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Case Report

Terminal 6p deletion syndrome mimicking CHARGE syndrome: A case report

Gabrielle Freire[a], Laura Russell[b] and Maryam Oskoui[a,c,*]
[a]*Department of Pediatrics, McGill University, Montreal, QC, Canada*
[b]*Department of Human Genetics, McGill University, Montreal, QC, Canada*
[c]*Department of Neurology & Neurosurgery, McGill University, Montreal, QC, Canada*

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Abstract. The clinical features associated with terminal 6p deletion syndrome include anterior eye chamber defects, hearing loss, congenital heart anomalies and characteristic facies along with developmental delays. These features overlap with a number of other conditions including CHARGE syndrome. This acronym stands for non-random association of anomalies including coloboma of the eye, heart anomalies, choanal atresia, retardation of growth and development, genital hypoplasia and ear anomalies/deafness now known to be caused by *CHD7* mutations. We describe a boy initially diagnosed with CHARGE syndrome who was subsequently found to have a terminal 6p deletion. Screening for 6p deletions in individuals presenting with atypical CHARGE syndrome may be warranted, with direct consequences for genetic counseling.

Keywords: CHARGE syndrome, 6p deletion syndrome, *CHD7* mutation

1. Introduction

In the last 15 yr, numerous case reports of terminal 6p deletion syndrome describe a classical phenotype. The syndrome is characterized by malformations involving the heart, eyes as well as typical facial features, developmental delay and hearing loss. This syndrome shares many features with CHARGE syndrome, which is well-defined with major and minor criteria including coloboma of the eye, heart anomalies, choanal atresia, retarded growth and development, genital hypoplasia and ear abnormalities [1]

In this article, we report the case of a 14-year-old boy with terminal 6p deletion syndrome who was previously misdiagnosed as having an atypical CHARGE syndrome without *CHD7* mutation.

2. Case Report

This patient is an only child born to non-consanguineous parents without family history of developmental disorders. He was born at term after an uneventful pregnancy and noted to have dysmorphic features including a boxy head, hypertelorism, downslanting palpebral fissures, a large forehead, dysplastic ears with unfolded helices and small ear lobules with a cartilaginous segment, a broad, depressed nasal bridge, retromicrognathia and a single palmar crease on the left. He had a right inguinal hernia and hydrocele, which required surgical repair at 1 yr of age, and a hypoplastic

*Corresponding author: Maryam Oskoui, Departments of Pediatrics and Neurology, McGill University, Montreal Children's Hospital, 2300 Tupper street, A-512, Montreal, QC, H3H 1P3, Canada. Tel.: +1 514 412 4446; Fax: +1 514 412 4373; E-mail: Maryam.oskoui@mcgill.ca.

penis. Dilated examination of the eyes showed bilateral Rieger's anomalies including hypoplasia of the iris, iridotrabecular adhesions and posterior embryotoxon. He also had congenital dyscoria with a left elliptical pupil and corectopia. His mitral valve was dysplastic causing systolic cardiac dysfunction. At 13 yr of age, his cardiac function deteriorated acutely warranting mitral valve replacement. He had recurrent serous otitis media requiring bilateral tympanostomy and had moderate to severe bilateral conductive hearing loss. At 12 yr of age, computed tomography of the temporal bones showed a cholesteatoma and bony erosion of the long process of the left incus. He had mild gross motor delay, which improved with time, sitting unaided at 15 mo and walking at 17 mo. A pervasive developmental disorder not otherwise specified was diagnosed at 5 yr of age.

A magnetic resonance imaging of the brain at 4-yrs-old revealed bilateral enlargement of the lateral ventricles with prominence and dysmorphism of the ventricles. A repeat magnetic resonance imaging at 13 yr after his cardiac surgery showed the same mild bilateral enlargement of the lateral ventricles as well as a small arachnoid cyst in the posterior fossa anterior to the medulla. The electroencephalogram done at the same time was normal.

He was initially diagnosed with CHARGE syndrome, in 1998, at 5 mo of age based on the following clinical grounds: mild brain dysgenesis, congenital heart defect, congenital dyscoria, dysplastic ears with recurrent serous otitis media and hearing loss, genital hypoplasia, facial anomalies and developmental delay. His karyotype was normal, and molecular analysis of *CHD7* detected no mutations. At 13 yr, an array comparative genomic hybridization was requested to explore the possibility of a microdeletion syndrome based on his atypical features for CHARGE syndrome. A terminal deletion of 324 oligonucleotides at locus 6p25.3–p25.2 (position: 128,203–3,207,672) was identified. The extent of the deletion was estimated to be 3.079 Mb long. The result was confirmed by fluorescence *in situ* hybridization analysis, and both parents were negative for this deletion.

