The Turkish Journal of Pediatrics 2024; 66(6): 703-712
https://doi.org/10.24953/turkjpediatr.2024.4565

Original Article

Impact of endocrine disorders associated with cleft lip and palate

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ABSTRACT

Background. Any impediment to the development of midline structures i.e. hypothalamus, pituitary and oral cavity may cause anatomical and functional issues. We aimed to determine the association of endocrine disorders with anatomic defects of midline structures i.e. cleft types and syndromes, as well as their impact on postoperative intensive care unit (ICU) admissions and complications.

Methods. A total of 6000 patients from the Cleft Lip and/or Palate (CLP) Treatment Center between September 2014 - February 2022 were included. Patients with physical findings or biochemistry that may indicate endocrine disorders were examined by the Division of Pediatric Endocrinology. Data concerning sex, operation age, cleft types, coexisting endocrine disorders, syndromes, echocardiography, postoperative complications as well as postoperative intensive care unit (ICU) admissions were recorded.

Results. The study group consisted of 78 patients with endocrine disorders, with a mean follow-up time of 59±7 months. One hundred and nine CLP operations were performed. The most common endocrine disorders coexisting in CLP patients were hypothyroidism (44.8%) and growth hormone (GH) deficiency (14.1%). Of the patients, 29.4% had genetic syndromes. The median age of operation in patients with endocrine disorders was 5 months (Q1-Q3: 4-8 months) for cleft lip and 15 months (Q1-Q3: 12-20 months) for cleft palate repair. Of the patients with CLP and endocrine disorders, 24% required postoperative ICU admission. Age of operation and ICU admission rates were higher compared to the general population of patients with CLP in our center ($p<0.01$).

Conclusions. Endocrine disorders, particularly hypothyroidism and GH deficiency, are frequent in CLP. Furthermore, our data suggest that endocrine disorders may complicate the postoperative course. Thus, investigation of these problems is crucial for appropriate treatment as well as adopting measures to successfully manage the postoperative course.

Key words: cleft lip, cleft palate, endocrine disorder, intensive care unit.

Cleft lip and/or palate (CLP) is the most common craniofacial anomaly in humans, with an estimated incidence of 1 in 700 live births, though this incidence may show geographical variation.[1,2] In embryonic life, there are close interactions between the hypothalamus, pituitary and the oral cavity. Any impediment to the development of these tissues may cause anatomical and functional problems. Facial clefts may indicate abnormalities in the pituitary and/or brain morphology and functions.[3,4]

In patients with CLP, intensive care unit (ICU) admission as well as postoperative

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Received 30th Mar 2024, revised 26th Jul 2024, 12th Sep 2024, accepted 3rd Nov 2024.

complications may lead to serious morbidities. Furthermore, they are a cause of financial and psychological burden to the patient and their families. Moreover, failure to investigate endocrine disorders that may be associated with midline defects i.e. CLP, may cause diagnostic delay of these disorders with complications in growth and development. In this study, we aim to investigate endocrine disorders that accompany CLP subtypes, and the association of these problems on the age of operation, postoperative need for ICU admission and complications.

Materials and Methods

Medical records of 6000 patients with CLP treated in the Plastic and Reconstructive Surgery Clinic of Hacettepe University, between September 2014 - February 2022 were reviewed following approval of the ethics committee (No: GO 22/416). Patients with genetically or clinically diagnosed syndromes like Down syndrome, DiGeorge syndrome, Kabuki syndrome, Goldenhaar syndrome etc., patients with a history of hypoglycemia, growth retardation, signs of cryptoorchidism/micropenis, patients with a second midline defect like holoprosencephaly, spina bifida etc. and/or any other malformation were analyzed by pediatric endocrinologists. All diagnostic investigations and imaging had been done in the respective departments prior to applying to our clinic for cleft repair, and if available, all patients were under treatment for their conditions.

