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The 22q11.2 Deletion in African-American Patients: An Underdiagnosed Population?

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Abstract

Findings associated with the 22q11.2 deletion often include congenital heart malformations, palatal anomalies, immunodeficiency, hypocalcemia, and developmental delay or learning disabilities. Often the clinical suspicion of the diagnosis in a patient with one or more of these findings is heightened based on the presence of a characteristic facial appearance. In our large cohort of 370 patients with the 22q11.2 deletion, we report the under-representation of African-Americans in our group, as well as, the paucity of craniofacial dysmorphism in these patients. We note that the absence of the typical facial features may result in decreased ascertainment in this population and, furthermore, may delay the implementation of palliative care, cognitive remediation, and recurrence risk counseling. We, therefore, suggest that the clinician's threshold of suspicion should be lower in African-American patients.

Keywords

22q11.2 deletion syndrome; DiGeorge syndrome; velocardiofacial syndrome

INTRODUCTION

The 22q11.2 deletion has been identified in the majority of patients with DiGeorge anomalad, velocardiofacial syndrome, and conotruncal anomaly face syndrome, and in some cases of autosomal dominant Opitz G/BBB syndrome and Cayler cardiofacial syndrome [Driscoll et

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al., 1992a,b, 1993; Burn et al., 1993; Giannotti et al., 1994; Matsouka et al., 1994; McDonald-McGinn et al., 1995; Fryburg et al., 1996; LaCassie and Arriaza, 1996].

The list of findings associated with the deletion is extensive and variable [McDonald-McGinn et al., 1997, 1999]. Some patients present with classic symptoms of DiGeorge anomaly including a conotruncal cardiac defect, hypocalcemia, and immune deficiency, others have the learning disability and velopharyngeal incompetence described in velocardiofacial syndrome. Additional patients present with only minimal findings of the deletion but gain clinical attention when these findings are coupled with the characteristic craniofacial features. These typical facies include: hooded eyelids, a prominent nasal root with a bulbous nasal tip, hypoplastic alae nasae, and auricular abnormalities [McDonald-McGinn et al., 1997, 1999]. It has been our experience that there is a paucity of the latter findings in our African-American patients [McDonald-McGinn et al., 1996]. Here we examine the dysmorphisms in both Caucasians and non-Caucasian patients with a 22q11.2 deletion, discuss how they differ and compare the incidence of non-Caucasians in our cohort of patients with a 22q11.2 deletion to our hospital based population.

MATERIALS AND METHODS

Three hundred and seventy patients with a 22q11.2 deletion were ascertained through The Children's Hospital of Philadelphia's multidisciplinary 22q11.2 deletion clinic. The laboratory diagnosis was made using fluorescence in situ hybridization with the commercially available N25 (D22S75) or TUPLE 1 probes. Patients ranged in age from birth to 52 years; 52% were female. Anthropometric measures including height, head circumference, and inter-pupillary distance were available for review on a total of 255 of the 370 patients. Of this group, 204 were Caucasian, 33 were African-American, 11 were Hispanic, four were Asian, and three were of mixed racial/ethnic background. Measurements were plotted on standard growth curves from the National Center for Health Statistics and particular attention was paid to the craniofacial features associated with the 22q11.2 deletion [Feingold and Bossert, 1974; McDonald-McGinn et al., 1997, 1999; National Center for Health Statistics, 1997]. Findings in non-Caucasians were compared to the Caucasian population.

RESULTS

Of the total group of 370 patients with a 22q11.2 deletion, 294 were Caucasian (79.5%), 45 (12%) were African-American, 15 (4%) were Hispanic, four (1%) were Asian, and the remaining 12 (3.5%) were of mixed racial/ethnic background. The racial/ethnicity was determined by full family history taken at clinic. These numbers are compared to our hospital based population figures which reveals a significant under representation of African-American patients in our cohort (Table I).