3. Discussion

CHARGE syndrome is an acronym describing an association of congenital anomalies, which were first grouped in a definition by Blake et al. [1] in 1998. The definition identified major and minor clinical criteria, which were relevant at the time of diagnosis. It was later refined by Verloes [2] in 2005. Genetic analysis of affected individuals led to the consistent identification of mutations in the *CHD7* gene. The diagnosis of CHARGE syndrome requires all four major criteria (choanal atresia, coloboma, characteristic ears and cranial nerve anomalies) or three major and three minor criteria (cardiovascular malformations, genital hypoplasia, cleft lip/palate, tracheoesophageal fistula, CHARGE facies, growth deficiency, developmental delay) [3]. Verloes [2] divided the diagnostic categories into typical, partial and atypical CHARGE syndrome and included only colobomas, choanal atresia and semi-circular canal hypoplasia in the major criteria.

The initial diagnosis of atypical CHARGE syndrome in our patient was made on the basis of one major (ear abnormalities) and four minor (cardiovascular anomaly, genital hypoplasia, facial anomalies and developmental delays) criteria. According to Verloes' [2] updated definition, he would not fit the criteria for atypical CHARGE syndrome with only four minor criteria. This new definition proves a useful tool in the differentiation of congenital syndromes by being more specific for CHARGE.

This case illustrates the clinical overlap between terminal 6p deletion syndrome and CHARGE syndrome. In the literature to date, 29 other patients with terminal 6p deletion syndrome have been reported. A summary of their physical findings is outlined in Table 1. The first example of shared features is cardiac malformations. A wide range of defects have been described for terminal 6p deletion syndrome and vary between patent foramen ovale, patent ductus arteriosus, septal defects and valvulopathies. Of the 29 patients described in the literature to date, 19 were reported to have cardiac anomalies. In CHARGE, cardiac malformations frequently occur, the most common of which is tetralogy of Fallot, followed by each of its constituents in various combinations or individually, and by vascular rings. As in terminal 6p Deletion syndrome, patent ductus arteriosus and atrial septal defects have also been reported [1–5]. Developmental delays are also commonly reported in both syndromes with a predominant component of motor delay in CHARGE syndrome. It is indeed part of the minor criteria for CHARGE syndrome and has been described in 19/29 patients reported with terminal 6p deletion syndrome. Finally, features like characteristic facies, external ear anomalies and genital hypoplasia have been described clinically in both

Table 1
Compilation of physical findings associated with 6p terminal deletion syndrome with comparison to our case and to CHARGE syndrome[5–14]

Physical Findings	6p terminal deletion[7–14]	Case described	CHARGE syndrome[5,6]
Facial anomalies	**29/29**		
Hypertelorism	25	+	–
Downslanting palpebral fissures	16	+	–
Abnormal epicanthal folds	6	+	–
Abnormal nasal bridge	17	–	+
Abnormal philtrum	8	+	–
Midface hypoplasia	8	–	–
Downturned corners of mouth	7	–	–
Migrognatia	4	+	–
High arched palate	7	+	–
Low set ears	1	–	+
Others	12	–	–
Ocular anomalies	**15/29**		
Corneal opacities	4	–	–
Posterior embryotoxon	10	+	–
Iris hypoplasia	5	+	–
Iridocorneal synechiae	7	+	–
Abnormal pupil	4	+	–
Anterior chamber dysgenesis	8	+	–
Microphthalmia	4	–	Major criteria
Coloboma	2	–	475/611 (78%)
Ear anomalies	**22/29**		
External ear malformation	10	+	512/543 (94%)
Ossicular malformation	2	+	–
Hearing loss	15	+	198/223 (89%)
Chronic otitis media	5	+	Major criteria
Semicircular canal anomaly	–	–	216/225 (96%)
Brain anomalies	**15/29**		
Dandy-Walker malformation (or variant)	12	–	–
Hydrocephalus	7	+	–
Cranial nerve anomalies	–	–	280/298 (94%)
Cardiac anomalies	**17/29**		489/626 (78%)
Atrial septal defect	5	–	+
Patent ductus arteriosus	7	–	+
Patent foramen ovale	5	–	–
Ventricular septal defect	2	–	+
Aortic valve anomaly	2	–	–
Others	4	Mitral valve dysplasia	Aortic arch anomalies Conotruncal defects Arteriosus canal defects
Gastrointestinal anomalies	**7/29**		
Hernias (umblical, inguinal)	5	+	–
Others	2	–	–
Genitourinary anomalies	8/29		
Hydronephrosis	2	–	–
Pelviectasis	2	–	–
Genital hypoplasia	2	+	279/456 (61%)
Others	2	–	Vesicoureteric reflux
Musculoskelatal anomalies	**16/29**		
Hip dysplasia	3	–	–
Scoliosis	4	–	Occasionally reported
Feet anomalies	9	–	–
Fifth clinodactyly	3	–	Occasionally reported
Palmar creases anomalies	5	+	–
Pectus excavatum	2	–	–
Hypotonia	12	–	–
Developmental anomalies			
Motor delay	19	+	147/149 (99%)
Speech delay	15	+	Minor criteria

+ = Feature present; – = Feature absent.

syndromes but when investigated in more depth reveal significant differences. The following characteristics, differing significantly between the two syndromes, will help identify which evaluation might be warranted in atypical cases.

