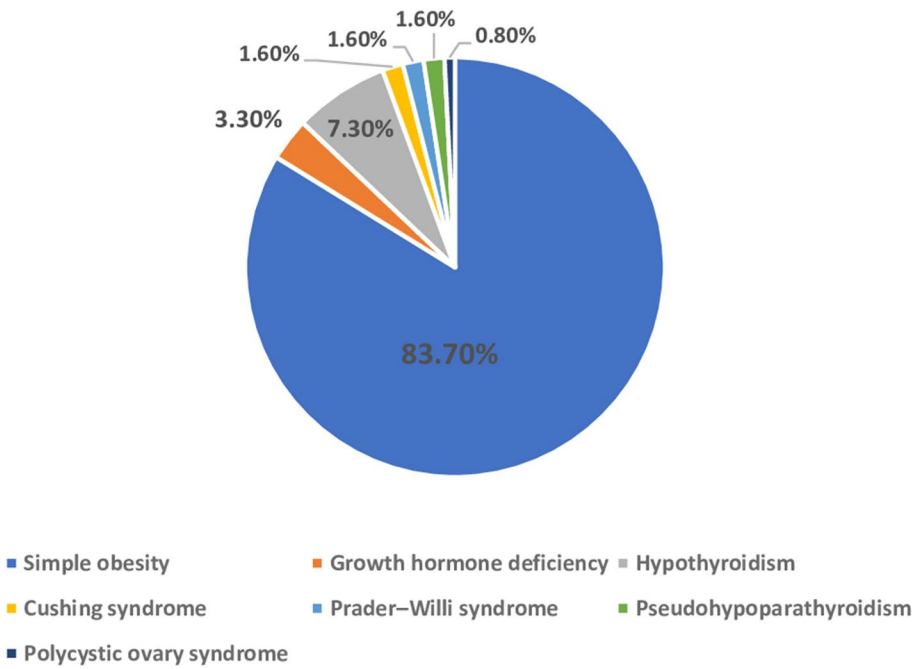

Fig. 3 Simple obesity is the most common cause of obesity (83.7%) among studied cases followed by hypothyroidism 7.3%), and growth hormone deficiency (3.3%)

alopecia with a positive family history (Fig. 4D). Parathyroid disorders were identified in 12 (1.6%) of all cases. Of them, 6 (50%) were hypoparathyroidism (4 cases Sanjad–Sakati syndrome, 1 case with autoimmune polyglandular syndrome, and 1 case isolated hypoparathyroidism), 4 cases had pseudohypoparathyroidism and 2 cases had hyperparathyroidism.

Puberty disorders

Puberty disorders were seen in 27 (3.6%) of all cases, precocious puberty was the most frequent pubertal condition, accounting for 18 (66.7%) cases of puberty disorders followed by delayed puberty 6 (22.2%) of puberty disorder cases, and premature thelarche in 3 cases. Idiopathic precocious puberty was the most common etiology in 14 cases, with two cases of central precocious puberty

