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Review Article

CLEFT LIP AND PALATE: ETIOLOGY, DIAGNOSIS AND MANAGEMENT: A LITERATURE REVIEW

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ABSTRACT

Cleft lip and/or palate fall within the most common congenital abnormalities of the craniofacial region. There are a lot of phenotypes and clinical features of this malformation, which differ according to the different anatomical structures involved. The etiology is multifactorial, genetic and environmental conditioned, and not already known. To provide a correct diagnosis and treatment is necessary a multidisciplinary study and intervention, that is why is really important the presence of a clinical team to solve this pathology. The interaction between different clinical professional figures guarantee an adequate support for patients and their families. The surgical treatment is the most common treatment use for this pathology, together with the orthodontic treatment. However today the optimal treatment is difficult to find because of the large variability of this pathology and the subjective response of each patient to the therapy.

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INTRODUCTION

The most common congenital malformations occurring in the craniofacial region are Cleft lip and/or palate (CL/P). These pathologies have a worldwide incidence about 1/700 live births^(1, 2). Several studies, from the international literature, have shown that both genetics and environmental factors are involved in the etiology of these pathologies, even if it is one of the most studied and interesting subject of research yet.

CL/P does not fall within the most common cause of mortality in developed countries, but it is an abnormality closely linked and related with impact and burden both social and economic. Social integration, speaking, hearing and feeding could be only some of the problems caused by CL/P. Every problems, caused by CL/P, could be correct at varying degrees by surgery, dental treatment, speech therapy and psychosocial intervention. It is clear the necessity of a multidisciplinary team management of these patients, with a close contact and support for the families, in specific and dedicated specialist centers.

The pediatrician is the main figure with the primary and global approach task for children with CL/P in association with professional figures from: radiology, genetic counseling, audiology, maxillofacial surgery, dentistry, orthodontics, otolaryngology, psychology, social work and speech pathology.

Epidemiology

CL/P have a worldwide incidence of 1/700 live births⁽²⁾. The highest birth prevalence rate (1/500 live birth) is reported for the Asian and Amerindian population. An intermediate prevalence rates (about 1/1000 live birth) is reported in European populations, while the African populations have the lowest prevalence (1/2500 live birth)^(3,4,5).

Cleft palate could be the only one pathology affecting the subject, while cleft lip could be associated or not with cleft palate. About 70% of all the CL/P cases and 50% of cleft palate only fall within non-syndromic pathologies. All the other cases are linked to cardiac, limb, ophthalmological syndromes and other.

Role of genetics

CP and CL/P are influenced by the action and the modification of several and multiple genes. The environment can also be responsible of the alteration of the genes or interact with hereditary alterations that cause the pathology. The manifestation of the disease (syndromic and non-syndromic) have been linked to some defects of grow factors and their receptors⁽⁶⁾, such as FGF8 and FGFR1 genes. TGFb is another family gene involved in the formation of the oral cleft, in particular: TGFb3, with the inactivation of its receptor TGF3bR2⁽⁷⁾ and the inactivation of BMP7^(8, 9). Different authors demonstrated the involving of transcription factors in

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the pathogenesis of cleft lip and/or palate: mutation in MSX1^(10, 11), TBX22⁽¹²⁾ and IRF6⁽¹³⁾.

Anatomical features

The deficiency or the not-fusion between maxillary and medial nasal processes (36th/37th day of gestation) causes labiomaxillary clefts⁽¹⁴⁾. This can lead to different phenotypes and clinical showing of the malformation:

Cleft Lip (CL): this problem can affect only one (unilateral) or the two (bilateral) sides of the upper lip. It can be complete or incomplete. The complete form, tissue interruption extends between free border of upper lip and nose base with problems in skin, mucosa, bone and muscles entirety and asymmetry of nose⁽¹⁾. The incomplete form affects only the free border of the lip without involve the nose and the entirety of the surrounding tissues.

Cleft Lip and Palate (CLP): this form is characterized by a fissuration that concerns upper lip, maxillary bone, alveolar bone and hard/soft palate. There are two forms: the unilateral (UCLP) and the bilateral form (BCLP). The unilateral form is characterized by a fissuration of the alveolar bone between the lateral incisor and the canine directing to the nasopalatine duct; from here cleft is in the middle of hard and soft palate creating an oro-nasal communication due to the muscle activity of tongue on the palatal processes⁽¹⁾. The BCLP is characterized by the fissuration of the two sides meet incorrespondence of the nasopalatine duct going on palate always in the middle⁽¹⁾.

