CASE REPORT

CHARGE syndrome – a rare cause of nose and ear anomalies. A case report

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ABSTRACT

CHARGE syndrome is an autosomal dominant or sporadic disorder, its genetic ethiology being given by the identification of CHD7. The most dominant features of this syndrome include: Coloboma, Heart defects, Atresia choanae, Retarded growth and development, Genital and/or urinary abnormalities, Ear anomalies and/or deafness. We present a 15-month-old patient with CHARGE syndrome with proeminent nose and ear anomalies, mild psychomotor retardation and motor and mental delay. Sequence analysis of the CHD7 gene (performed at Nijmegen Medical Centre, Holland) detected mutations of this gene, confirming the diagnosis of the syndrome. Our report emphases the importance of a very early diagnoses in order to start the proper management measures.

KEYWORDS: CHARGE syndrome, optic nerve coloboma, cochlear nerve agenesis, choanal hypoplasia

INTRODUCTION

The CHARGE syndrome (MIM 214800), described for the first time in 1979 by Hall and Hittner independently[1,2], is a rare genetic condition, with an incidence of approximately 1 in 10,000[3,4]. It can be inherited in an autosomal dominant manner or can be sporadic. Its name is an acronym summarizing the dominant features: **C**oloboma, **H**eart defects, **A**tresia choanae, **R**etarded growth and development, **G**enital and/or urinary abnormalities, **E**ar anomalies and/or deafness[5]. In 60-70% of patients with clinically diagnosed CHARGE syndrome, heterozygous *CHD7* (chromodomain helicase DNA-binding protein 7, MIM 608892) mutations have been identified[6-8].

Herein, we report a patient with CHARGE syndrome diagnosed on the basis of specific clinical features and confirmed by genetic testing.

CASE REPORT

We present the case of a 15-month-old girl, born from healthy, unrelated parents, after a normal pregnancy and birth, with a birth weight of 3000 g, birth length of 48 cm, occipitofrontal circumference of 32 cm, Apgar score 8, with good postnatal adaptation, but with feeding difficulties and failure to thrive during the first two months.

Subsequently, the child presented a slightly delayed psychomotor development. She held her head at 6 months, she sat at 8-9 months, she didn't walk alone and she babbled at 10 months. The clinical evaluation showed stature and ponderal hypotrophy - height 68 cm (<2 SD), weight 8 kg (<2 SD) -, occipitofrontal circumference 44 cm (Pc 10), frontal and occipital hemangiomas and dysmorphic facial features (broad forehead; malformed, asymmetric ears, with the right ear smaller than the left one, left preauricular tag; asymmetric palpebral fissures, with the right fissure smaller than the left one; hypertelorism; bilateral optic nerve coloboma; right choanal hypoplasia; prominent nasal bridge and columella, flat midface and micrognathia) (Figure 1a, b). Also, she presented bilateral square hand, short fingers, hockey-stick palmar crease (Figure 2a, b) and right facial palsy and hypotonia. A mild psychomotor retardation with a motor and mental age of 10 months were associated. Cerebral MRI showed bilateral cochlear nerve agenesis, right facial nerve hypoplasia and cerebral hypotrophy.

Our patient presented three major diagnostic characteristics of CHARGE syndrome - ocular coloboma, choanal atresia or stenosis, cranial nerve dysfunction or anomaly, characteristic CHARGE syndrome ear, associ-