Patients diagnosed with endocrinological disorders, who provided adequate demographic and perioperative retrospective data were included in the study. Patients with insufficient demographic information and less than 6 months of follow-up data, those who had surgeries other than primary CLP repair, who lacked a definitive endocrine disorder diagnosis, or those who do had an endocrine disorder diagnosis but had been operated on in other clinics were excluded from this study. Data from a total of 6,000 patients were examined. Of these patients, 266 had been consulted with pediatric endocrinology, and 100 patients were diagnosed with endocrinological disorders. Eight of these patients were not patients who underwent primary CLP repair at our center, but were patients who had undergone surgery for reasons such as revision or alveolar cleft surgery. Fourteen patients could not be included in the study because they did not have 6-month follow-up data at our center after diagnosis (it is assumed that they were followed up at centers in their own city/country). A total of 78 patients met the inclusion criteria. Of these patients, 72 had accompanying endocrinological anomalies, while 6 patients had metabolic disorders discovered during the endocrinology consultation: Type 1 diabetes mellitus (n=1), congenital adrenal hyperplasia (n=1), and genetic metabolic diseases (n=4). The flow chart of included and excluded patients is given in Fig. 1. All surgeries were performed by the same surgical team.

Data concerning sex, age of operation, cleft types, endocrine diseases, other anomalies and syndromes accompanying CLP, echocardiography findings such as atrial septal defect (ASD), ventricular septal defect (VSD), patent ductus arteriosus (PDA), patent foramen ovale (PFO) and other cardiac anomalies, postoperative complications and ICU admission were recorded. Following examination by a genetics specialist, those who were diagnosed with a syndrome were considered as syndrome-related patients with CLP.

Cleft types were classified into 3 groups: isolated cleft lip (uni- or bilateral), isolated cleft palate (Veau 1 cleft palate or Veau 2 cleft palate), cleft lip with cleft palate (Veau 3 cleft palate or Veau 4 cleft palate).

Endocrine evaluation was performed with a detailed physical and hormonal evaluation of disorders of midline endocrine structures. Hypothyrodism was defined as low serum free thyroxine level (<12 pmol/L). Hypothyroidism was classified as primary and central according

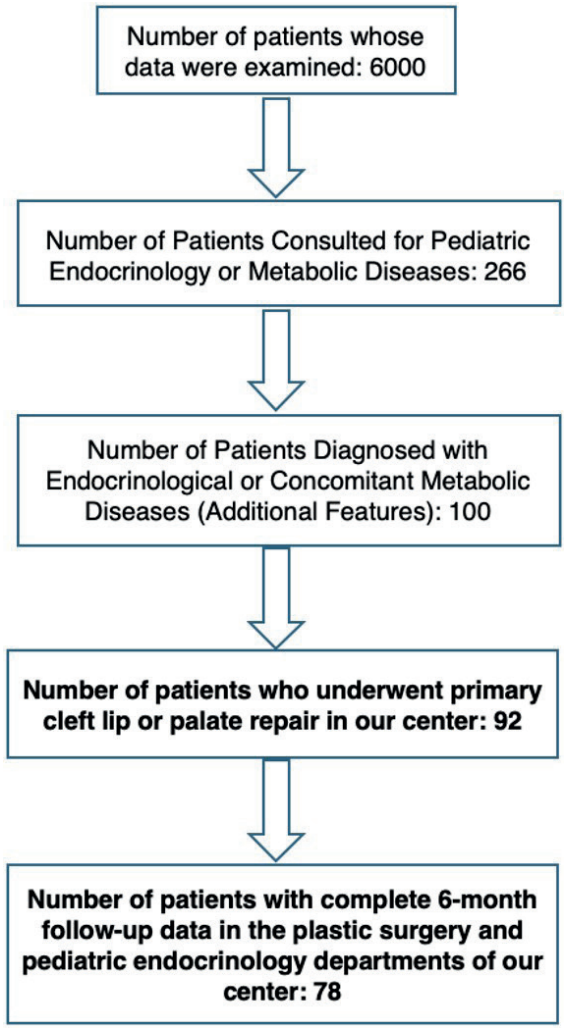

Fig. 1. Flow chart of included and excluded patients.

