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Prenatal Findings in Cardio-Facio-Cutaneous Syndrome

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Our study was designed to analyze prenatal manifestations in patients affected with cardio-facio-cutaneous syndrome (CFCS), in order to define indications of DNA testing in utero. Prenatal features were extracted from a national database and additional data were collected from 16 families contacted through the French association of CFC-Costello syndrome. We collected results of ultrasound scan (USS) biometrics, presence of congenital birth defects, and polyhydramnios. From the database, increased nuchal translucency was present in 13% of pregnancies, polyhydramnios in 52%, macrosomia and/or macrocephaly in 16%. Of the 16 pregnancies, 81% were complicated by abnormal USS findings. Polyhydramnios was reported in 67%. Head circumference, biparietal diameter, and abdominal circumference were above the 90th centile in 72%, 83% and, 81% of fetuses, respectively. Contrasting with macrosomia, femur length was below the 10th centile in 38%. Urinary tract abnormalities were found in 47% of fetuses. Most CFCS fetuses showed a combination of macrocephaly, macrosomia, and polyhydramnios, contrasting with relatively short femora. This growth pattern is also seen in Costello syndrome. We suggest that screening for CFCS and Costello gene mutations could be proposed in pregnancies showing this unusual pattern of growth parameters. © 2015 Wiley Periodicals, Inc.

Key words: cardio-facio-cutaneous syndrome; prenatal findings; fetal ultrasound; short femora; fetal macrosomia; *BRAF* mutation

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INTRODUCTION

RASopathies are a family of clinically related genetic disorders due to a deregulation (commonly resulting in increased or sustained activity) of the RAS/mitogen-activated protein kinase (MAPK) pathway. This pathway plays an essential role in the control of cell cycle and differentiation. Somatic-activating mutations are involved in tumor development and about 30% of tumors carry a mutation in any of the canonical RAS [Fernández-Medarde and Santos, 2011]. RASopathies include neurofibromatosis type 1, Noonan syndrome (NS) and its variants (CBL syndrome, SHOC2 syndrome, Noonan-multiple lentigines syndrome), Costello syndrome (CS), cardio-facio-cutaneous syndrome (CFCS), and linear sebaceous nevus syndrome [Tidyman and Rauen, 2009].

CFCS is characterized by facial dysmorphism, dermatologic abnormalities, growth retardation, congenital heart disease (CHD) (pulmonary stenosis, other valve dysplasia, septal defects), and/or hypertrophic cardiomyopathy. Facial dysmorphism

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consists of sparse curly hair, absent or sparse eyelashes and eyebrows, high forehead, relative macrocephaly, bitemporal narrowing, hypoplastic supraorbital ridges, hypertelorism with downslanting palpebral fissures, ptosis, short nose with anteverted nares, deep philtrum, and low-set posteriorly rotated ears. The risk of malignancies (acute lymphoblastic leukemia, lymphoma) appears marginally increased [Reynolds et al., 1986; Rauen, 1993; Roberts et al., 2006; Allanson et al., 2011; Kratz et al., 2011]. Intellectual disability, ranging from moderate to severe, is almost constant in patients with *BRAF* mutations [Yoon et al., 2007]. Abe et al. [2012] estimated that the prevalence of CFCS in Japan was 1/810,000 individuals. There are no data available for other countries.

CFCS is caused by mutations in four different genes [Rauen, 1993; Tidyman and Rauen, 2009; Allanson et al., 2011]. Among cases with a known mutation, *BRAF* accounts for approximately 75% of patients, *MEK1* and *MEK2* for 20–25% together, and *KRAS* for less than 5%. Currently, there are no diagnostic criteria, and distinction between RASopathies tends to rely on genotype. Among patients who screen negative for *BRAF*, *MEK*, and *KRAS*, some have mutations in genes associated with NS. Because there are no clinical criteria to distinguish CFCS from severe NS, those patients tend to switch from one diagnosis to the other based on the molecular result. Making a clinical diagnosis is sometimes difficult, especially in the neonatal period [Nava et al., 2007; Digilio et al., 2011]. NS is a frequent, genetically heterogeneous condition with an incidence of 1/1,000–2,500 births [Houweling et al., 2010; Roberts et al., 2013]. CS is a rare and severe condition with a high risk of malignancies and neurological involvement [Gripp and Lin, 1993]. Almost all cases are due to activating mutations in *HRAS*. Prenatal findings of NS and CS have been extensively studied, whereas little data is available on fetal CFCS [Witters et al., 2008; Allanson et al., 2011; Myers et al., 2014].