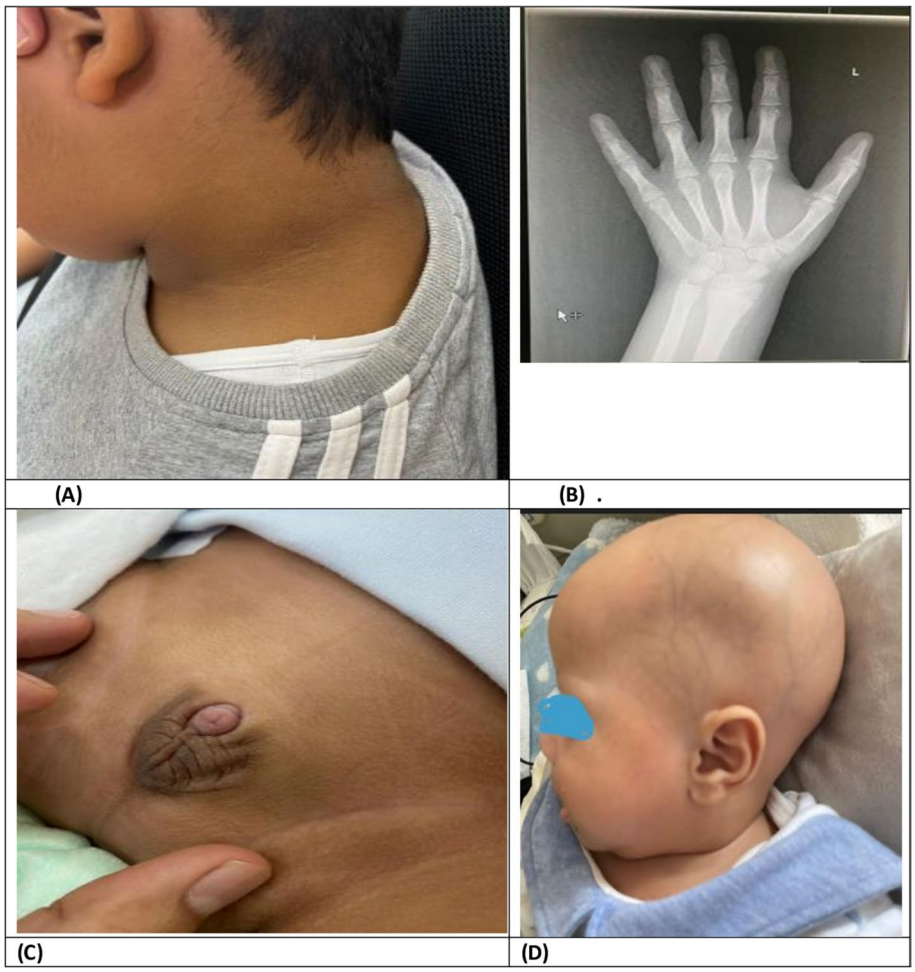

Fig. 4 A 9-year-old obese boy with acanthosis nigricans (**A**); X-ray hand of a 7-year-old female with precocious puberty showing advanced bone age (**B**); a 1-month patient presented with ambiguous genitalia showing closed labia that includes folds resemble a scrotum and enlarged clitoris which resemble a penis (**C**); a 3-month-old presented with hypocalcemia and alopecia diagnosed as type 2 vitamin D-dependent rickets (**D**)

and two cases of peripheral precocious puberty diagnosed as congenital adrenal hyperplasia (Fig. 4B). The majority of cases (65%) were female, and the mean age was 5.4 ± 2.3 years. There are 6 (22.2%) cases of delayed puberty, with two sisters having premature ovarian failure-10.

Adrenal gland disorders

A variety of adrenal disorders were implicated in 22 (3%) of all cases, with primary adrenal insufficiency being the most common in 18 (81.8%) cases, two cases having Cushing syndrome, and 2 cases having premature adrenarche. Among cases with primary adrenal insufficiency, congenital adrenal hyperplasia due to CYP21A2 gene mutation was the most common cause 13 (59.1%), with 3 cases having primary adrenal insufficiency as part of an autoimmune polyendocrine syndrome, two cases had familial glucocorticoid deficiency due to NNT gene mutation. The mean age was 3.4 ± 1.3 years with female predominance (63%). The burden of adrenal gland disorders includes one case of CAH presented with adrenal crisis, psychological impact from ambiguous genitalia, 2 cases of CAH developed obesity, and growth suppression with glucocorticoid therapy. In addition to one mortality among CAH patients. The 2 cases of Cushing syndrome have obesity, growth retardation, and hypertension.

Syndromes with endocrine features

Syndromes with endocrine features were observed in 14 (1.9%) of all cases. There were 6 cases of Down syndrome, 3 cases with Turner syndrome, 2 cases of Prader-Willi syndrome, one case of Silver-Russell syndrome and 2 cases of polycystic ovary syndrome. The burden of this syndrome includes one case of mortality among Down syndrome cases.

Glucose and lipid metabolism disorders

Problems of glucose and lipid metabolism were reported in 7 (0.9%) of all cases. hypoglycemia was a comm cause in 5 patients (Ketotic hypoglycemia in 3 patients, and nesidioblastosis in 2 cases). Two cases of familial hypercholesterolemia were reported.

Sex development and gender disorders

Disorders of sexual development and gender were diagnosed in 6 (0.8%) of all patients, and all of them were 21α-hydroxylase deficiency (Fig. 4C).

Pituitary and hypothalamic disorders

Pituitary disorders were reported in 4 (0.5%) of all cases, 2 cases with hypopituitarism, one case of central diabetes insipidus, and one case of prolactinoma.