to TSH levels. A high TSH level accompanied by a low free thyroxine level was called primary, and a normal or low TSH level was called central hypothyroidism Some patients were on thyroid medication upon admission, and their initial pretreatment thyroid hormone levels were unknown, those were grouped into hypothyroidism, etiology unknown. Adrenocorticotropic hormone (ACTH) deficiency (secondary adrenal deficiency) was diagnosed by low morning serum cortisol (<3 μg/dL) associated with low/normal ACTH concentration or impaired peak cortisol (<19.8 μg/dL) during hypoglycemic episode or low-dose corticotropin stimulation test. Growth hormone (GH) deficiency was investigated if the patients' height was ≥2 SDS below the mean or when growth velocity was below the 25th percentile for age and sex. GH deficiency was diagnosed with low insulin-like growth factor 1 (IGF1) and insulin-like growth factor binding protein 3 (IGFBP3) and a peak GH less than 10 ng/mL in two GH stimulation tests (levodopa, clonidine). Patients with a height SDS below -2, but whose examinations for GH deficiency were not completed were defined as "short stature" only. Urinary output >2 L/m^2/day along with low urinary versus high plasma osmolality (urinary-to-plasma osmolality ratio <0.7), hypernatremia during fluid deprivation test, and elevation of urinary osmolality above 600 mOsm/kg in response to nasal 1-desamino-8-D-arginine vasopressin suggested central diabetes insipidus. Syndrome of inappropriate antidiuretic hormone secretion (SIADH) was diagnosed with clinical euvolemia without edema or dehydration and plasma osmolality <275 mOsm/kg, urinary osmolality >100 mOsm/kg and fractional sodium excretion (FENa) >1%. Male patients with micropenis and/or cryptoorchidism were grouped as patients with suspicious hypogonadism. Some patients were followed until puberty, and the data in their files were examined in terms of pubertal disorders. Delayed or absent pubertal development was defined as low serum sex steroid levels associated with inappropriately low or normal luteinizing hormone in girls older than 13 years and in boys older than 14 years.

Diagnosis of precocious puberty in girls was based on breast development (Tanner stage ≥ 2) before age 8 years and a peak LH level ≥5 IU/L during gonadotropin releasing hormone (GnRH) test. Biochemical data of the patients were also analyzed retrospectively. In the face of apparent hypocalcemia and hyperphosphatemia inappropriately low plasma parathyroid hormone (PTH) levels suggested hypoparathyroidism.

One patient presented with hyperglycemia and was diagnosed with type 1 diabetes mellitus based on International Society for Pediatric and Adolescent Diabetes (ISPAD) 2022 guidelines[5],

which was considered to be a coincidental development rather than association.

Data concerning postoperative ICU needs of patients were collected from medical files. Postoperative complications are listed as fistula formation in the repaired palate and dehiscence of the repaired lip.

Statistical analysis

For numeric variables, descriptive statistics such as mean, standard deviation, median were calculated. Normally distributed variables are presented as mean ± standard deviation and non-normally distributed variables are presented as median (interquartile range: Q1-Q3). In statistical analysis, patient-based situations were accepted as independent events and spread of numeric variables was evaluated with the Kolmogorov-Smirnov normality test.

Comparisons between two independent groups were made by Mann-Whitney U test because the assumptions of parametric tests were not met. The relationships between categorical variables and operation-based situations were analyzed with chi-square test. Comparisons of our results with a generally accepted known value were made with one-sample Wilcoxon signed rank test. All analyses were done using IBM SPSS version 23 (IBM, 2015). The statistical significance was considered to be $p<0.05$.

Results

A total of seventy-eight patients diagnosed with endocrine disorders (n=78) were included in this study, encompassing 109 surgical procedures for CLP. Among the patient cohort, 59% (n=46) were male, while 41% (n=32) were female. Of the 109 operations, 43.1% (n=47) were for cleft lip repair and 56.9% (n=62) were for cleft palate repair. The mean follow-up time was 59+/-7 months. The median age of surgery was 5 months (Q1-Q3: 4-8 months) in patients with cleft lip who had endocrine disorders. The median age of surgery was 15 months (Q1-Q3: 12-20 months) in those with cleft palate and endocrine disorders. In our clinic, the median age of surgery for the general population of patients with cleft lip is 3 months and for patients with cleft palate is 9 months (unpublished data). The age of surgery for both cleft lip and cleft palate patients with endocrine disorders were delayed significantly, compared to those who did not have an endocrine disorder ($p<0.01$). Out of these 78 patients, 7.3% (n= 6) had isolated cleft lip (uni- or bilateral), 29.4% (n= 23) isolated cleft palate (Veau 1 or Veau 2), 63.3% (n= 49) had both CLP (Veau 3 cleft palate or Veau 4 cleft palate). All endocrine abnormalities are listed in Table I. The most frequent endocrine disorder was hypothyroidism, in 44.8% (n=35) of the patients. Among these patients, 15 had central hypothyroidism and 5 had primary

Table I. Associated endocrinological and metabolic diseases (N=78).