The purpose of our study was to collect all prenatal data, including birth defects, amniotic fluid anomalies, and detailed analysis of growth parameters, in order to identify potential markers of fetal CFCS. We chose to study only patients with a *BRAF* mutation who represent 75% of all CFC patents and constitute a clinically homogeneous group.

METHODS

In the first part of study, we reported results of a questionnaire used in a clinical database of RASopathies. This database is maintained in the Department of Genetics of Robert DEBRE Hospital, the only laboratory in France to screen the whole panel of CFCS and NS genes. The database includes clinical pictures, physical measurements, and descriptive items, collected through a written questionnaire filled by the clinicians when samples are submitted for diagnosis. The questionnaire includes four items about prenatal history (nuchal translucency, polyhydramnios, macrocephaly, and macrosomia).

In a second part of study, parents of CFC patients were contacted through referring clinicians and the family support group. Those who agreed to participate had a phone interview to obtain their oral consent and information held by the family. Using hospital records and/or patient documents, we collected results of maternal serum screening test, ultrasound scan (USS) biometrics (thickness of nuchal translucency (NT), head circumference (HC), biparietal diameter (BPD), abdominal circumference (AC), femur length (FL), estimation of fetal weight (EFW)), the presence of CHD, and polyhydramnios. Biometric data were converted into centiles for term based on the French references (College of Fetal Ultrasonographists [Créquat et al., 2000]). Data were pooled in groups, based on the periods recommended by in France for serum screening and systematic USS: 13–25-weeks gestation (WG) and late pregnancy (USS performed after 28 WG). Further investigations were performed when the initial scan yielded abnormal results. Sex, gestational age at delivery, birth weight, height, and head circumference were converted into centiles by the software and curve AUDIPOG [Mamelle et al., 1996].

RESULTS

In the first part in the clinical database maintained by the laboratory, prenatal data were available for 69 patients carrying *BRAF* mutations. Increased nuchal translucency was present in 13% of pregnancies (9/69), polyhydramnios in 52% (36/69), macrosomia and/or macrocephaly in 16% (11/69).

In the second part of results from the family support group, descriptive data were available for 16 pregnancies and biometrics for 14 (Table I). There were 12 boys and four girls. All children had *BRAF* mutations. Among 10 first trimester USS, increased nuchal translucency was present in two fetuses. Amniocentesis or CVS was performed in 75% of pregnancies (12/16). Indications were abnormal maternal serum screening (one fetus), increased NT (two fetuses), advanced maternal age (three fetuses), history of a previ-

TABLE I. Fetal Measurements in Centiles of 14 Pregnancies

		HC	BPD	AC	EFW		FL
Second trimester	Mean ± SD	70 ± 26	78 ± 23	82 ± 9	56 ± 31	Mean ± SD	34 ± 31
	>90th c	3/9 (33%)	5/10 (50%)	2/9 (22%)	1/6 (16%)	<10th c	2/11 (18%)
	>95th c	2/9 (22%)	4/10 (40%)	0/9 (0%)	1/6 (16%)	<5th c	2/11 (18%)
Third trimester	Mean ± SD	93 ± 7	89 ± 20	93 ± 7	91 ± 14	Mean ± SD	30 ± 31
	>90th c	8/11 (72%)	10/12 (83%)	9/11 (81%)	7/9 (77%)	<10th c	5/13 (38%)
	>95th c	7/11 (63%)	8/12 (66%)	7/11 (63%)	5/9 (55%)	<5th c	4/13 (30%)

HC, head circumference; BPD, biparietal diameter; AC, abdominal circumference; FL, femoral length; EFW, estimated fetal weight; c, centiles.