Tall stature

Two female patients presented with tall stature and were diagnosed with congenital adrenal hyperplasia (peripheral precocious puberty) at the ages of 5 and 6 years.

Salt and water regulation disorders

Psychogenic polydipsia was reported in one case and nephrogenic diabetes mellitus was reported in one case.

Tests and male reproductive tracts

Two reported cases of micropenis and one case of hypospadias with undescended tests.

Ovaries and female reproductive tracts

Two reported cases of polycystic ovary syndrome. One case with Mullerian duct defect type 1.

Morbidity and mortality among studied patients

Pediatric endocrine disorders have a significant impact on public health because they may cause long-term disability. It has a social, psychological, and economic burden on the health system. In addition, in the current work, mortality was found in two (0.3%) cases (one congenital adrenal hyperplasia and one Down syndrome). The cause of death for Down syndrome is not specified in the patient file. PED is a substantial source of morbidity in 26 cases. Most of them were reported with obesity, adrenal gland disorders, glucose, and lipid disorders, and syndromes with endocrine manifestations.

Discussion

The prevalence of endocrine disorders varies between different countries of the world. It is likely due to the impact of genetic factors, environment, and the interaction between infection and malnutrition [8]. Improved knowledge about the pattern of PED might affect early diagnosis and management of these disorders that improve their outcomes. Worldwide, data on the prevalence of endocrine diseases in children and adolescents is limited. Therefore, we aimed to evaluate the pattern and clinical outcomes of non-diabetic endocrine disorders in children and adolescents in the pediatric endocrine clinic in Al-Baha Region, Saudi Arabia, to give baseline data and raise awareness among pediatric endocrinologists in planning priorities for research and prevention.

In Saudi Arabia, pediatric endocrinology is an established specialty; in this study, we enrolled 744 cases with various pediatric endocrine disorders during the study period and we found that the most frequent non-diabetic pediatric endocrine disorders in our locality were thyroid disorders (31.5%), short stature (23.7%), obesity (16.5%), and calcium phosphate metabolism disorders (15.7%). This result is in line with previous research [9].

In the current study, PED has been seen as slightly more common among females than males. This is similar to the pattern found in previous research [10] but differs from the pattern reported by Jarett et al. [11]. The increased number of girls in our study may be explained in part by the fact that thyroid diseases (the commonest cause in our study) are more common in females.

Pediatric thyroid disorders represent a major medical health problem worldwide. In the current study thyroid disorders were the most frequent pediatric endocrine disorders in our region, accounting for 31.5% of all cases with the majority being due to congenital hypothyroidism followed by Hashimoto thyroiditis. Hypothyroidism cases were detected by the screening program and all cases showed normal intellectual and neurological development without any morbidity with thyroxine replacement therapy. This contrasted with reports of rickets and metabolic disorders as the commonest pediatric endocrine disorder in previous research [10–12]. This disparity is most likely due to the increasing referral of cases of thyroid disorders by the efficient national newborn screening program launched by the Saudi Ministry of Health to detect and treat congenital hypothyroidism resulting in the diagnosis of more cases of hypothyroidism [13]. In addition, our center is the only referral pediatric endocrine center in the region. In line with our result, Yelluri et al. suggest that congenital hypothyroidism is more prevalent than acquired hypothyroidism. However, Al-Qahtani et al. in Saudi Arabia reported that Hashimoto's thyroiditis is more prevalent [14, 15].

In Saudi Arabia, children's and adolescents' growth and development have received increasing attention with socioeconomic development. The etiology of a child's short stature involves heredity, race, sex, nutrition, and a variety of endocrine hormones, which is very complex [16].

In this study, short stature was the second most common endocrine issue accounting for 23.7% of all cases. Constitutional short stature constituted a significant proportion of the diagnosis in this group (47.7%). Contradictory to our results El Mouzan et al. reported a lower prevalence rate [17]. Some environmental factors such as high altitude, a predominance of rural areas exceeding 60%, and a high prevalence of malnutrition that have been documented in the Southwestern regions, in addition to genetic factors, may account for at least part of the high prevalence of short stature in our region [18]. In addition, a higher rate of referral to our clinic because we are the only referral center in the region, increased attention in endocrine issues by a family physician, increased trust in our clinic, the presence of facilities for diagnosis, and increase awareness may be responsible for this high prevalence [19]. The higher frequency of short stature is not surprising because stature is a major developmental stage and a main cause for concern by parents and this may also suggest a possible new trend in pediatric endocrine disorders in our locality in Saudi Arabia. However, further research is required to identify the causes and then establish preventive strategies.

