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Original Article

Growth hormone deficiency in cleft lip and palate patients

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Abstract

Introduction: Failure to thrive (FTT) is relatively common among cleft patients, most common attributed to feeding problems during the 1st month of life. The close association between midline clefts and pituitary gland abnormalities prompted us to determine the frequency of growth hormone deficiency (GHD) in cleft patients, which is a preventable cause of FTT and easily treated.

Methods: Any cleft patient with FTT was studied in a cross-sectional study and when the patient's height was under the 3rd percentile of normal, growth hormone was checked after clonidine administration. Growth hormone was checked before and 30, 60, and 90 minutes after clonidine use.

Results: Of 670 patients with cleft lip or palate, 31 patients (4.0%) had some kind of growth retardation according to weight, height, or head circumstance. 18 patients were under the 3rd percentile of normal height. GHD was detected in 8 patients out of 18 patients and overall frequency of GHD among cleft patients with growth retardation was 25.8% (8 out of 31). 7 patients of 8 were male, whereas one was female and half of the patients were syndromic.

Conclusion: Cleft patients have many problems with normal feeding, and all kind of support should be provided to achieve near-normal feeding and they should be monitored for normal growth. Any patient with growth retardation, especially height decrease, should be assessed for growth hormone deficiency.

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Introduction

One of the most common congenital anomalies in the head and neck region is oropharyngeal cleft. The incidence of cleft lip and palate has been reported to be 1 in 700 live births, which might be isolated or associated with other syndromes.[1,2] It seems incidence of cleft lip and palate is a little lower in our country as some authors estimated it from 0.8 to 1.03 in 1000 live birth.[3,4]

Approximately 250000 children with clefts are born all over the world annually, necessitating complicated and multiple surgeries and special care. Orofacial cleft is a multifactorial entity, with predisposing factors such as race, nutritional deficiencies, viral infections during pregnancy, heredity, environmental toxins, mother's contact with tobacco, use of alcohol, and some medications such as phenytoin and steroids.[2,5] Some problems associated with this condition include hearing problems,

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nutritional disturbances, speech and interpersonal relationship problems, facial disfigurement, psychosocial problems, and growth and development problems.[5]

Growth deficiencies in patients with oropharyngeal cleft are attributed to nutritional problems, recurrent infections of the respiratory tract and the middle care, endocrine diseases, hospitalizations and multiple surgeries, and psychosocial conditions. The majority of nutritional problems result from problems with sucking milk from the mother's breast due to the inability to create a negative pressure for sucking; therefore, a long-time is spent on nutrition and oral nutrition begins with a delay and is associated with some limitations due to the possibility of aspiration and obstruction of airways.[6,7]

Another important reason for growth deficiencies in these children during the 1st month of life is a lack of proper instructions for parents in relation to nutrition of such children. In general, the incidence rate of growth retardation in the general population is 5-6%; however, in children with cleft lip and palate it has been reported to be approximately 21%.[8]

One of the factors affecting growth is the growth hormone. Children deficient in growth hormone have normal height and weight at birth, but at 2-3 years of age present due to failure to thrive (FTT) and in the long term due to symptoms and signs such as a delay in maturation, hypoglycemia during fasting state and hypogenitalism.[9,10] In patients with cleft lip and palate, despite proper education on nutrition and proper treatment and healthcare and also several months after successful reparative surgery, still a sizeable proportion of these patients do not attain proper height and weight parameters.

A lot of efforts are underway to identify other factors involved in these conditions for proper treatment. One of these factors is growth hormone deficiency (GHD). The aim of the present study was to evaluate the prevalence of GHD in patients with cleft lip, and palate so that the deficiency can be identified and treatment can be instituted on time to prevent complications threatening these children.

Methods

The present cross-sectional study was carried out on patients with different kinds of orofacial clefts, referring to the Pediatric Hospital in Tabriz, Iran, from 2008 to 2012. The inclusion criteria consisted of all the children with growth disorders in the form of a decrease in head circumference, height and weight or weight and height below the 3rd percentile or children with slow growth rate or arrest of growth in the form of the interruption of two growth curves. Height, weight, and head circumference were accurately measured in all the children. Height, weight, and head circumference at birth were extracted from the delivery documents and the type of cleft lip and palate was extracted from the associated documents or from the patients' surgical files. It is important to note that GHD leads to short stature and other reasons should be sought for a decrease in weight and head circumference. Therefore, patients with conspicuously short stature were selected as follows for the study. The children's growth data were transferred on standard growth curves (National Center for Health Statistics) and the children's heights were calculated for the 50th and 3rd percentiles.

