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Case Report

Global Developmental Delay, Congenital Deafness, and Club Feet

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Abstract

Primary care pediatricians see a wide spectrum of children with developmental delay with and without dysmorphic features. Searching for a genetic cause can be challenging. We describe a 24 month old child with global developmental delay, congenital nystagmus, deafness, and club feet. Because chromosomal microarray analysis (CMA) provides a higher diagnostic yield (15-20%) than conventional G-band karyotype analysis (3%), we performed CMA and diagnosed our patient with a chromosome 18 deletion, DeGrouchy Syndrome.

INTRODUCTION

DeGrouchy syndrome is a rare genetic disorder caused by a deletion of genetic material within one of the two copies of chromosome 18. Because there are no common breakpoints in the gene, the size of the deletions varies widely and there is significant phenotypic variation [1-3]. The incidence is estimated at 1:50,000 of live-born infants. The main clinical features include short stature, round face with short philtrum, palpebral stenosis and large ears. Intellectual deficiency is mild to moderate. The aim of our report is to describe a variant of the disorder.

CASE PRESENTATION

A 24 month old Hispanic female presented for a routine well child visit. She had a history of global developmental delay, congenital nystagmus, deafness, and club feet. Recently, the mother noted abnormal movements of her upper extremities on two occasions that lasted a few seconds. She had no color changes but was 'grouchy' afterwards [4-7].

She was born at 35 weeks gestation by spontaneous vaginal delivery. Her birth weight, length, and head circumference were 2,295g (25–50th %), 42.5cm (10–25th %), and 30.5 cm (10–25th %) respectively. She was discharged home after three days. Because she failed her newborn hearing screening test, brainstem auditory evoked responses (BAERs) were performed at 6 weeks of age. Results indicated mild sensitivity loss in the right ear and moderate primarily conductive loss in the left ear. Repeat BAER at three and five months of age showed moderate bilateral conductive hearing loss. Acoustic emittance measures could not be done due to failure to maintain a hermetic seal in the ear canals [8]. Her ear exam showed bilateral narrowing of the external auditory canals (EACs). CT (brain) at four months of age indicated narrowed bilateral bony EACs and occlusion with soft tissue. Hearing aids were prescribed. An MRI of the brain at 1 year of age showed incomplete myelination; probably acceptable for the patient's age. There were no migration anomalies [9,10].

Her past surgical history included two Achilles tendon releases for her clubfeet and she now wears bilateral ankle foot orthoses. Developmentally she can stand with support (average for a 9-month old), babble (average for a 9-monthold), put blocks in a cup (average for a 13-month), and reach for toys (average for a 6-month old).

On examination, her weight, length, and head circumference were 10.9kg (18%), 84cm (29%) and 46.5cm (25%), and 84cm (29%) respectively. She had noobvious dysmorphic features but had bilateral fine horizontal nystagmus, strabismus, small EACs, bilateral club feet, and generalized hypotonia. The rest of the physical examination was unremarkable (Figures 1,2). The differential diagnosis for her clinical findings is seen in (Table 1).

Chromosomal microarray analysis (CMA) revealed a chromosome 18 deletion or DeGrouchy syndrome [11,12]. There was a large copy number LOSS of chromosome band 18q21.32q23 of approximately 19.317 Mb in size. High resolution Gurrs-Trypsin-Giemsa (GTG) banding showed 550 abnormal female chromosome analysis with a terminal deletion of the long arm (q) of one chromosome 18 at band 18q21.3. Her renal ultrasound was normal. Currently she is receiving Early Intervention Services for developmental delay and undergoing a neurological evaluation for possible seizures [13].

DISCUSSION

Genetic testing for children with intellectual disabilities, autism spectrum disorders or multiple anomalies is

Table 1: Differential Diagnosis.