ous child with Down syndrome (one fetus), and abnormal USS findings (five fetuses). In one fetus, CS was suspected. *HRAS* sequencing on DNA extracted from cultured amniotic cells ruled out the diagnosis. Polyhydramnios was reported in 67% of pregnancies (10/15). HC, BPD, and AC were above the 90th centile in 72% (8/11), 83% (10/12), and 81% (9/11) of fetuses (Table I), respectively. In 77% of fetuses, there was true macrosomia, defined as EFW greater than the 90th centile. Contrasting with macrosomia, FL was below the 10th percentile in 38% of fetuses (5/13) and below the 15th centile in 53% (Table I). The contrast between macrosomia/macrocephaly and decreased femoral length is illustrated in Figures 1 and 2. Urinary tract abnormality was found in 47% (7/15); one renal cyst and six cases of pyelectasis. Hepatomegaly was noted in 20% (3/15). In one fetus, CHD was suspected because of a decreased mitral to tricuspid valve distance but this finding was not confirmed on postnatal ultrasound. Delivery occurred between 35 and 42 weeks of gestation. Mean weight was 3417 ± 622 g (74th centile), mean height 49 ± 3 cm (55th centile), and mean HC 35 ± 2 cm (73th centile). Cardiac abnormalities were diagnosed postnatally in 53 % of infants.

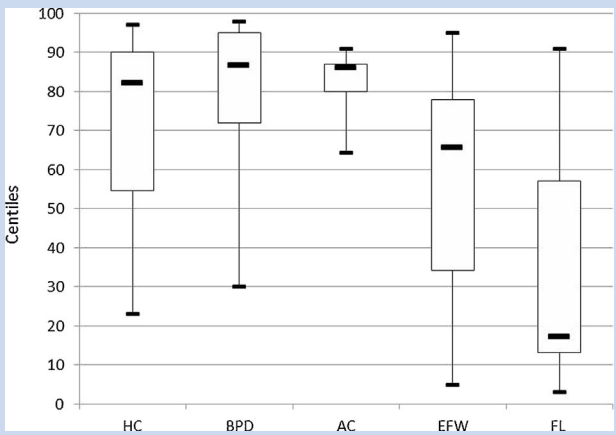

FIG. 1. Graphic representation of fetal measurement during second trimester in centiles (based on the of the French fetal ultrasound college represented as a box plot). HC, head circumference; BPD, biparietal diameter; AC, abdominal circumference; FL, femoral length; EFW, estimated fetal weight.

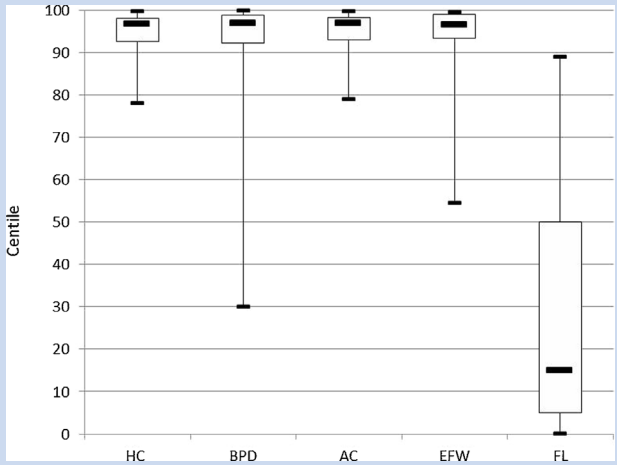

FIG. 2. Graphic representation of fetal measurement during third trimester in centiles. (based on the of the French fetal ultrasound college represented as a box plot). HC, head circumference; BPD, biparietal diameter; AC, abdominal circumference; FL, femoral length; EFW, estimated fetal weight.

DISCUSSION

CFCS is clinically and genetically heterogeneous. Patients harboring *BRAF* mutations, accounting for 75% of molecularly characterized CFCS patients, may have severe neurological outcome [Yoon et al., 2007]. As NS is far more frequent than other RASopathies, prenatal features of NS have been reported by several authors, who identified potential predictive factors of poor prognosis [Menashe et al., 2002; Schlüter et al., 2005; Houweling et al., 2010; Bakker et al., 2011; Baldassarre et al., 2011; Croonen et al., 2013; Gaudineau et al., 2013; Myers et al., 2014]. Abnormal prenatal findings are present in approximately half of NS patients [Baldassarre et al., 2011]. Most commonly, features are increased nuchal translucency or cystic hygroma, reported in 30–53%, and polyhydramnios, in 38–57%. Various non-specific USS findings have also been reported, such as hydrothorax, renal anomalies, and ascites [Schlüter et al., 2005; Houweling et al., 2010; Myers et al., 2014]. Interestingly, CHDs, which affect 60% of NS, are poorly detected in utero [Menashe et al., 2002; Bakker et al., 2011; Myers et al., 2014].

