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Endocrine abnormalities of patients with cleft lip and/or cleft palate during the neonatal period

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Background/aim: There are close interactions among the developing oral cavity, pituitary gland, and central nervous system (CNS) in early embryonic life. In this study we aimed to screen endocrine abnormalities in patients with orofacial clefts in the neonatal period.

Materials and methods: Thirty-one patients with isolated orofacial median clefts were included in the study. Pituitary, thyroid, and adrenal hormones were measured at the first week and remeasured in the third or fourth weeks. Imaging studies were done for detection of CNS anomalies in all patients.

Results: Endocrine abnormality was detected in 22 (70.9%) patients. The number of patients with single and multiple endocrine abnormalities were 13 (41.9%) and 9 (29%), respectively. Thyroid hormone-related disorders were detected in 10 (32.3%) patients. Growth hormone deficiency was detected in 4 (12.9%) patients. Adrenocorticotrophic hormone and/or glucocorticoid deficiency was detected in 5 (16.1%) patients. Neonatal hypoglycemia due to endocrinological abnormalities was detected in 6 (19.4%) patients. Defected mini-puberty was seen in 2 (15.4%) patients. There was no relationship between the types of orofacial cleft and endocrine abnormalities.

Conclusion: Endocrinological evaluation of the patients with orofacial clefts in the neonatal period is a worthwhile endeavor to detect hormone deficiencies regardless of the type of the cleft.

Key words: Endocrine system diseases, cleft lip and palate, newborn

1. Introduction

Orofacial median clefts, including cleft lip (CL), cleft palate (CP), and both clefts (CLCP), are the most common birth defects of the human face (1,2) These anomalies may be isolated or occur as a part of some syndromes (1–3). The frequency of orofacial clefts is 1/500–550 live births in whites, but it varies in different geographical regions (3). In Turkey, the incidence of CP and/or CP is 0.95‰, and that of isolated CL is 0.77‰ (4). Risk factors for orofacial clefts are various. Genetic and epigenetic factors, maternal exposure to tobacco smoke and alcohol, poor nutrition, viral infections, medical drugs, environmental toxins, and teratogens in early pregnancy play roles in the emergence of the orofacial clefts (3).

There are very close interactions between the development of the hypothalamus, pituitary gland, and oral cavity in early embryonic life. Any impediment during development of these tissues may lead to the anatomical and functional disorders (5,6). Therefore, facial clefts can be a sign of abnormal pituitary gland and/or brain morphology and functions (7,8).

Generally, early studies have focused on the growth and anthropometric features of patients with CL/CP. There are also case reports of pituitary hormone deficiencies in children and adults who have isolated or syndromic orofacial median clefts (8,9). Only in a few studies were endocrine abnormalities associated with midline cerebral and/or facial anomalies investigated in pediatric patients (10–15). However, in these studies, the study population was derived from patients who were referred to an endocrinology unit and already had clinical findings of abnormal endocrine functions. Growth features of these patients are very unique, and while there are quite a few studies on growth in children with isolated CLCP, studies in individuals after childhood are rare (16–18). However, modern health care and appliances have greatly improved the feeding of infants with isolated CLCP (19,20).

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To date, there has been no scanning study about endocrine functions in neonates with orofacial median clefts. Therefore, in this study we aimed to investigate endocrine abnormalities and accompanying clinical signs and findings, specifically pituitary and thyroid functions, and ability of mini-puberty in newborns with orofacial clefts. Additionally, we aimed to detect relationships with central nervous system (CNS) findings including anomalies and pituitary gland dimension with endocrine abnormalities.

2. Materials and methods

In this cross-sectional study, 31 (77.5%) nonsyndromic and 9 (22.5%) syndromic patients with orofacial median clefts, for a total of 40 neonates, were followed at our neonatology unit. Syndromic patients with cleft(s) were not included in the final evaluation of the study because of the possible additional endocrinological and/or morphological disorders. Informed consent from all parents and ethics committee approval were obtained.

Hormone studies of the subjects were done at 2 different times in their first month of life. The timing of the initial hormone study was within the first week and the second was within the third or fourth week for the detection of the gonadotropin surge in mini-puberty. Data on pituitary hormones including growth hormone (GH), adrenocorticotrophic hormone (ACTH), gonadotropins [follicle-stimulating hormone (FSH) and luteinizing hormone (LH)], and prolactin (PRL) were collected. Levels of thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), and urine and breast milk iodine were also evaluated within the scope of the study. Elevated TSH levels due to decreased fT4 resulting from iodine deficiency was assumed as a single endocrine abnormality as well as decreased fT4 levels due to TSH deficiency (central hypothyroidism).