Cleft Palate (CP): this problem involves only the palate: cleft hard and soft palate or cleft soft palate only. Frequently, fissuration departs from nasopalatine duct up to soft palate. To understand this kind of alteration is extremely important to determine and understand the skeleton growth and the possibilities of intervention on the tissues involved and compromised by the pathology. Studies demonstrated how the UCLP and BCLP forms have a significantly greater tissues deficiency than the unilateral CL and CP⁽¹⁵⁾, so they could be considered as the most serious forms to face in the multidisciplinary rehabilitation.

Environmental factors

The environment can strictly influence the spread of this pathology. Maternal smoking in the early peri-conceptual period can cause the modification of certain genes, influencing metabolic pathways and the development of the pathology^(16, 17, 18, 19). High doses of maternal alcohol consumption in short period of time can increase the risk⁽²⁰⁾, and teratogens such as valproic acid can be associated with CP⁽²¹⁾. Even nutritional factors can influence the risk of CL/P, for example folate deficiency⁽²²⁾, but wider studies are required, in the future, to clarify this aspect and to evidence the real effects. Other environmental exposure such as infections, radiation, stress, obesity and hyperthermia can cause CL/P^(23, 24, 25).

Diagnosis

The diagnosis of CL/P can be made in different periods: antenatal and perinatal periods⁽¹⁾. It requires a multidisciplinary approach, because several specialists could be involved in the diagnosis. Using ultrasound scanning is now possible to diagnose CL in utero from about 17 week of gestation, even if false positive and missed defects have been reported. This

method can fail in caso of small CL/P, that is why orofacial clefts are often not discovered until birth. It is clear how the gynaecologist plays an important role for an early diagnosis^(26, 27). During the antenatal period, submucous clefts of palate may be present, but it is very difficult to diagnose early⁽²⁸⁾. The early diagnosis in antenatal period allows to steer parents to a multidisciplinary care team for an adequate counselling and help. If CL/P is diagnosed in antenatal periods it would be helpful to arrange for a neonatologist or a pediatrician to be available at the time of delivery to recognize possible respiratory difficulties or other congenital anomalies⁽¹⁾.

Pediatricians have the role to identify and confirm the anatomical defects and to determine the clinical form of the abnormality. In the perinatal period the oral cavity and the whole palate should be well examined. The use of a tongue depressor and palpation are useful methods to perceive submucosal alterations. The presence or absence of teeth, degree of hard and soft palate clefting, presence or absence of the uvula, evidence of pitting of the lips or palate, nasal regurgitation of fluids, a bifid uvula or a translucent central zone in palate are other important signs for the pediatrician⁽²⁹⁾.

Other physical anomalies are sometimes associated with CL/P such as velopharyngeal insufficiency (VPI); if the specific investigations used to reveal this pathology are positive, surgery is recommended. It is clear the importance of a careful examination of the infants in delivery room, to identify any airway or physical problems that can suggest an associated genetic disorder⁽³⁰⁾.

Treatment

The few days of life are the optimal time for the first evaluation of the child by CL/P team. The eventual treatment plan of care is formulated in a team meeting and communicated to the family of the child. Regular monitoring by the care team is recommended, to observe the growth and later ear, nose and throat, speech and developmental issues⁽³¹⁾. It is important to promptly advise the parents about the birth of a child with a congenital defect. Consultants or a pediatrician should help them and communicate the news as soon as possible. Ideally the parents should be put in touch with a member of the multidisciplinary care team within 24 hours of birth⁽³¹⁾. In the first period after the delivery, the most important problems that can be experienced are respiratory and feeding difficulties. Special instruction and assistance should be given to parents, and a lactation consultant or speech therapist should work with parents⁽²⁹⁾.

The fabrication of baby plates (presurgical orthopedics)⁽³²⁾ is claimed as a helpful system for feeding improvement and facilitation of CL/P repair. Now there is no evidence to support or discredit any of these claims and the practice remain empirical. Other ways to help child and parent with feeding problems are special bottles and teats, produced in a wide variety, attesting the persistent difficulties experienced by clinicians. Nasogastric feeding is not always required and it should be avoided if possible. Instead, a nasopharyngeal airway is required in case of obstruction and either severe respiratory difficulties due to the anatomical abnormalities. The optimal timing and approach for the surgical intervention varies depending by the center examined. Most of the British center repair lips 3 months after birth and palate between 6 and 12

months. The presurgical orthopedic techniques may be used. Molding devices are placed to help remodel the alveolar segments. These may be employed in conjunction with the skin redraping with nasal alveolar molding. Another diffuse method is the "functional repair" by Delaire⁽³³⁾. Lots of oral-maxillofacial surgeons advocate this method reach better outcomes for midface growth compared with techniques usually applied by plastic surgeons. Anyway, cross study in Europe demonstrated a poor result for the function method compared to the usual method performed by plastic surgeons.