System	Chromosome 18q- (DeGrouchy Syndrome)[7]	Chromosome 22q11.2 (Diverge Syndrome)[6]	Trisomy 18 (Edwards Syndrome)[5]	Kallmann Syndrome (hypogonadotropic hypogonadism)[4]
General	Mid face hypoplasia, broad nasal bridge. May have no dysmorphic features. Behavior problems with autistic features	Micrognathia, cleft lip/ palate,elongated face, almond-shaped eyes, wide nose, and small ears, dental problems. Global developmental delay	Micrognathia, cleft lip and/ or palate. Poor growth. Global developmental delay	May have cleft lip or palate and/or dental abnormities. Developmental delay. Psychiatric problems
Central Nervous System	Microcephaly, hypotonia, seizure disorders	Craniosynostosis, seizure disorders (idiopathic or secondary to hypocalcemia), tethered cord	Microcephaly with prominent occiput	Diminished or absent sense of smell (80 – 90%). Cerebella ataxia. Bimanual synkinesis of the hands
Eyes	Microphthalmia, epicanthal folds, strabismus, nystagmus, coloboma of iris, corneal opacities	Almond shaped eyes, strabismus, anophthalmia, sclerocornea	Wide spaced eyes with narrow palpebral fissures, ptosis, coloboma, cataract, corneal opacities	Abnormalities of eye movement, coloboma, ptosis. Increased incidence of color blindness
Ears	Abnormalities of the pinna (low set or protruding), stenotic or atretic external auditory canal, hearing impairment	Abnormalities of the pinna (low set and posteriorly rotated), Conductive and sensorineural hearing loss	Abnormalities of the pinna (low set and malformed), hearing impairment	Hearing impairment
Cardiovascular	Septal defects	Conotruncal malformations	Septal defect, patent ductus arteriosus, polyvalvular disease	None reported
Renal	Horse shoe kidney, hydronephrosis, polycystic kidney, absent kidney	Renal anomalies	Renal anomalies	Unilateral renal agenesis – single kidney
Musculoskeletal	Short stature, scoliosis, genu varum	Scoliosis with or without vertebral anomalies, and craniosynostosis	Arthrogryposis, short sternum, clenched hands, short sternum	Scoliosis
Limbs	Long thin tapered hands, abnormal skin ridge patterns of fingers and palms, abnormal placement of thumbs and toes, abnormalities of feet (club feet, pes planus, pes cavus)	clubbed feet, polydactyly	Clenched fists with overriding fingers, small finger nails, underdeveloped thumbs, radial abnormalities (aplasia/ hypoplasia), webbing of 2nd and 3rd toes, clubfoot or rocker bottom feet	Ectrodactyly (split hand/ foot malformation, shortened middle metacarpal
Genitalia	Females: hypoplastic labia Males: undescended testis, micropenis, hypospadias, chordae	Females: normal. Males: normal	Females: normal Males: undescended testis	Females : normal Males: undescended testis, micropenis
Other	Low IgA levels	Laryngotracheoesophageal anomalies, gastrointestinal anomalies, hypocalcemia, frequent infections. Psychiatric disorders		Generally diagnosis of exclusion at work up for delayed puberty
Magnetic Resonance Imaging	Characteristic with poor differentiation of gray and white matter on T2-weighted images. (Leukodystrophy)	Cavum septum pellucidum and white matter abnormalities	Choroid plexus cysts, agenesis of corpus callosum, mega cisterna magna, neural tube defects.	Characteristic with absent olfactory bulbs may have absent olfactory sulci and hypoplastic anterior pituitary gland.
Chromosomes	Distal deletion of the long arm of chromosome 18	Contiguous microscopic deletion of 30 – 40 genes on q arm of chromosome 22 near the middle at location 11.2 90% due to new mutation; 10% autosomal dominant	Trisomy 18; full (most common), mosaic or partial	Nerve cell migration abnormalities of olfactory and gonadotropin-releasing hormone nerve cells. Genetic heterogeneity. X-chromosome – ANOS1 Autosomal dominant - *FGFR1*, *PROKR2*, *PROK2*, *CHD7* or *FGF8* genes (causing KS types 2, 3, 4, 5 and 6, respectively) Autosomal recessive - PROKR2 and PROK2

Figure 1 Facial features.

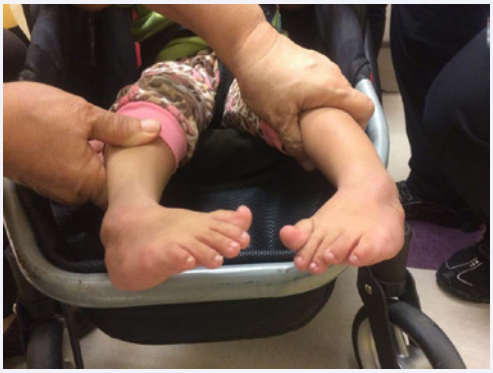

Figure 2 Club feet.

recommended by the America Academy of Pediatrics [1]. Testing done by chromosomal microarray analysis (CMA) has a significantly higher diagnostic yield (15-20%) than conventional G-banded karyotype analysis (3%) [2,3]. Our patient had features, symptoms and signs that are part of multiple other syndromes (Table 1). In view of this, chromosomal analysis was helpful in identifying the correct diagnosis and facilitated correct management.

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