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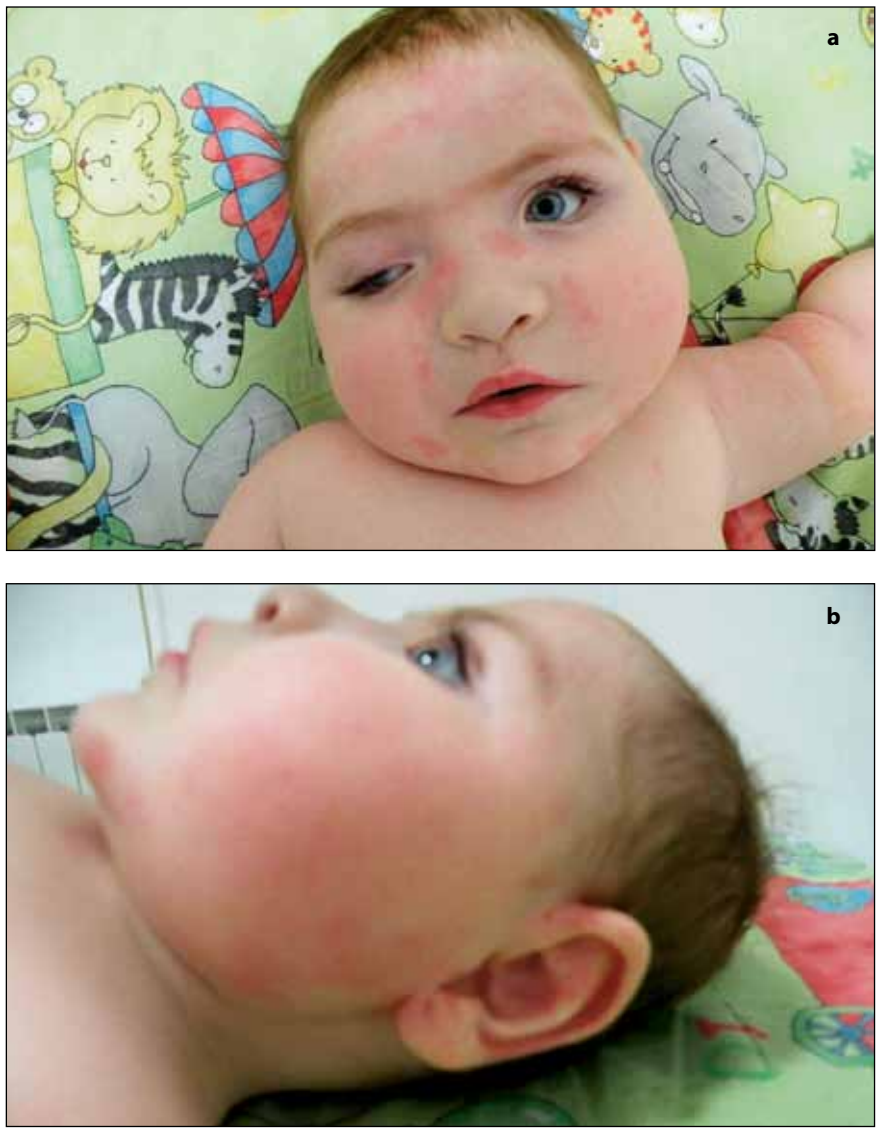

Figure 1 a. Frontal view of the patient's face showing dysmorphic features; b. lateral view of the patient showing left ear with preauricular tag.

ated with three minor characteristics (developmental delay, growth delay, distinctive facial features).

Sequence analysis of the *CHD7* gene (performed at Nijmegen Medical Centre, Holland) detected mutations of this gene, confirming the diagnosis of CHARGE syndrome.

The management of this case included physical therapy and cognitive stimulation. ENT, regular ophthalmologic and neurological evaluations were recommended.

DISCUSSIONS

It is very important for a child with CHARGE syndrome to be diagnosed very early in order to start the proper management measures. Diagnosis of CHARGE syndrome is based on a combination of major and minor characteristics. The major diagnostic characteristics are[5]: ocular coloboma, choanal atresia or stenosis, cranial nerve dysfunction or anomaly (hypo-/anosmia, facial palsy, hypoplasia of auditory nerve, swallowing problems with aspiration), characteristic CHARGE syndrome ear (short, wide ear with little or no lobe, "snipped off" helix, prominent antihelix that is often discontinuous with tragus, triangular concha, decreased cartilage, often protruding and usually asymmetric; ossicular malformations; Mondini defect of the cochlea; temporal bone abnormalities; absent or hypoplastic semicircular canals).

The minor diagnostic characteristics are[5]: genital hypoplasia, developmental delay, cardiovascular malformation, growth deficiency, orofacial cleft, tracheoesophageal fistula, distinctive facial features (square face with broad prominent forehead, prominent nasal bridge and columella, flat midface).