Concomitant endocrinological and metabolic diseases	Number (%)
Hypothyroidism	35 (44.8%)
• Central hypothyroidism	15 (19.2%)
• Primary hypothyroidism	5 (6.4%)
• Etiology unknown	15 (19.2%)
Hypogonadism	4 (5.1%)
Suspicious hypogonadism	
• Micropenis	3 (3.8%)
• Cryptorchidism	14 (17.9%)
• Micropenis & cryptorchidism	2 (2.5%)
Growth hormone deficiency	11 (14.1%)
Diabetes insipidus	4 (5.1%)
Central adrenal insufficiency	5 (6.4%)
SIADH	1 (1.3%)
Short stature	6 (7.6%)
Multiple pituitary hormone deficiency	3 (3.8%)
Hypoparathyroidism	9 (11.5%)
Precocious puberty	4 (5.1%)
Type 1 diabetes mellitus*	1 (1.3%)
Congenital adrenal hyperplasia*	1 (1.3%)
Genetic metabolic diseases*	4 (5.1%)**

SIADH: Syndrome of inappropriate antidiuretic hormone secretion.
*Conditions appearing coincidentally in CLP patients
**mitochondrial disease, mucopolysaccharidosis, molybdenum cofactor deficiency, dihidrolipoamide dehydrogenase deficiency.

hypothyroidism; the etiology of hypothyroidism in the remaining 15 patients was unknown. A second endocrine disorder was present in 10/15 of the patients with central hypothyroidism. None of the 5 patients known to have primary hypothyroidism had any other accompanying endocrine disorders. Among patients with hypothyroidism whose etiology could not be determined 2/15 had a second endocrine disorder (1 cryptorchidism, 1 short stature). Of the patients in our series, %37.1 (n= 13) were detected through neonatal screening, and %6.9 (n= 22) of the patients, including patients with central hypothyroidism, were diagnosed as a result of advanced examinations performed by the pediatric endocrinology department at our center.

Of the patients, 5.1% (n= 4) had a diagnosis of hypogonadism. Nineteen patients had micropenis and/or cryptorchidism, however their files did not include the hormonal investigations required for a diagnosis of hypogonadism. The number of patients and their percentages in the study population are given in Table I. It was observed that endocrine anomalies were less prevalent in patients with isolated cleft lip (n= 6/1190, 0.5%), whereas in bilateral CLP patients (n= 21/997, %2.1) these anomalies were significantly more prevalent (p=0.0014). The accompanying endocrine abnormalities of syndromic patients are given in Table II.

Nineteen patients (24%) with clefts who had endocrine disorders required postoperative ICU admission. The rate of postoperative ICU admissions was 34% (n=2/6) in isolated cleft lip patients, and 43.5% (n=10/23) in isolated cleft palate patients. The rate of postoperative ICU admissions in cleft palate and lip patients was 14.5% (n=7/49). Postoperative ICU admission rates in patients with endocrine disorders were found to be significantly higher than in those without (p<0.01). In the case of cleft lip operations, postoperative ICU admission was

Table II. Distribution of accompanying endocrine disorders in syndromic and non-syndromic patients (N=78).

Accompanying endocrinological disorders	Syndromic patients (N=23), n (%)	Non- syndromic patients (N=55), n (%)	p-value
Hypothyroidism	6 (26.1%) - 2 with Down syndrome - 1 w/ Turner syndrome - 1 w/ Sathra-Chotzen syndrome - 1 w/ Emmanuel syndrome - 1 w/ 18q deletion	29 (52.7%)	0.03
Hypogonadism	7 (30.4%) - 1 with Down syndrome - 1 w/ Goldenhaar syndrome - 1 w/ Smith-Magenis syndrome - 1 w/ Opitz G/BBB syndrome - 1 w/ Patau syndrome - 1 w/ Carnevale syndrome - 1 w/ overgrowth syndrome	16 (29.1%)	0.90
Growth hormone deficiency	1 (4.3%) (Kabuki syndrome)	10 (18.2%)	0.16
Diabetes insipidus	1 (4.3%) (18q deletion)	0 (%0)	0.29
Central adrenal insufficiency	1 (4.3%) (Carnevale syndrome)	4 (7.3%)	1.00
Hypoparathyroidism	6 (26.1%) (DiGeorge syndrome)	3 (5.4%)	0.02
Precocious puberty	1 (4.3%) (Rubinstein-Taybi syndrome)	3 (5.4%)	1.00

Table III. Patients with endocrine diseases who are admitted to intensive care unit after cleft lip and cleft palate surgery.