In CS, increased birth weight is a diagnostic criterion. In most patients, the pregnancy is marked by polyhydramnios, fetal overgrowth, and relative macrocephaly [Van den Bosch et al., 2002; Hennekam, 2003; Kuniba et al., 2009; Lin et al., 2009; Smith et al., 2009; Myers et al., 2014]. This combination is rather non-specific. In such a context, abnormal positioning of wrists, fetal arrhythmia (fetal paroxysmal tachycardia), or characteristic facial features are additional clues for the diagnosis of CS [Lin et al., 2009; Myers et al., 2014]. Unlike NS, increased nuchal translucency is rarely reported in CS (from 2 to 5%) [Lin et al., 2009]. Discordance between cephalic and abdominal parameters above the 75th and 90th centiles and femoral length at the 25th centile was noted in a previous report [Van den Bosch et al., 2002]. Lin et al. [2009] reported shortened long bones in 4–29% of patients with *HRAS* mutation. This sign is not mentioned by Smith et al. [2009]. However, in an updated version of their series, the same authors reported that 37% of 28 fetuses had short femora [Rauen et al., 2008].

Contrasting with NS and CS, little data is available on prenatal CFCS. Of the two patients reported by Witters et al. [2008] only one had a *BRAF* mutation. This fetus had macrocephaly, macrosomia, relatively short femurs, and bilateral pyelectasia. In a series of 140 patients with *BRAF* mutations compiled by Allanson et al. [2011], polyhydramnios was reported in 62% and macrosomia in 34%, without further details. Of the nine patients reported by Myers et al. [2014] 1/9 (11%) had macrocephaly, 2/9 (22%) had HC above the

90th centile, and polyhydramnios was present in 8/9 (89%). Femoral length was not recorded. In our series, 13/16 pregnancies (81%) showed abnormal findings. Incidence of polyhydramnios is consistent with literature data. Macrosomia and macrocephaly were present in more than 75% of fetuses. Interestingly, we observed a trend to femoral shortening. A similar pattern of growth was previously reported in CS fetuses. Hydronephrosis or pyelectasia were reported in 47%.

CFC patients with *BRAF* mutations show a pattern of developmental anomalies in utero similar to CS and NS. When compared to those found in NS, prenatal anomalies are more frequent and more severe in CFCS and CS. In contrast, increased nuchal translucency, which occurs in half of NS patients, is not a frequent finding in CS and CFCS. In all three conditions, CHDs, accounting for more than half of patients postnatally, are usually undiagnosed in utero [Achiron et al., 2000; Menashe et al., 2002]. Prenatally, most CFCS and CS show a similar non-specific combination of macrocephaly, macrosomia, and polyhydramnios, contrasting with relatively short femora. This pattern of growth parameters could be a good clue for suspecting CS or CFCS in an overgrown fetus. In both conditions, prenatal diagnosis would allow accurate parental counseling, pregnancy management, and anticipation of neonatal management. Molecular diagnosis of CS has a very high positive prediction value, as—by definition—the diagnosis is ruled out if *HRAS* sequence is normal. Conversely, molecular genetic testing of CFCS is tricky, due to genetic heterogeneity. Moreover, there is a clinical overlap with NS. We suggest that panel screening of CS and CFCS or all RASopathy genes could be proposed in the presence of the paradoxical association of abdominal circumference greater than the 90th centile, femur at/or below the 10th centile and polyhydramnios.

CONCLUSION

Prenatal presentation of CFCS was most often characterized by polyhydramnios with macrosomia, confirming the results of previous studies [Witters et al., 2008; Allanson et al., 2011; Myers et al., 2014]. In addition, most of CFCS fetuses showed paradoxical femoral shortening, contrasting with high cephalic and abdominal parameters. We suggest that a panel of RASopathy genes screening could be proposed in the presence of this unusual pattern of growth parameters.

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