Hormone levels including fT3, fT4, TSH, PRL, FSH, and LH were determined with an automated immunoassay analyzer by the Siemens ADVIA Centaur XP Immunoassay System (Ireland). Growth hormone and ACTH levels were measured with the Immulite 2000 XPi Immunoassay System (Ireland). Iodine measurements in urine and breast milk were done by modification of the Sandell–Kolthoff reaction (21) as described by Dunn et al. (22).

Results of the thyroid function tests including fT3, fT4, and TSH levels were evaluated according to Kapelari et al. (23). Age-appropriate ranges for GH were evaluated for each week separately according to Kurtoğlu et al. (24). Determined FSH and LH levels by using immune-chemiluminometric assay were evaluated for each sex according to Schmidt and Schwarz (25). Deficiency of either one or both of the gonadotropins was evaluated as a single endocrine abnormality. ACTH levels were assessed spontaneously and/or together with serum cortisol levels during neonatal hypoglycemia. A level of blood sugar lower than 2.6 mmol/L (47 mg/dL) was defined as neonatal hypoglycemia in asymptomatic or symptomatic cases. GH levels were measured in hypoglycemic patients during hypoglycemia. Mini-puberty was defined as the surge of both gonadotropins since the end of the first postnatal week (26,27). Age-appropriate normal levels of PRL were evaluated according to Endocrine Sciences by Esoterix (28).

For those patients with abnormal thyroid hormone levels, thyroid ultrasonography (US) and/or scintigraphy by technetium-99m pertechnetate was performed. In patients with suspected iodine intake disorders (iodine deficiency or overload), urinary and maternal (breast milk) iodine levels were also measured. Breast milk (maternal) and urine (neonatal) iodine levels of less than 10 μg/dL (reference range: 10–20 μg/dL) were considered as low. Patients who had ACTH deficiency with/without glucocorticoid deficiency were examined by adrenal US for detection of surrenal gland size. Normal size of the surrenal gland was assumed as 15 × 3 mm (length × thickness) (29).

Patients with any (single or multiple) hormone deficiencies were scanned for CNS anomalies and hypophysis dimensions with magnetic resonance imaging. The criterion of pituitary hypoplasia was pituitary height below 3.5 ± 0.5 mm (30). The rest of the patients, who had no endocrine abnormality, were scanned by cranial US.

Abnormal physical examination findings, especially in males who exhibited the characteristics of undervirilization including cryptorchidism (unilateral/bilateral), bifid scrotum, and micropenis (indicative of congenital gonadotropin and GH deficiency), were recorded.

Patients who had abnormal thyroid function tests were treated according to the etiologic factors. Hypoglycemia resulting from endocrine abnormalities was treated with appropriate modalities. Patients who had elevated serum Na levels, urine volume, urinary density, and urinary Na levels were measured to make a diagnosis of central diabetes insipidus (DI). The patients with DI were treated by sublingual desmopressin acetate.

All patients were included in a multidisciplinary clinical follow-up program from the early infancy period, which consisted of orthodontia, plastic surgery, ear-nose-throat, and pediatric endocrinology units.

Statistical analysis was done with using SPSS 15.0 (SPSS Inc., Chicago, IL, USA). Nonparametric tests including the Kruskal–Wallis H test, the chi-square test, and Fischer's exact test were used for analysis.

3. Results

During the study period, a total of 40 newborns [20 females (50%), 20 males] with CL/CP were diagnosed. The number of patients (not included in the study) with syndromic CL/CP was 9. Diagnoses of these 9 patients were as follows: De Morsier (SOD), ectrodactyly–ectodermal dysplasia–cleft syndrome (EEC), Pierre-Robin sequence, Goldenhar syndrome, Tracher-Collins syndrome, partial trisomy of Cr10q, Fraccaro syndrome (49 XXXY), campomelic dysplasia, and CHARGE association. After the removal of the syndromic subjects, 31 nonsyndromic newborns [16 females (51.6%), 15 males (48.4%)] with orofacial median clefts were finally enrolled into the study.

Mean gestational age of the cases was 37.4 ± 3.6 weeks and mean birth weight was 2904.7 ± 291.3 g. Clinical features and types of orofacial median clefts of the patients and their associated genetic conditions are summarized in Table 1. Isolated complete/incomplete CL was detected in 5 (16.1%) patients, isolated complete/incomplete CP in 7 (22.6%) patients, and CLCP in 19 (61.3 %) patients.