Accompanying endocrinological disorders	ICU admissions after cleft lip surgery, number/total (%)	ICU admissions after cleft palate surgery, number/total (%)
Hypothyroidism	5/22 (23%)	7/24 (29%)
Hypogonadism	5/17 (29%)	5/17 (23%)
Diabetes insipidus	3/4 (75%)	0/1 (0%)
Central adrenal insufficiency	2/2 (100%)	3/3 (100%)
SIADH	1/1 (100%)	0/0 (0%)
GH deficiency	1/6 (16.7%)	2/9 (22.2%)
Hypoparathyroidism	0/2 (0%)	1/6 (16.7%)
Precocious puberty	1/2 (50%)	2/4 (50%)
Congenital adrenal hyperplasia	1/1 (100%)	0/0 (0%)

Note that a patient may have only cleft lip surgery, only cleft palate surgery, or both cleft lip and palate surgery.
GH, growth hormone; ICU, intensive care unit; SIADH, Syndrome of inappropriate antidiuretic hormone secretion.

significantly higher in patients with impaired water metabolism (diabetes insipidus, DI: n=4; SIADH: n=1) compared to other comorbidities ($p<0.05$). Of patients with DI, 75% (n=3) were admitted to the ICU after cleft lip surgery ($p=0.019$). Again, only the patient with SIADH required ICU admission after cleft lip surgery (100%). The rate of ICU admissions following cleft lip repair procedures in patients diagnosed with precocious puberty was 50% (n=1); it was 29% (n=5) for patients with hypogonadism, %16.7 (n=1) for patients with GH deficiency and %23 (n=5) for patients with hypothyroidism.

None of the patients with hypoparathyroidism had the need for postoperative ICU admission after cleft lip repair. Patients with adrenal insufficiency (central adrenal insufficiency n=5, primary adrenal insufficiency due to congenital adrenal hyperplasia n=1) also had significantly higher ICU admission rates following both cleft lip and cleft palate operations ($p<0.05$). Table III shows the patients who were admitted to ICU after CLP surgery with endocrine diseases mentioned in the results.

In addition to endocrine abnormalities, 53.9% (n=42) had variable cardiac anomalies while thirty-six patients (46.1%) had normal echocardiography findings (see Table IV). As postoperative complications, oronasal fistula formation was seen in 18% (n=13) of cleft palate patients, and dehiscence of the repaired lip was seen in 3% (n=2) of the patients in the current cohort.

Discussion

The most common congenital anomaly of the head and neck region is the CLP deformity. During the development of cranial features, there is a close interaction between the oral cavity and the pituitary gland. Diencephalon and oral ectoderm are in close relation, especially in the first two stages of development of the pituitary.[6,7] In a study performed on mice, it was shown that the anterior pituitary is dramatically affected in mice with orofacial clefts.[2] In the present study, a comprehensive endocrine evaluation was not conducted for

Table IV. Echocardiography findings of the patients.

Echocardiography finding	Number (%)
Normal	36 (46.1%)
ASD	10 (12.9%)
VSD	4 (5.1%)
PFO	7 (8.9%)
PDA	2 (2.5%)
Other cardiac anomalies	4 (5.1%)
Patients with more than one cardiac anomaly	16 (20.6%)

ASD, atrial septal defect; PDA, patent ductus arteriosus; PFO, patent foramen ovale; VSD, ventricular septal defect.

all patients; only those presenting with overt clinical symptoms underwent endocrine assessment. Among the total cohort, 78 out of 6000 patients (1.3%) were identified to have endocrine disorders associated with CLP. Some of these associations may be coincidental, such as cases with type 1 diabetes or primary adrenal insufficiency due to congenital adrenal hyperplasia, or genetic metabolic diseases. However, most are caused by common developmental pathological processes affecting midline structures. To the best of our knowledge, there is only one study with a very small number of participants investigating accompanying endocrine anomalies in neonatal patients with CLP, regardless of whether there was any symptoms or not. It was found that 70% (22/31) of CLP patients had some kind of hormonal disorder, 13 having a single endocrine abnormality, while 9 had multiple endocrine deficiencies.[2] Our study is valuable in its depiction of the prevalence of symptomatic endocrine disorders in CLP patients and the impact of those on the operation.