An important part of the lip repair includes nasal recontouring and reconstruction of the sphincter of the lip. In addition, attempts are made to re-establish the nasal width if necessary⁽¹⁾. Repair of the cleft palate is usually performed after 9 months of age. In the past, surgery was performed around 4-6 years of age, but this was deleterious for the patient's speech development. It is recommended to perform surgery when the child begins to develop plosives "b, d and g" in speech (at about 11-12 months of age)⁽¹⁾. Surgical revision may be necessary, but they have to be performed after the complete healing has occurred and inflamed tissues have softened⁽³¹⁾. In preschool years the major problems are: speech and language development, ear nose and throat monitoring, somatic growth and development, and general dental welfare. In some patients, even after surgery, subsequent speech disorders can occur, requiring many interventions (about 75% of patients) throughout childhood and adolescence to achieve acceptable speech production and language competence^(31, 29, 34).

Factors that can cause speech disorders are: dental and occlusal problems, oronasal fistulas, hearing problems and velopharyngeal insufficiency. Children with cleft palate are subject to the same factors that influence the speech and language development in patients without clefts: neurological, cognitive, developmental, environmental, and emotional influences⁽³⁵⁾.

The therapy of speech and language disorders can be surgical or nonsurgical, using palatal training appliances, speech bulb, biofeedback speech treatment or an obturator. Normally the speech development occurs around 6 years of age, and this is the best moment to start speech therapy⁽³¹⁾ and to monitor speech development constantly with an orthodontic and surgical management⁽³⁶⁾. The orthodontic management of dental anomalies usually begins in the school age years, until adulthood. Initially, no active orthodontic treatment is required, but the orthodontist can be involved in the construction of a palatal obturator to help in feeding during infancy. The orthodontist is strictly involved in the therapy with the eruption of the primary and permanent dentition. In particular, if the cleft involves the alveolar process the teeth could be abnormal, malformed, supernumerary or absent. A regular attendance at the dentist and good oral hygiene is recommended. An active occlusal manipulation is to avoid until permanent dentition is established⁽²⁹⁾.

During the school years orthodontic management, alveolar bone grafting and psychological support are the main intervention in patients with CL/P. The alveolar bone grafting permits the creation of a normal alveolar architecture through which teeth can erupt and subsequently be moved orthodontically. During this procedure the surgeon can also repair and modify fistulas and the appearance of the nose.

In patients with multiple lip and palate operations the maxillary growth can be modified and resulting in a hypoplastic maxilla and fattened midface. The minor cases can be treated only with an orthodontic appliance, while the major and sever maxillary deficiencies are treated with Le Fort I advancement (the same technique for small and larger discrepancies). This kind of intervention is usually performed after the complete growth and develop of the face, to avoid a second intervention.

During the school age, the orthodontist has an important role. The definitive orthodontic treatment can proceed three or four years after bone grafting phase (around 12-13 years). Treatment of the early mixed dentition often includes maxillary partial braces and maxillary expansion. Often patients with CL/P develop a maxillary retrusion that can be treated with an anterior orthopaedic protraction. Expansion before bone grafting is better considered, and lead to best results in particular in severely constricted arches⁽³¹⁾.

In the school age, all the psychological problem and difficulties in social relations must be treated with a self-acceptance therapy and positive relationship with parents. During adolescence, the orthodontist can treat with orthodontic appliances all the remaining problems concerning teeth alignment. In this period can be also appear some disharmony not evident before. Some studies on adults shown that the early palatal surgery can be responsible for such growth problem of the face, but this treatment is necessary for an adequate speech develop during childhood⁽³⁷⁾. Nowadays the ideal timing for the first surgical treatment to reduce the risk of problems in the facial growth and to improve speech development in unknown.

CONCLUSIONS

Cleft lip and palate are birth defects that affect different structures and functions such as language, breathing, nutrition, esthetics, growth and development of the craniofacial district. The real etiology is still unknown, but environmental and genetic factors are involved in this pathology. There is not only one phenotypes or clinical picture concerning this pathology, and this is why is still so difficult to find a unique way to solve and treat this abnormality. The manifestation can be different and depending by the individual, and even the treatment can lead to different results depending by each subjects conditions, even in patients with the same malformation. Probably there are various techniques to obtain a good result. All surgeries can determine scar tissues that can be modify and inhibit the normal facial growth. The timing of the surgical intervention is dictated by functional and esthetics aspects, and also by the growth period. It is clear that a surgical intervention to reconstruct the abnormal structures is necessary to guarantee an adequate growth and function development. Best results are obtained with surgical and orthodontic treatment combined.

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