Of the 45 African-American patients, five were adults; four of whom were ascertained through an affected child. The remaining adult was diagnosed with VCFS clinically, as a teenager through the Cleft Palate Clinic, and subsequently reached adulthood and had confirmatory deletion studies. The remaining 40 patients were children. Twenty-five of the children were identified in infancy solely on the basis of their cardiac defect as part of our conotruncal cardiac anomaly screening program; seven children came to the attention of Clinical Genetics in infancy because of their cardiac defects and dysmorphic features; four children met criteria for a clinical diagnosis of DiGeorge anomaly; two children were offspring of affected adults, both of whom were diagnosed prenatally with the deletion; one child was identified following referral from a behavioral intervention unit with a history of a learning disability; and one child was diagnosed following referral because of a history of hypocalcemia in infancy and a non-

verbal learning disability consistent with the 22q11.2 deletion (Fig. 1) [Goldmuntz et al., 1993; Moss et al., 1999].

Review of the clinical genetics evaluation performed in a subset of patients (Table II) revealed that seven of 33 (21.2%) African-American patients had none of the classic facial characteristics of the deletion and only three of 33 (9.1%) had three of the four typical characteristics including a bulbous nasal tip, prominent nasal root, hooded eyelids, and auricular abnormalities (Fig. 2 and Fig 3). This is compared to a similar group of Caucasian patients where 11/204 (5.4%) had no typical facial features and 63/204 (30.9%) had three of the four characteristics (Fig. 4). Eighteen African-American patients had auricular abnormalities (Fig. 5) as their only dysmorphism. Atypical findings noted in the African-American cohort included extra nuchal skin in two non-cardiac patients and ptosis in another. In addition, we identified several anthropometric measures, which were found to be variant from the norm (two standard deviations below the mean) including: midfacial depth, lower facial depth, nasal breadth, and auricular height and breadth [Minugh-Purvis et al., 2000].

Of the four Asian patients, one child (Fig. 6) with cleft palate and growth hormone deficiency was ascertained through the endocrinology clinic following our report of the association of growth hormone deficiency and the 22q11.2 deletion; and one was diagnosed in infancy with congenital heart disease, cleft palate, and myelomeningocele [Nickel et al., 1993,1994; Nickel and Magenis, 1996; Weinzimer et al., 1998]. Another child was ascertained through Child Development with a history of cleft palate and a learning disability and the fourth child was self-referred following the a diagnosis of the 22q11.2 deletion with a history of congenital heart disease, cleft palate, and a terminal transverse defect of one upper extremity. One of the four children had no dysmorphic features and only one was found to have three of the four classic craniofacial characteristics (Table II).

Of the 11 Hispanic patients several had typical dysmorphic features more closely resembling those of the Caucasian patients (Fig. 7). Whereas, the three patients of mixed ethnicity had variable facial features.

Growth parameters, including head circumference and interpupillary distance revealed only minor differences between Caucasians and non-Caucasians. However, short stature was notably more common among Caucasians, Hispanics, and Asians as compared to African-Americans (significance $> P = 0.05$ using χ^2 analysis) (Table III).

DISCUSSION

We report our anthropometric and craniofacial findings in both Caucasian and non-Caucasian patients with the 22q11.2 deletion. In looking at our large cohort of 370 patients, only 12% are African-American. This is in contrast to our hospital's population of patients where 42% are African-American. To explain this discrepancy, one might speculate that the deletion is less common in certain ethnic groups. Based on our own cohort, however, we found no difference in the numbers of Hispanic, Asians, and patients of mixed background as compared to our hospital's overall population (Table I). Therefore, the best method of answering this question would be by performing a newborn screening study. However, with the exception of auricular anomalies, we did find a paucity of the typical craniofacial features associated with the 22q11.2 deletion in African-American patients. Thus, this may offer an explanation for the under-representation of this group in our cohort. In particular, we found a lack of noticeable nasal differences amongst the African-American cohort including a dearth of patients with hypoplastic alae nasae, a prominent nasal root or a bulbous nasal tip. In addition, we found hooding of the eyelids in only 6% of African-American patients as compared to 26% of

Caucasians. This may be explained in part by the underlying influence of ethnic and racial background on craniofacial development.

