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CHARGE syndrome: an overview on dental and maxillofacial features

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Abstract. – OBJECTIVES: CHARGE is an acronym referring to the aspects of this rare syndromic condition. Patients with CHARGE association are today considered as subjects lacking in pathognomonic dental alterations. The present study is aimed at adding to the body of evidence of the cases reported in literature and the continuous clinical research which show a clinical picture which is strongly associated with patients afflicted by this syndrome.

PATIENTS AND METHODS: We report a case-series of 8 patients with CHARGE syndrome. The dental features associated with CHARGE syndrome are from case-reports, but without a congruity that can lead to a definition of the dental condition typical of the CHARGE phenotype.

CONCLUSIONS: The systemic problems affecting these patients are predominant in compromising their quality of life: this is the reason for a frequent lack of a diagnostics and interceptive phase, relative to oral diseases. We report new oral pathological conditions affecting CHARGE patients. Knowledge of these pathological conditions may induce dentists to carry out specific diagnoses of these patients, thus, avoiding the deterioration of oral conditions.

Key Words:
CHARGE Syndrome, Facial Nerve Palsy, Maxillofacial Pathologies, Syndromic dental alterations.

Introduction

CHARGE is an acronym referring to the features of this rare syndromic condition: (C) coloboma of the iris or retina; (H) heart defects or cardiac malformations; (A) atresia/stenosis of the choanae, with difficulty in breathing properly; (R) retardation of growth and development; (G) genital anomalies, generally in males, whose penis can be small and the testicles undescended; (E) ear abnormalities, both of the inner and external ear[1,2].

In a significant number of patients there is unilateral or bilateral facial palsy, which is often partial: approximately 40% of children with CHARGE association has a Bell's palsy (VII cranial nerve) and approximately 30% has swallowing problems (IX and X cranial nerve). In children with facial palsy, an auditory sensorial deficit is frequently reported (VIII cranial nerve)[3,4].

Choanal atresia or stenosis is one of the most suggestive and representative findings; atresia can be membranous or bony, monolateral or bilateral, and often occurs as a fetal malformation with severe neonatal complications, requiring an emergency surgical treatment[5].

Approximately 80% of children with CHARGE association were born with heart defects. Some are of slight importance, others require pharmacological therapies or surgical operations. Some heart defects of affected children can put their life at risk[6].

There is also the typical presence of a congenital anomaly, consisting in the cleft or defect of one of the structures of the eye. It can involve the absence (coloboma) of the inferior portion of the optic nerve head, and of choroid, ciliary body, iris, retina, crystalline lens and/or eyelids. Caused by an incomplete fusion of the fetal fissure during gestation, coloboma can be associated to other anomalies such as microphtalmia[7].

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Boys and girls with CHARGE association often require hormonal therapies to reach puberty[8]. It is also possible to find kidney abnormalities, urinary tract disorders and especially reflux problems. Some documented associations between nephropathies and tracheoesophageal fistulas suggested an overlapping with the *VATER/VACTERL* association: this overlapping is rarely associated with limb anomalies. There can also be an overlapping with Goldenhar syndrome[9].

Finally, children with CHARGE association can have other birth defects, such as malformations of the lips, tongue and palate, and low immunologic response.

The actual incidence of this syndrome remains unknown. In most cases it is sporadic, with a low risk of recurrence (~2%). In the rare familial cases, there is an autosomic dominant transmission of the disease, with a 50% potential risk of family transmission. The incidence of children with CHARGE association is approximately one case every 10/12.000 births. In the absence of a familiar history and mutations in the *CHD7* gene (70% of cases), it is impossible to give a prenatal diagnosis of the disease[10].

A multidisciplinary approach is of vital importance with respect to assessment, treatment and rehabilitation[11,12].

The cause of CHARGE syndrome remained unknown for a long time. However, many aspects supported the involvement of genetic factors, particularly phenotype concordance in monozygotic twins, the absence of environmental factors, a significantly high paternal age at conception, and the presence, in some cases, of chromosome abnormalities.

In 2004, thanks to the array-CGH approach, another potentially involved gene was identified in the q12 region of chromosome 8, namely *CHD7*[13] (Chromodomain Helicase Dna-Binding Protein 7).

The gene codes for a protein of 1967 aminoacids with functions of helicase, particularly present at the level of brain, kidneys and skeletal muscle. The pattern of fetal expression of *CHD7* gene is well correlated with the developmental anomalies peculiar to CHARGE syndrome[14].

Further studies confirmed the major role of *CHD7* mutations in causing CHARGE syndrome (69 patients out of 107), but excluded the presence of genotype-phenotype correlations[15].

A molecular study on 74 patients with CHARGE association, by means of the "real-time" PCR method, showed that there are no deletions of the *CHD7* gene in CHARGE patients. Mutations in the CHD7 gene were also present in 70% of the considered cases; they were "nonsense" and "missense" mutations, as well as splicing site and "frameshift" mutations[16,17].

Still today, in the literature there is no prenatal diagnosis of CHARGE association[10].

The dental features associated with CHARGE syndrome have been presumed on the basis of case-reports, but without sufficient congruity to allow a definition of the typical dental condition of the CHARGE phenotype. In our work we have analyzed the well-known dental and maxillofacial features usually associated to CHARGE phenotype; moreover, we have investigated about some orofacial clinical conditions likely caused by a CHARGE-related pathology. Our aim is to update the CHARGE associated orofacial anomalies.

Patients and Methods

We report a case series of 8 patients affected by CHARGE syndrome.

Our patients were all females, aged from 9 to 12 years old, recruited from 8 different private dental practice.