Currently, there is widespread public concern in Saudi Arabia about rising obesity rates among children and adolescents. It is projected that Saudi children who are currently overweight or obese will carry the burden of their excess weight into adulthood, making a compelling rationale for initiating and monitoring the effective implementation of obesity prevention programs [20, 21].

In the current work, obesity was seen in 16.5% of all cases, and simple obesity is the commonest cause. This result was in line with a previous report [12, 20]. These are likely to contribute to the rise in pediatric endocrine disorders in our environment particularly the emergence of type 2 diabetes and metabolic syndrome. Of our obesity cases, 10 cases have metabolic syndrome, 6 cases have either elevated blood pressure or hypertension, 6 cases have type 2 diabetes and two cases have obstructive sleep apnea. All these would eventually contribute to increased morbidity in children [22–24].

The high prevalence of obesity in our region may be related to genetic background, sustained economic development, and increased political stability, which has affected children's nutritional status, and this finding highlights the need for urgent intervention programs to improve the health choices of children and adolescents in terms of food and physical activities.

Calcium and phosphate metabolism disorders constitute 18.5% of pediatric endocrine cases. Vitamin D deficiency was found in 5% of cases. This was lower than previous reports [25, 26]. All the cases have been improved with calcium and vitamin D therapy with no reported morbidity. The lower prevalence rate of vitamin D deficiency may be due to most cases of vitamin D deficiency in our region being seen in General Pediatric clinics rather than endocrine pediatric clinics.

Puberty disorders are a common cause for referral to pediatric endocrine clinics. Pubertal disorders were reported in 3.6% of cases, and idiopathic precocious puberty was the most frequent pubertal disorder. This prevalence rate is not surprising because puberty is a major developmental stage [27] and a main cause for concern by parents when it occurs early or late and precocious puberty was related to overweight and obesity among our children [28].

Pediatric endocrine disorders have a significant impact on public health because they may cause long-term disability, social, psychological, and economic burdens [28]. In the current work, mortality was found in two (0.3%) cases (one congenital adrenal hyperplasia and one Down syndrome). PED is a substantial source of morbidity in 26 cases, most of them were reported with obesity, adrenal gland disorders, glucose, and lipid disorders, and syndromes with endocrine manifestations. This is in line with a previous report [29].

In summary, our study has reported higher numbers of pediatric endocrine disorders, thyroid disorders were the most common cause, along with growth, obesity, and calcium phosphate metabolism disorders. The burden of non-diabetic pediatric endocrine disorders varies among the different cases including mortality and morbidities, especially among cases with obesity. This baseline data is useful for planning PED care at institutional and national levels.

The limitation of this study was the retrospective design which can result in missing data in the patient records, hence, PED trends may be tied to the local system. Another potential restriction is a lack of generalizability in other countries and different regions in Saudi Arabia.

Conclusions

Thyroid disorders, growth disorders, calcium phosphate metabolism disorders, and obesity were the commonest PED cases in our study. Pediatric endocrine disorders have a substantial source of morbidity and mortality among Saudi children and adolescents. This baseline data is useful for planning PED care at institutional and national levels.

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Authors' contributions

AHA designed the work, drafted the work, and substantively revised it. AF designed the work; drafted the work, and substantively revised it. RA data

collection and revised the manuscript. FJ data collection and revised the manuscript. SA data collection and revised the manuscript. AA data collection and revised the manuscript. AKA data collection and revised the manuscript. ASA data collection, revised the manuscript, and data analysis. AAA data collection, revised the manuscript, and data analysis. All authors read and approved the final manuscript.

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Availability of data and materials
The data that support the findings of this study can be provided by the corresponding author upon reasonable request to protect study participants privacy.

Declarations

Ethics approval and consent to participate
The research proposal was approved by the Research Ethics Committee of Al-Baha College of Medicine (REC/PEA/BU-FM2022/28). The confidentiality of data was maintained throughout the study. Informed written consent was taken from the children's parents for participation and uses will be made for their images.

Consent for publication
Not applicable.

Competing of interests
The authors declare that they have no competing interests.

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