In comparison, Hispanics were likely to have dysmorphisms which were similar to their Caucasian counterparts (Table II). In looking at our Asian subgroup, the numbers were too small to make a reliable assessment. Head circumference, height, and interpupillary distance were not contributory in making the diagnosis in any category.

The paucity of dysmorphic features among African-American patients has been noted in other syndromic diagnoses. Hudgins et al. [1998] reported that the typical facial characteristics in African-American patients with Prader–Willi syndrome were lacking and suggested that the “clinicians threshold of suspicion of Prader–Willi syndrome should be lower in African-American individuals with hypotonia and developmental delays.”

We would echo these sentiments as regards the 22q11.2 deletion. Furthermore, we would suggest microdeletion studies in non-Caucasian patients who present with even minor symptomatology of the 22q11.2 deletion regardless of their facial appearance in an effort to provide appropriate clinical management, cognitive remediation, and genetic counseling in a timely manner for these patients.

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Fig. 1. Nine-year-old non-dysmorphic male with a 22q11.2 deletion referred with a history of hypocalcemia in infancy and a non-verbal learning disability.



Fig. 2. Mother and daughter with the 22q11.2 deletion. Neither had dysmorphism consistent with the deletion.



Fig. 3. Father and son with the 22q11.2 deletion. Both were hyperteloric. In addition, the father had upslanting palpebral fissures, a bulbous nasal tip, hypoplastic alae nasae, and small ears with overfolded helices.



Fig. 4. Caucasian patient demonstrating the typical hooded eyelids, bulbous nasal tip and hypoplastic alae nasae.



Fig. 5.
African-American patient with auricular abnormalities as the only typical dysmorphism.



Fig. 6. Vietnamese patient ascertained with a history of cleft palate and growth hormone deficiency. He was noted to be hyperteloritic with hooding of eyelids and mild overfolding of his helix.



Fig. 7. Hispanic child demonstrating hooded eyelids, auricular anomalies, prominent nasal root, bulbous nasal tip, and hypoplastic alae nasae.

TABLE I

The Children's Hospital of Philadelphia: Frequency by Race/Ethnicity

	Patients with a 22q11.2 deletion (N = 370) (%)	Hospital population (%)^a
Caucasian (N = 294)	79.5	50
African-American (N = 45)	12	42
Hispanic (N = 15)	4	1
Asian (N = 4)	1	1
Other (N = 12)	3.5	6

^aCategory determined by patient report.

TABLE II

Patients With a 22q11.2 Deletion and Frequency of Facial Features by Race/Ethnicity (N = 255)

	No dysmorphisms (%)	Three or more features of the deletion (%) ^a	Bulbous nasal tip (%)	Prominent nasal root (%)	Hooding of eyelids (%)	Auricular anomalies (%)
Caucasian (N = 204)	5.4	30.9	62.3	2.5	25.5	83.3
African-American (N = 33)	21.2	9.1	12.1	15.2	6.1	78.8
Hispanic (N = 11)	0	36.4	81.8	9.1	36.4	90.9
Asian (N = 4)	2.5	2.5	2.5	50	0	7.5
Other (N = 3)	0	0	33.3	0	0	100

^aBulbous nasal tip, prominent nasal root, hooding of the eyelids, auricular anomalies.

TABLE III

Patients With a 22q11.2 Deletion and Selected Features by Race/Ethnicity (N = 255)

	Microcephalic (<5%) (%)	Macrocephalic (>95%) (%)	Hypertelorism (>95%) (%)	Short stature (<5%) (%)
Caucasian (N = 204)	19.1	2.0	13.2	35.8
African-American (N = 33)	9.1	3.0	15.2	15.2
Hispanic (N = 11)	27.3	0	45.5	36.4
Asian (N = 4)	0	0	25	50
Other (N = 3)	33.3	0	0	0