The initial hormone analysis of the neonates was performed at 5.2 ± 2.6 days of life and the second evaluation was at the 18.4 ± 9.6 days. No endocrine abnormality was detected in 9 (29%) of the subjects with orofacial median clefts. Single endocrine deficiency was detected in 13 (41.9%) patients. The distribution of the multiple hormone deficiencies were as follows: 2 hormone deficiencies in 6 (19.3%) patients, and 3 or more hormone deficiencies in 3 (9.7%) patients.

3.1. Relationship between type of cleft and endocrine abnormalities

All patients with CL also had hormone deficiencies; 4 of 5 (80%) had multiple hormone deficiencies and the remaining 1 was diagnosed with DI. There was no endocrine abnormality in 4 (57.1%) of the patients with CP while 3 (42.9%) patients had single hormone deficiency. In the CLCP group, 4 (21.1%) patients had no endocrine abnormalities, 10 (52.6%) patients had a single deficiency, and 5 (26.3%) patients had multiple hormone deficiencies. There was no significant relationship between the form of orofacial median cleft and rate of hormone deficiencies. The characteristics of endocrine abnormalities in patients are summarized in Table 2.

3.2. Type of the endocrine abnormalities

A total of 10 (32.3%) patients had thyroid hormone- and TSH-related disorders. TSH and fT4 deficiency resulting in central hypothyroidism was detected in 5 (50.0%) patients. All of these also had multiple hormone deficiencies. Free T4 and/or fT3 deficiency and elevated TSH levels due to iodine deficiency was detected in 5 (16.1%) patients. GH deficiency was detected in 4 (12.9 %) patients and 3 of these 4 also had multiple hormone deficiencies. Deficiency of ACTH and/or cortisol was detected in 5 (16.1%) patients and all of them had multiple hormone deficiencies. Adrenal gland dimensions of these patients were within the normal range.

The deficiency of gonadotropin(s) was detected in 13 (41.9%) newborns (in 7 females and 6 males) during initial readings. Defect of ability of mini-puberty was detected in 2 (15.4%, 1 female and 1 male) patients. The female had both gonadotropin deficiencies, but the male had LH deficiency, and both of them had also multiple hormone deficiencies. One patient who had both gonadotropin deficiencies died before the second measurement. Prolactin deficiency was detected in 1 male (5%) newborn. He also had LH deficiency and had successful mini-puberty.

DI was detected in 1 (5%) patient as isolated. The patient with isolated DI was also diagnosed with semilobar holoprosencephaly.

3.3. Clinical findings of the patients

The number of neonates who underwent neonatal hypoglycemia (transient and prolonged) due to

Table 1. Clinical features and type of clefting of subjects.

			n (%)	Σ (%)
Birth weight (mean ± SD)	2904.7 ± 291.3 g			
Sex	Female		16 (51.6)	31 (100)
	Male		15 (48.4)	
Type of clefting	Cleft lip	Complete	2 (6.5)	5 (16.1)
		Incomplete	3 (9.7)	
	Cleft palate	Complete	4 (12.9)	7 (38.7)
		Incomplete	3 (9.7)	
	Cleft lip and palate		23(57.5)	19 (61.3)

Table 2. Endocrine abnormalities of the cases.

		Hormone(s)	n (%)	Case no.	Clinical findings in neonatal age (case no.)	Sex [female (F), male (M)]	Concomitant genital abnormalities in males (case no.)	Small pituitary (case no.)
Single endocrine abnormality		GH	1 (3.2)	35	ND (35)	M	ND (35)	ND
		ADH	1 (3.2)	2	DI (2)	F	-	ND
		fT4 (I_2)	4 (12.9)	10, 12, 22, 27	-	M, M, F, M	-	ND
		Gonadotropin(s)	7 (22.5)	6, 14, 16, 17, 21, 24, 31	-	F, F, F, F, F, M, M	Micropenis (24), ND (31)	ND
Multiple endocrine abnormalities	Two endocrine abnormalities	LH, PRL	1 (3.2)	4	-	M	ND (4)	ND
		Central hypothyroidism, gonadotropin(s)	2 (6.5)	1, 25	-	F, M	ND (25)	ND
		Central hypothyroidism, ACTH	2 (6.5)	5, 20	Transient hypoglycemia (5), prolonged hypoglycemia (20)	M, F	ND (5)	ND
		GH, ACTH	1 (3.2)	30	Prolonged hypoglycemia (30)	M	Micropenis (30)	ND
		GH, ACTH, LH	1 (3.2)	3#	Prolonged hypoglycemia (3)	M#	Micropenis	Yes
	Three or more endocrine abnormalities	Central hypothyroidism, ACTH, FSH, cortisol	1 (3.2)	23	Prolonged hypoglycemia	M	-	ND
		fT4 (I_2), GH, gonadotropins	1 (3.2)	13*	Transient hypoglycemia	F*	-	Yes

*: Female had not experienced mini-puberty , #: male had not experienced mini-puberty.