One of the most striking points among our findings is the low frequency of endocrine disorders in patients with isolated cleft lip (n=6, 0.5%), whereas in bilateral CLP patients (n=21, %2.1) these anomalies were significantly more prevalent (p=0.009). In accordance with our results, Rudman et al.[8] also found that bilateral CLP is the most commonly associated type with GH deficiency. These findings suggest that the association between CLP and hypothalamic-pituitary anomalies in the early stages of embryonic life should be further investigated.

In our clinic, the mean age of surgery is 3 months for cleft lip patients, and 9 months for cleft palate patients. In our study, it is evident that delaying the timing of surgical intervention for CLP patients with endocrine or genetic disorders may lead to early feeding difficulties and, subsequently, speech impairments later in life. In patients with endocrine disorders accompanying CLP, reaching the weight required for surgery may be delayed and there may be developmental delays. Additionally, delays in anesthesia administration due to abnormalities in blood laboratory values and developmental abnormalities can postpone surgical intervention. While it is essential for these patients to undergo surgery under optimal pediatric and anesthetic conditions, we believe that performing surgery beyond the routine timeline may adversely impact outcomes, such as speech development. A comprehensive study including speech parameters in these patients whose surgery time is delayed may also be beneficial.

In our practice, the postoperative ICU requirement rate for cleft surgery is overall 6.2%.[9] However, this rate was found to be 24% in our study group. This emphasizes the importance of the postoperative ICU in CLP patients with endocrine disorders and concomitant metabolic diseases. In our series, hypothyroidism was the most common endocrine disorder associated with CLP. Hypothyroidism, if not diagnosed and treated preoperatively, may danger the patient's life intra- or postoperatively leading to bradycardia and hypothermia.

Furthermore, in our study, an additional accompanying endocrine disorder was present in 12 of the 35 patients with hypothyroidism. The prevalence of congenital hypothyroidism in the general population and in Türkiye is 1 in 3000-4000 and 1 in 650 respectively. Previous studies show that hypothyroidism may be seen 18-24 times more frequently in patients with CLP.[10] In our series, the prevalence was 6/1000. Furthermore, national newborn screening with TSH levels is not able to detect all cases with central hypothyroidism[11], which was the most common type of hypothyroidism in our cases. Thus our findings suggest that it could be beneficial to consider examining CLP patients for hypothyroidism and other hormonal deficiencies prior to surgery in select cases, such as those who have suspicious physical examination findings like hypotonia, or even minor anomalies in biochemical blood tests, which may indicate a water or cortisol metabolism disorder, since they are not only common, but also easy to investigate and may

predict the presence of other more serious endocrine problems that may be life-threatening during the operation.

GH deficiency is the other common endocrine disorder in our series. There is no definitive incidence study on GH deficiency in Türkiye. Therefore, a comparison cannot be made with our series. According to the study by Feldt-Rasmussen and Klose[12], the general incidence of GH deficiency is thought to be 2-3:10,000. Other studies show that the prevalence of growth delay in the general population is 5-6%, while it is 21% in children with CLP.[13] The growth delay in these patients is thought to be associated with problems in feeding during the early infancy period. However, the close relationship between midline clefts and pituitary anomalies should also be considered as a preventable and easily treatable cause of growth delay in these infants. In a study by Rudman et al., the prevalence of GH deficiency was determined to be 40 times higher in patients with clefts.[8] Given that GH deficiency was identified by pediatric endocrinology in 11 out of the 6000 patients included in our study, we conclude that GH deficiency occurs 6 to 9 times more frequently in patients with CLP compared to the general population.