Figure 2 a. Patient's right hand, posterior view; b. patient's right hand, anterior view showing hockey-stick palmar crease.

A definite diagnosis of CHARGE syndrome can be established in patients with all four major characteristics or three major and three minor characteristics[5]. A probable/possible CHARGE syndrome can be defined in subjects with one or two major characteristics and several minor characteristics[5].

Occasional features may include: renal malformations (dysgenesis, horseshoe or ectopic kidney), hand anomalies (polydactyly, abnormal palmar creases, atypical split hand/foot deformity), omphalocele or umbilical hernia, scoliosis or hemivertebrae[5].

In our patient, the diagnosis of definite CHARGE syndrome was made based on the presence of three major characteristics (ocular coloboma, facial nerve palsy and cochlear nerve agenesis and ear malformations), associated with three minor characteristics (developmental delay, growth delay, distinctive facial features).

The differential diagnosis include: DiGeorge syndrome (characterized by congenital heart disease, palatal malformation, particular facial dysmorphism, immune deficiency, hypocalcemia, intellectual disability, and caused by a deletion on 22q11.2 chromosome); Kallmann syndrome (characterized by hypogonadotropic hypogonadism and anosmia or hyposmia)[8]; VACTERL association (a combination of **v**ertebral anomalies, **a**nal atresia, **c**ardiac anomalies, **t**racheo**e**sophageal fistula or esophageal atresia and **r**enal and **l**imb anomalies); Cat-eye syndrome (characterized by coloboma of the iris, anal atresia with fistula, preauricular tags and/or pits, heart and renal malformations, and caused by inv dup(22)(q11); renal coloboma syndrome (characterized by retinal/optic nerve colobomas, kidney abnormalities and occasional hearing loss, and caused by mutations in *PAX2)*[9].

In 60-70% patients with CHARGE syndrome, *CHD7*

gene mutations were identified[6-8]. *CHD7* is localized on 8q12.1-12.2 chromosome, coding a chromodomain helicase DNA-binding protein 7 (CHD7). CHD7 is a transcriptional regulator that binds to enhancer elements in the nucleoplasm. CHD7 also functions as a positive regulator of ribosomal RNA (rRNA) biogenesis in the nucleolus[10]. CHD7 is essential for the formation of the multipotent migratory neural crest, which acquires a broad differentiation potential and ability to migrate throughout the body, giving rise to craniofacial bones and cartilages, peripheral nervous system, pigmentation and cardiac structures[11].

The management measures depend on patient's clinical manifestations and must be applied very early. The evaluation of the airway, feeding, heart and hearing must be performed in the first day of life. A multidisciplinary team, including an ENT specialist, an ophtalmologist, a pediatrician, a pediatric neurologist, a psychologist and a geneticist should work together for the evaluation and establishment of the therapeutical measures[12]. For choanal atresia surgical correction should be performed very early[13]. Also, a special attention should be paid to hearing problems (hearing aids, speech therapy)[14]. Physical therapy and cognitive stimulation should be started in the first months of life. A regular audiologic, ophtalmologic and neurologic evaluation is recomandated in all children with CHARGE syndrome.

Other therapeutic approaches are: feeding or swallowing dysfunction (oral stimulation, occupational therapy), gastroesophageal reflux (Nissen fundoplication, G-tube insertion), renal malformations (renal ultrasound), growth retardation (endocrine evaluation; growth hormone replacement therapy could be considered in some children), hearing loss (hearing aids, such as frequency modulation system, bone conduction aids, cochlear implants or sign language and speech therapy)[15].

In our patient, physical therapy and cognitive stimulation have already been started with good evolution (the child made progresses in psychomotor development), but there are concerns regarding hearing and ophthalmological problems, due to the bilateral cochlear nerve agenesis and the bilateral optic nerve coloboma, respectively.

CONCLUSIONS

CHARGE syndrome is a rare genetic condition characterized by heart and genital defects, nose and ear anomalies, retarded growth and development. Even if this disease is a rare cause of deafness or nose malformations, it should be taken into consideration when other anomalies are associated.

From our point of view along with a correct and complete diagnose, physical therapy and cognitive stimulation should be started in the first months of life.

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