Children whose heights were below 2 standard deviation (SD) from the mean, by the other word, below the 3rd percentile of normal height, were selected. Growth hormone stimulation test was carried out using 5 mcg/kg of oral clonidine up to a maximum of 150 mcg/kg and the serum levels of growth hormone were evaluated using enzyme-linked immunosorbent assay (ELISA) at baseline and at 30, 60, and 90-minute intervals after administration of clonidine. If any of the four tests showed the GH level over 10 ng/ml, GHD was ruled out. However, if all the four tests showed GH levels below 10 ng/ml, GHD was confirmed and the child was considered a candidate for treatment with growth hormone.

Data were analyzed with SPSS software (version 17, SPSS Inc., Chicago, IL, USA),

using descriptive statistical techniques.

Results

In the present study, 670 patients with cleft lip and palate from 2008 to 2010 were evaluated. Of all these patients, 31 subjects (4%) had one of the growth defects of short stature, low weight, and low head circumference, with a mean age of 4.3 ± 1.33 years and an age range of 1.5-6 years. There were 22 (71%) and 9 (29%) male and female subjects, respectively. The most common type of cleft was cleft palate (32.3%).

Concomitant anomalies were observed in 8 patients (25.8%), which consisted of anomalies of the heart, central nervous system, urogenital system and musculocutaneous structures. In 16 patients (51.6%), the weight was correspondent with the 3rd percentile or lower and height in 15 patients (48.4%) was between the 3rd and 25th percentiles. The heights of 18 patients (58.1%) were correspondent with the 3rd percentile and lower, and the heights of 13 patients (41.9%) were between the 3rd and 25th percentiles. The head circumference of 20 patients (64.5%) was correspondent with the 3rd percentile and lower; in 2 patients (6.4%) it was between the 3rd and 25th percentiles; in 8 patients (25.8%) it was between the 25th and 50th percentiles; and in 2 patients (6.4%) it was between the 50th and 75th percentiles.

In 18 patients who were below the 3rd percentile in height serum levels of growth hormone were assessed. GHD was confirmed in 8 patients (44.4%). Of all the subjects with growth retardation, means 31 patients, 8 (25.8%) exhibited GHD, consisting of 7 males (87.5%), and 1 female (12.5%). Of 8 patients with GHD; 4 patients (50.0%) had bilateral cleft lip and palate; 2 patients (25.0%) had only cleft palate; one patient (12.5%) had complete unilateral cleft lip and palate; and one patient (12.5%) had partial bilateral cleft lip and palate. GHD was more prevalent in complete bilateral cleft lip and palate and solitary cleft palate compared to other types of clefts. Four patients (50.0%) were syndromic and 4 patients (50.0%) were non-syndromic.

Discussion

Cleft lip and palate is one of the etiologic agents for GHD. GHD might be manifested as growth deficiency. Congenital GHD might be associated with other genetic abnormalities, such as structural defects of the brain or mid-face.[9] The aim of the present study was to determine the frequency of GHD in cleft lip and palate patients with FTT, which was calculated as high as 25.8%.

Rudman et al.[11] reported a prevalence rate of 32% for GHD in cleft patients with short stature, which was higher than that in the present study. They reported 8 cases of GHD among 25 children with height below the 3rd percentile; 4 children of these 8 children (50%) had total deficiency. They did not provide any information about other etiologic factors for growth deficiency; in addition, no information was provided in relation to the therapeutic procedures for these children. In the present study, all the 31 children had received instructions and complete nutritional care from the early months of life and nutritional etiologies had been ruled out for their growth retardation. Rudman et al.[11] reported that the most frequent type of cleft type associated with GHD was bilateral cleft lip and palate consistent with the results of the present study.