†: Patients had small-sized adrenal glands.

fT4: Free thyroxine, (I_2): iodine deficiency, fT4 (I_2): ft4 deficiency due to iodine deficiency, GH: growth hormone, FSH: follicle-stimulating hormone, LH: luteinizing hormone, ACTH: adrenocorticotropic hormone, TSH: thyroid-stimulating hormone, Central hypothyroidism: decreased fT4 levels due to TSH deficiency, PRL: prolactin, ADH: antidiuretic hormone, ND: not determined.

endocrinological abnormalities was 6 (19.4%). The ratio of transient and prolonged neonatal hypoglycemia was 2/4. Common endocrinological disorders of patients with prolonged neonatal hypoglycemia were GH and ACTH and/or cortisol deficiency. Characteristics of the patients who underwent hypoglycemia are summarized in Table 2.

Findings of undervirilization were detected in 3 (20%) males. Two of them also had GH deficiency and 1 of them both gonadotropin deficiencies. An undervirilized male neonate who had GH, ACTH, and LH deficiency also had a small pituitary gland and defected ability of mini-puberty.

3.4. Radiologic studies and associated endocrine abnormalities

Brain and/or pituitary magnetic resonance imaging was performed in 10 (32.3%) patients. The rest of the patients (n = 21, 67.7%) were scanned by US. The number of patients who had no CNS anomalies was 26 (83.9%). Neither cranial anomalies nor endocrine abnormalities were detected in 6 (19.4%) patients.

The number of patients with small pituitary glands was 2 (6.4%). Deficiencies of GH and gonadotropin(s) were the common endocrine abnormalities in those patients. Three detected brain anomalies (and accompanying endocrinological abnormalities) were as follows: semilobar holoprosencephaly (with DI), corpus callosum hypoplasia (with TSH-fT4, FSH, ACTH, and cortisol deficiency), and triventricular hydrocephalus with arachnoid cyst (without any endocrine abnormality). There was no statistical significance between the presence of CNS anomalies and endocrine abnormalities. The CNS anomalies and endocrine abnormalities of our patients are summarized in Table 3.

Table 3. CNS anomalies and associated hormone deficiencies of cases.

Anomalies (case no.)	n (%)	Hormone deficiency
Small pituitary gland (3 and 13)	2(6.4)	GH, ACTH, LH and GH, central hypothyroidism, LH-FSH
Semilobar holoprosencephaly (2)	1 (3.2)	ADH
Triventricular hydrocephalus (15)	1 (3.2)	ND
Hypoplasia of the corpus callosum (23)	1 (3.2)	Central hypothyroidism, ACTH, FSH

GH: Growth hormone, FSH: follicle-stimulating hormone, LH: luteinizing hormone, ACTH: adrenocorticotropic hormone, ADH: antidiuretic hormone, Central hypothyroidism: decreased fT4 levels due to TSH deficiency, ND: not determined.

Two patients (6.4%) died within the neonatal and early infancy period due to severe cardiac and CNS anomalies, and aspiration pneumonia.

4. Discussion

The present study has shown that newborns with orofacial clefts have various and important endocrine abnormalities, even if not symptomatic. All newborns with orofacial median clefts should be scanned for endocrine abnormalities regardless of the type of the cleft.

There are inevitable very close interactions between the oral cavity and pituitary gland during the development of these parts of cranium. The development of the pituitary gland consists of 4 distinct stages (31,32). The diencephalon and oral ectoderm are in very close interaction, especially during the first 2 stages of the pituitary development. The stage of developing the rudimentary Rathke's pouch is the most critical step in early pituitary organogenesis, because the oral ectoderm transforms to the anterior pituitary lobe and invaginated ventral diencephalon to form the posterior pituitary lobe making a band in between (32,33). Finally, the anterior and intermediate lobes of the pituitary gland derive from the oral ectodermal placode, while the posterior pituitary is derived from the neural ectoderm. A recent study in mice showed that anterior pituitary is indeed majorly affected in those with orofacial clefts (34). To act on this knowledge, the type and severity of orofacial clefts may be considered to be parallel to the accompanying pituitary defects. However, our results showed that there is no clear relationship between the number of hormone deficiencies and type of the orofacial median clefts. Therefore, we suggest that endocrine abnormalities should be investigated in all newborns with orofacial median clefts regardless of cleft severity.