Considering the problems faced by short individuals in society, it is important to diagnose and treat GH deficiency, which is a common and treatable cause of short stature in patients with CLP. Early intervention with GH therapy can improve growth outcomes and mitigate the social prejudices associated with short stature. This would help improve psychosocial well-being of these children. We therefore recommend that children with craniofacial clefts who exhibit growth delay undergo further evaluation for GH deficiency through GH stimulation testing. Additionally, growth retardation should be recognized as an easily assessable parameter and a potential indicator of hypopituitarism. In our series, hypogonadism and findings suggestive of hypogonadism were common endocrine abnormalities accompanying CLP. The derangement in the hypothalamus – pituitary - gonad axis may lead to hypogonadotropic hypogonadism. Mini-puberty, or physiological puberty during early infancy, offers a good opportunity to objectively assess hypogonadotropic hypogonadism at a time when surgery plans for infants with CLP are typically being formed. Such evaluation is also easy, practical, and may be predictive of hypopituitarism, i.e. deficiency of other pituitary hormones. In our study population, retrospective research was conducted on patients who were diagnosed with pubertal anomalies, hypogonadism and growth retardation later in life, and it was discovered that all of these patients were admitted to the ICU at the time of their cleft operations. It may be speculated that the abnormal laboratory results caused by the hormone deficiencies and accompanying disorders and midline defects may have contributed to their admission to the ICU following anesthesia.

Another potential problem in cleft lip/palate patients is adrenal insufficiency, which, if untreated, could be fatal, especially under the stress of an operation. Poor adrenal reserve caused by secondary adrenal insufficiency may not be able to withstand the stress of surgery and may result in life-threatening intraoperative hypoglycemia and hypotension. According to our research, patients with secondary adrenal insufficiency were more likely than those without any underlying conditions or those with other hormone deficits to require postoperative ICU stay following both CLP repair procedures. For such patients, early diagnosis and treatment of adrenal insufficiency is crucial, as well as anticipatory planning for postoperative ICU conditions before the operation. Our study's key finding is that it is crucial to identify endocrine problems in infants with orofacial clefts since failure to do so could result in the demise of the patient. More extensive and prospective research is required on this topic.

Analysis of accompanying congenital anomalies in our patient population showed that 29.4% of the patients had clinically or genetically diagnosed syndromes. Our results are consistent with the study conducted by Vallino-Napoli et al. on 2022 CLP patients, which reported that one out of every 3 patients had accompanying anomalies.[14] These defects are prevalent enough in CLP patients to warrant a thorough investigation for associated syndromes and congenital malformations.

According to the literature, oronasal fistula formation occurs in 23% of patients within the general cleft population following repair procedures, while dehiscence of the repaired lip is observed in 0-7.5% of cases.[15,16] Our patient population also showed similar results: oronasal fistula formation was seen in 18% (n=13) of cleft palate patients, and while dehiscence of the repaired lip was seen in 3% (n=2) of the patients.

As for cardiac anomalies in our patient population, 42 patients (53.9%) had at least one cardiac anomaly. The most common isolated cardiac anomaly was ASD, seen in 12.9% of the patients. Of the patients, 5.1% had VSD only, 8.9% had PFO only, 2.5% had PDA only, while 20.6% of the patients had more than one type of cardiac anomaly. In a study by Çalış et al.[17] the rate of cardiac anomalies in the general cleft population was found to be 15.6%. Our findings may suggest that in CLP patients with endocrine disorders, the incidences of a cardiac anomaly or multiple cardiac anomalies are higher, therefore a preoperative screening with echocardiography may be beneficial in preventing possible postoperative complications.

The retrospective nature of the study, having a single-center patient population are the limitations of this study. It is also probable that since the institution is a major referral center of complicated pediatric cases, the rate of CLP patients with endocrine disorders are higher compared to other patient populations presented in the literature.

Conclusion

The two endocrine conditions most commonly seen in CLP patients are hypothyroidism and GH deficiency. Endocrine conditions, which also include ACTH deficiency, may delay the age at which lip and palate repair procedures are performed, and may increase the need for postoperative ICU admissions. Therefore, in select cases, especially when the patient presents with failure to thrive or with syndromic features, it could be beneficial and reasonable to screen the patients before surgery with simple blood tests such as the thyroid hormone, GH and ACTH levels, because identifying hypothyroidism or GH deficiency may help predict other significant endocrine diseases that are life-threatening if left untreated.

Ethical approval

This study was conducted following approval of the ethics committee of Hacettepe University. (No: GO 22/416).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: GÇ, EB, MÇ, FFÖ; analysis and interpretation of results: GÇ, EB, NE, MÇ, FFÖ, DCE, NG, AÖ; draft manuscript preparation: GÇ, NE, EB, AÖ. All authors reviewed the results and approved the final version of the manuscript.

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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