Akin et al. reported a prevalence rate of 12.9% for GHD in newborns with cleft lip and palate, considering the fact that syndromic patients with cleft were not included in the statistics.[2] Akin et al.[2] screened all the newborns, irrespective of the absence of symptoms, for hypophyseal hormones and showed that 70% of cleft lip and palate patients had hormonal disorder; however, in the present study, only children over 1 year of age were evaluated, who were symptomatic despite therapeutic interventions. Given a high prevalence rate of nutritional disorders in these children during the first year of life, which give rise to growth deficiencies, if a decision is made to carry out growth hormone screening, it is advisable to carry it out at older ages. In addition, Akin et al. did not report the type of cleft(s) in cases

in which GHD had been confirmed, concluding that there was no relationship between the severity of cleft and its type, cerebral anomalies in radiographic examinations and hypophyseal hormone deficiencies, necessitating hormonal screening of all the subjects with clefts.[2]

In the present study, the prevalence of FTT was 4%, with a higher rate in males an in patients with cleft lip and palate; these results appear to be more correct compared to the results of a study by Pandya and Boorman,[8] who demonstrated no differences in the incidence of FTT between boys and girls because, in general, clefts are more common in boys compared to girls. They also showed that growth deficiency is more common in patients with cleft palate, consistent with the results of the present study, which might be attributed to more severe nutritional disorders and multiple and more delayed surgeries in these patients.

Pandya and Boorman[8] reported a 43% prevalence rate for growth deficiencies, which decreased to 21% after follow-ups, provision of instructions for parents and nutritional interventions. In their study, 30% of children with clefts had syndromic growth deficiencies. A mildly higher prevalence of FTT in the study by Pandya and Boorman might be attributed to the definition of growth, height and weight deficiency below the 5th percentile in that study. The higher prevalence rate of FTT in patients with bilateral and unilateral cleft lip and palate compared to its lower prevalence rate in patients with cleft lip might be attributed to nutritional deficiencies in these children, as shown and reported by Pandya and Boorman.[8] The higher prevalence rate of GHD in patients with clefts might be attributed to a higher prevalence rate of anomalies associated with cleft palate. On the other hand, a high proportion of patients with clefts have cleft palate. In the present study, GHD was higher in boys and in syndromic patients; however, in the study carried out by Rudman et al.[11] the male-to-female ratio was 1:1.

Zarate et al.[1] reported no differences in the incidence of FTT between cleft lip and cleft palate, which is not consistent with the results of the present study, in which the incidence of growth deficiency was higher in cleft palate compared to cleft lip. Zarate et al.[1] believed that nutritional disorders were the most important factors involved in growth deficiencies. However, in the subjects in the present study nutritional problems were solved by early initiation of half-solid food (at 4 months of age), by use of special bottle heads, by provision of instructions for parents and by availability of a pediatrician to supervise and monitor the course of growth as were advised by other authors.[12,13]

The overall prevalence of clefts is 1 in 700 live births; however, the prevalence of non-syndromic cleft palate is much lower and is more common in girls (1:2000).[14] The prevalence of cleft lip with or without non-syndromic cleft palate is more common in boys. In the present study, too, the prevalence of FTT and GHD was higher in boys with clefts.

Laron et al.[15] evaluated two patients with typical symptoms and signs of GHD, with height score of -3 and -4. The subjects had hypophyseal hormone deficiency. They concluded that it is advisable to evaluate hormone deficiencies in cleft patients with FTT.

Two studies have reported GHD in 1 of 1800 children and in 1 of 30000 children.[16,17] In the later study, organic etiologic agents was in 25% of the subjects and 15% of the subjects had malformations, one of the various types of cleft in the craniofacial region, resulting from poor development of the hypophysis, leading to GHD.[17]

Based on the results of the later study the prevalence of GHD is higher in patients with clefts compared to the general population. Therefore, screening for levels of growth hormone is important in children with FTT and craniofacial cleft. Early diagnosis and treatment will contribute a lot to attaining proper height and correcting the complications resulting from GHD in these children.

Conclusion

GHD is common in patients with cleft lip and

palate due to the relationship between fetal oral cavity and hypophysis. After exclusion of nutritional etiologic factors for growth retardation in children with clefts, it is possible to exclude one of the most important reasons for growth retardation by evaluating growth hormone levels in all the patients with different kinds of clefts, who have FTT. Therefore, it is suggested that all the newborn babies with clefts should be under the supervision of a pediatrician from birth in relation to growth parameters and nutritional instructions be provided. In the cases of FTT and height below the 3rd percentile, all the subjects should be screened for GHD.

Conflict of Interests

Authors have no conflict of interest.

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