Otorhinolaryngologic Manifestations in Charge Association

Thesis

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أعراض الأذن والأنف والحنجرة لمتلازمة شارج

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CONTENTS

List of Abbreviations

CA	Choanal Atresia
CGH	Comparative Genomic Hybridization
CLP	Cleft Lip And Palate
CPSP	Canadian Pediatric Surveillance Programme
C.T	Computerized tomography
ECG	Electrocardiography
EEG	Electroencephalography
GERD	Gastroesophgeal Reflux Disease
HCG	Human Chorionic Gonadotrophin
KTP	Potassium Titanyl Phosphate Laser
LHRH	Luteinizing Hormone Releasing Hormone
MRI	Magnetic Resonance Imaging
Nd-Yag	Neodymium-doped Yttrium aluminum garnet Laser
TEF	Tracheo-esophageal fistula.

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Introduction

CHARGE, is the acronym created by Pagon and her coworkers in 1981 ***(Pagon et al., 1981)*** to describe six features of a complex genetic disorder. Since 1981, the diagnostic criteria have been revised, and they will continue to be revised. At present, the criteria include more than 20 physical anomalies, deficits in *all* sensory modalities, and a behavioral phenotype that is unique and diagnosis is based on clinical evaluation of the presence of certain major and minor features ***(Blake et al., 1998)*** and/or the presence of microdeletions in the CHD7 gene on chromosome 8 ***(Vissers et al., 2004)***.

The acronym "CHARGE" denotes the nonrandom association of coloboma, heart anomalies, choanal atresia, retardation of growth and development, and genital and ear anomalies, which are frequently present in various combinations and to varying degrees in individuals with CHARGE syndrome. No single feature is universally present or sufficient for the clinical diagnosis of CHARGE syndrome, and numerous guidelines have been published to aid in establishing a likely clinical diagnosis ***(Pampal, 2010; Janssen et al., 2012)***.

AIM OF WORK

The aim of this study is to highlight ENT anomalies present in CHARGE association to help in early detection and review the proper plan of treatment for these anomalies.

Chapter I

GENERAL CHARGE

Epidemiology

The true incidence of CHARGE syndrome is not known, with estimates ranging from 0.1-1.2/10,000 live births. A national surveillance study of CHARGE syndrome patients has been conducted through the Canadian Pediatric Surveillance Programme (CPSP) from September 2001-2004 revealing that the highest incidence of CHARGE syndrome in Canada was estimated at 1:8,500 live births so the true incidence of CHARGE syndrome reported internationally may therefore be underestimated ***(Janusz et al., 2012; Janssen et al., 2013)***.

The incidence of genetic CHARGE syndrome is unknown, due, in large part, to the cost prohibitive nature of genetic analysis of a wide population. Studies of individuals with genetic CHARGE suggest a slight female predominance (59%:41%), but larger studies are needed to offer a definitive female-to-male ratio ***(Allen, 2012; Lalani et al., 2012)***.

Causes

CHARGE syndrome is an autosomal dominant condition with genotypic heterogeneity. Most cases (58-

71% in unselected CHARGE referrals and as many as 90% of patients who meet criteria for typical CHARGE syndrome) are due to mutations of the CHD7 gene leading to haploinsufficiency ***(Jongmans et al., 2006; Jiang et al., 2012)***.

Microdeletions encompassing the entire *CHD7* gene or affecting individual *CHD7* gene exons occur in a minority of cases. If the CHD7 mutation analysis is normal, obtaining studies for del/dup of *CHD7* and then an array of comparative genomic hybridization (CGH) are the next steps ***(Udaka et al., 2007; Bergman et al., 2012a)***.

CHD7 is a member of the chromodomain helicase DNA-binding (CHD) protein family that plays a role in transcription regulation by chromatin remodeling. Most recently, a review of 379 published cases of clinically diagnosed cases of CHARGE syndrome in which CHD7 mutation testing was undertaken found that 67% of cases were due to a CHD7 mutation ***(Zentner et al., 2010; Bergman et al., 2012b)***.

Although one case report detailed *CHD7* duplication, which did not result in a CHARGE-like phenotype. Numerous case reports have described individuals clinically diagnosed with CHARGE syndrome who harbor various presumably pathologic cytogenetic abnormalities, including 22q11.2 deletions, 14q22-q24.3 inverted duplications, and 9p-, and single gene mutations ***(Monfort et al., 2008; Bergman et al., 2012b)***.

Pathophysiology

Many different types of gene mutations have been observed in patients with genetic CHARGE syndrome. These include nonsense, frameshift, missense, and splice-site mutations. It is unclear whether the type of genetic mutation affects phenotype, but future studies may reveal significance ***(Wincent et al., 2008; Vatta et al., 2013)***.

Many authors however know that even identical genotypes can produce different phenotypes. One study analyzed monozygotic twins with identical mutations on exon 16 of chromosome 8. While both twins presented with bilateral coloboma, cardiac malformations, and growth restriction, they differed greatly in the severity of cardiac