There is a relationship between the hypothalamus and pituitary morphology as well as pituitary dimensions and pituitary hormone deficiencies, especially deficiency of GH (33). A recent study focused on comparing anthropometric features and pituitary gland volumes in individuals with and without CL and/or CP showed that males and females with clefts had shorter lengths than healthy ones but mean pituitary volumes for each sex were similar to those of healthy individuals (35). In our series, the patients with severe CNS anomalies including semilobar holoprosencephaly and corpus callosum hypoplasia had normal pituitary gland dimensions, but they had multiple endocrine deficiencies. Interestingly, a patient with triventricular hydrocephalus had no endocrine deficiency. In accordance with previous studies, our patients with small hypophyses showed multiple hormone deficiencies, and the common deficient hormone was GH. These results support the hypothesis that varying midline morphologic defects of the anterior hypothalamus could produce endocrine abnormalities as findings of the hypothalamic pituitary dysfunction.

Congenital hypothyroidism and orofacial clefts may be present as a part of some syndromes (36,37) or as a result of some mutations (38). Our study region, Central Anatolia, is an endemic area for iodine deficiency (39). In our series, the major reason for hypothyroidism was iodine deficiency. The commonness of iodine deficiency in patients with orofacial clefts could suggest an etiological relationship between iodine deficiency and cleft formation because deficiencies of the thyroid hormones and iodine disrupt the production of some factors acting in the intrauterine period (39,40).

Mini-puberty is defined as the initial activation of the hypothalamo–pituitary–gonadal axis during the first months of life. The rise of gonadotropins and sex steroids begins at the end of the first postnatal week, peaks at 3 months, and falls at 2 to 3 years in females and 6 to 9 months in males. In females, the increase in FSH is pronounced, while the LH increase is more prominent in males (26,27). Defected physiologic activity of the pituitary–gonadal axis may result in hypogonadotropic hypogonadism during early infancy. Determination of mini-puberty in at-risk infants, such as undervirilized males, those with congenital adrenal hypoplasia, and those with midline

CNS defects, is especially important for achieving healthy puberty (26,40,41). In light of these findings we suggest that ability of mini-puberty should be evaluated in patients with orofacial clefts as well as the above-mentioned at-risk ones.

Bell et al. reported that of 169 neonates who had neonatal hypoglycemia due to GH deficiency, over one-third had anatomical lesions either in the hypothalamic–pituitary area or midline facial defects, and over half of males had micropenis (42). In male infants, GH deficiency can present as micropenis as well as prolonged hypoglycemia and hyperbilirubinemia in the neonatal period. On the other hand, prolonged neonatal hypoglycemia and hyperbilirubinemia is also associated with ACTH and/or glucocorticoid deficiency as well hypothyroidism. In our series, all GH-deficient newborns underwent neonatal hypoglycemia or prolonged hypoglycemia. However, the common feature of our patients with prolonged hypoglycemia was multiple hormone deficiencies, such as thyroid hormones and ACTH-glucocorticoid.

Adrenal insufficiency may develop during surgical procedures or infections, and middle ear infections are often seen (43). In patients with orofacial median clefts who also have limited adrenal reserve, such as ACTH-cortisol deficiency and small-sized adrenal glands, reconstructive surgical operations of the orofacial median clefts may be life-threatening depending on the magnitude of the surgical procedure due to emerging hypoglycemia, hypotension, and cardiovascular collapse. The most important point of this study is that it revealed that recognition of endocrine abnormalities in patients with orofacial clefts in the neonatal period is vital since lack of diagnosis can even result in death in these patients.

In conclusion, orofacial clefts, which are the most common anomaly of the face, are an important and early sign of hypothalamo-pituitary hormone insufficiencies as well as morphologic defects of CNS. Endocrinological evaluation of these patients in the neonatal period makes it easy to detect hormone deficiencies prior to emerging late clinical findings. Based on the results of this study, we recommend that the cleft palate team or craniofacial team that conducts the follow-up and treatment of patients with orofacial median clefts should also address the pediatric endocrinological standpoint.

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