In terminal 6p deletion syndrome, the *FOXC1* gene has been recognized to be involved in eye development. Deletions are thought to cause ocular malformations such as Rieger's anomaly, posterior embryotoxon or anterior chamber dysgenesis [6]. These are one of the most consistent and unique features of terminal 6p deletion being present in 15/29 patients and have not been described in CHARGE syndrome. Its definition only includes colobomas, usually involving the retina. Therefore, a full dilated eye examination may help in differentiating the syndromes.

Abnormalities of the external ear, ossicular malformations and/or sensorineural hearing loss are commonly seen in patients with terminal 6p deletion syndrome. Ear anomalies were present in 22/29 patients and mixed hearing loss was present in 15/29 patients reported in the literature. Similarly, patients with CHARGE syndrome present with characteristic cup-shaped external ears, lack of ear lobes and triangular conchae. Moreover, they also commonly present with sensorineural hearing loss [3–4]. However, semi-circular canal hypoplasia is very specific to CHARGE, and its presence on imaging may help in differentiating the syndromes.

Structural neurological anomalies are also frequently described (15/29) in patients with terminal 6p deletion syndrome and include Dandy-Walker malformation and hydrocephalus. These contrasts with CHARGE syndrome where abnormalities found on brain imaging include olfactory bulb hypoplasia and/or arrhinencephaly as well as cranial nerve abnormalities.

Concurrently, the most recent definition of CHARGE syndrome underlines significant hypothalamo-hypophyseal axis abnormalities. This is thought to be the cause of genital hypoplasia and pubertal delays in 61% of patients with CHARGE by leading to decreased gonadotropin release [4,5]. Normal levels of gonadotropins in the blood might have cued the diagnosis towards terminal 6p deletion syndrome in our patient with genital hypoplasia.

The most consistent anomaly of 6p deletion syndrome is typical facial features. Indeed, hypertelorism was described in 25/29 patients in the literature. Downslanting palpebral fissures and flat nasal bridge were described in 16 and 17 patients, respectively. This typical facies is quite different from the anomalies described in CHARGE syndrome, which includes square-shaped head, sloping forehead, wide nasal bridge and small mouth. Cleft lip and palate have also been commonly (30% of patients) described in CHARGE syndrome [3,4]. Careful re-evaluation of the facial features might help in the differentiation process.

Lastly, choanal atresia and cranial nerve anomalies are unique to CHARGE syndrome and have not been described in patients with terminal 6p deletion syndrome. Choanal atresia is one of the cardinal features of CHARGE syndrome, being present in 38-55% of patients and cranial nerve anomalies, being present in 62-100% of patients in the latest reviews, is part of the new diagnostic criteria [2–4].

In conclusion, ear abnormalities, cardiac abnormalities, genital hypoplasia and developmental delays are features that are common to both terminal 6p deletion syndrome and CHARGE syndrome. These characteristics cannot help differentiate the two syndromes based on clinical grounds only. On the other hand, anterior chamber dysgenesis, posterior embryotoxon, specific structural brain anomalies (including Dandy-Walker malformation and hydrocephalus), and characteristic facial features (including hypertelorism, flat nasal bridge, downslanting palpebral features) are present only in terminal 6p deletion syndrome whereas hypothalamic-hypophyseal deficiencies, choanal atresia, semi-circular canal hypoplasia and cranial nerve anomalies are unique to CHARGE syndrome.

In cases of atypical CHARGE syndrome, we recommend looking for features consistent with terminal 6p deletion syndrome and features unique to CHARGE syndrome: a careful physical examination of facies, a dilated eye examination by an ophthalmologist looking for Rieger's anomaly or colobomas, a blood test for gonadotrophins levels, as well as brain and ear imaging, looking for structural anomalies and semi-circular canal hypoplasia. Further genetic testing should be pursued with either array comparative genomic hybridization, molecular or fluorescence *in situ* hybridization analysis for both *CHD7* mutations and terminal 6p deletion in cases that are ambiguous. A definitive diagnosis will lead to a more adequate expectant case management as well as appropriate genetic counseling.

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