From the anamnesis we found some common features among all the patients (Table I), such as a bilateral choanal atresia already clinically evident at the birth , or as a congenital sensorineural hypoacusis caused by a deficiency of the eighth pair of cranial nerves, which is the reason for which all the studied patients use a cochlear implant.

8 patients have also suffered from ocular diseases, of various severity, all with neonatal onset. The clinical diagnosis of CHARGE syndrome was confirmed by means of a molecular analysis of mutations in the CHD7 gene: the mutations were occurred in 6 patients on 8.

To better investigate on the oral and maxillofacial features of these patients, we performed accurate odontostomatological and otolaryngologic examinations, followed by an analysis of the cephalometric data carried out by orthodontists and maxillofacial surgeons, so to take in consideration all the possible deviations from the physiological parameters.

Results

These patients showed a deficit in the ninth and tenth pair of cranial nerves: this condition has developed a lacked coordination of the soft palate,

Table I. Synoptic table describing the major features of the cases.

Patients	Coloboma	Heart diseases	Atresia choanae	Retarded growth	Genital hypoplasia anormalies	CHD7 gene mutation	Ear
1	X	X	X	X	n.e.	X	X
2	X	X	X	X	n.e.	X	X
3	X	X	X	X	n.e.	X	n.e.
4	X	n.e.	X	X	n.e.	X	X
5	X	X	X	X	n.e.	X	X
6	X	X	X	X	n.e.	X	X
7	X	X	X	X	n.e.	X	n.e.
8	X	X	X	n.e.	n.e.	X	X
Cases	8	7	8	7	n.e.	8	6

CHARGE related pathologies founded in our patients (Coloboma, Heart defect, Atresia choanae, Retarded growth and development, Genital hypoplasia, Ear anomalies/deafness) Legend. x: present; n.e. : not evaluable.

the rhino-pharynx and the epiglottis while swallowing and breathing, leading to frequent "*ab-ingestis*" pneumonia.

In 4 cases, we found patients with a sided palsy of the facial nerve (VII pair of cranial nerves): these patients were taking an amimic facies and a monolateral labial ptosis. This condition was associated with a short nose-labial filter and with a labial incompetence, however, the most impressive evidence was a slight facial asymmetry, only in these 4 patients (Table II).

The patients was affected with autistic traits and stereotyped movements, including a constant night bruxism in 2 of them.

The intraoral examination was rather difficult due to the poor relational capabilities of the large part of the involved subjects; however, we found that these patients were suffering from periodontal diseases, mainly caused by poor oral hygiene. Oral breathing was diagnosed in almost all subjects.

Discussion

CHARGE patients can have one or more congenital dental anomalies, such as taurodontism of the pulp chambers, hypodontia, ectopic eruption, submergence of primary molars, agenesis and supernumerary teeth[19].

Agenesis, malformations and ectopic eruptions of teeth of the frontal group lead to a wrong attitude in phonation, with a reduced tongue coordination[20,21].

As we have above reported, problems such as the uncorrected tongue motility can lead to a lacking in soft palate coordination. Breathing problems can be ascribed to the narrowing of the airway due to choanal atresia. Among the less frequent findings, cleft lip, cleft palate, micrognathia, ogival palate and facial palsy have been observed[22].

The low incidence of this syndrome has made it difficult to define a correct and comprehensive

Table II. Synoptic table describing the most interesting findings of the cases.

Patients	Deficit 7 CN	Deficit 9 CN	Deficit 10 CN	Facial Asimmetry	Bruxism	Parodontal Diseases	Oral Breathing
1	No	X	X	No	n.e.	n.e	n.e.
2	X	X	X	X	X	X	X
3	No	X	n.e.	No	n.e.	n.e.	No
4	No	X	X	No	n.e.	n.e.	No
5	X	X	X	X	n.e.	X	X
6	X	X	X	X	X	X	X
7	X	X	X	X	n.e.	X	n.e.
8	No	X	X	No	n.e.	n.e.	X
Cases	4	8	7	4	2	4	4

Legend. x: present; n.e. : not evaluable; No: absent; CN: Cranial Nerve

dental picture: we find altered phonation, breathing and swallowing due to the simultaneous presence of neurological and muscular alterations. In this case-series we also found periodontal pathologies slightly related to this syndromic condition: etiopathogenesis of periodontal diseases is activated by poor oral hygiene, due to the poor oral hygiene showed in these patients. Moreover, we think it could be a co-factor the traumatic stimulation of bruxism which gives a chronic trauma to periodontal structures. Additionally, the lack of coordination of many muscles of the stomatognatic system, associated with the frequent hypotonicity of monolateral mimic muscles caused by a sided paralysis of the facial nerve, and also associated with the mechanical action derived from bruxism, can lead to bad postural which may explain the slight facial asymmetry identified in 4 cases we have reported.

Conclusions

Patients with CHARGE association are today considered as patients lacking in pathognomonic dental alterations. The present study is aimed at adding to the body of evidence of cases reported in literature and continuous clinical research which show a clinical picture which is strongly associated with patients afflicted by this syndrome.

The systemic problems affecting this patients are predominant in compromising their quality of life so leading to neglect of dental concerns and intervention only in case of evident pathologies, missing the interceptive phase which is fundamental to reduce or avoid the risk of severe dental pathologies.

The collaboration between internists, dental surgeons, psychologists and geneticists should be the basis for an essential diagnostic and therapeutic approach that can guarantee the young patients with CHARGE association a more predictable prognosis for problems which will arise and so lead to a better quality of life.

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Consent Statement

Written informed consent was obtained from all the patients for this publication.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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