Clinical Report

Beare-Stevenson Syndrome: Two South American Patients With FGFR2 Analysis

Rosa Andrea Pardo Vargas,1* Gustavo Henrique Boff Maegawa,2 Silvia Castillo Taucher,1 Júlio César L. Leite,2 Patricia Sanz,1 Juan Cifuentes,3 Mauro Parra,1 Hernán Muñoz,4 Carlos Magno Maranduba,5 and Maria R. Passos-Bueno5

1Sección de Genética, Hospital Clínico Universidad de Chile, Santiago, Chile
2Servicio de Genética Médica, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil
3Departamento de Obstetricia y Ginecología, Clínica Davila, Santiago, Chile
4Departamento de Obstetricia y Ginecología, Hospital Clínico Universidad de Chile, Santiago, Chile
5Centro de Estudos do Genoma Humano, Universidade de Sao Paulo, Sao Paulo, Brazil

We report two patients with Beare-Stevenson syndrome. This syndrome presents craniosynostosis with or without clover-leaf skull, craniofacial anomalies, cutis gyrata, acanthosis nigricans, prominent umbilical stump, furrowed palms and soles, genital and anal anomalies. Both female newborn patients presented at birth with craniofacial anomalies, variable cutis gyrata in forehead and preauricular regions, prominent umbilical stump and anogenital anomalies. Furrowed palms and soles were also observed. The radiologic examination showed a cloverleaf-form craniosynostosis. Chromosomes were normal. They were born with respiratory distress and were connected to mechanical ventilation for ventilatory support. Both of them died in 50 days after birth due to secondary complications. The molecular analysis of these patients identified the mutation Tyr375Cys in the FGFR2 gene.

INTRODUCTION

The Beare-Stevenson syndrome (BSS) is characterized by cutis gyrata, acanthosis nigricans, craniosynostosis, ear defects, anogenital anomalies, skin/mucosal tissue tags, and prominent umbilical stump [Hall et al., 1992]. It was first described by Beare et al. [1969] and 9 years later Stevenson et al. [1978] reported a similar case. In 1992, Hall et al. discussed Beare-Stevenson cutis gyrata syndrome reporting four patients [Hall et al., 1992].

Recently, evidence was presented that Beare-Stevenson syndrome [MIM 123709] is caused by a mutation of the FGFR2 gene and two different mutations were identified [Przylepa et al., 1996; Krepelová et al., 1998; Wang et al., 2002]. Twelve cases of this syndrome have been previously reported [Beare et al., 1969; Stevenson et al., 1978; Hall et al., 1992; Andrews et al., 1993; Bratanic et al., 1994; Ito et al., 1996; Przylepa et al., 1996; Krepelová et al., 1998; Hsu et al., 2001].

We describe two infants with craniofacial anomalies, craniosynostosis, cutis gyrata, choanal atresia, prominent umbilical stump, anogenital anomalies, and excessive furrowed palms and soles. A molecular analysis in the FGFR 2 gene of both patients revealed the Tyr375Cys mutation.

CLINICAL REPORTS

Patient 1

The propositus was the female product of a 39-weeks gestation born in Santiago (Chile) to a 28-year-old mother and a 36-year-old father. The couple was unrelated and there was no history of X-ray exposure. She developed Varicella at 8 weeks pregnancy without fever. Her 5-year-old brother is normal. There was no family history of mental retardation or congenital malformations. Conventional sonography (Toshiba Eccose SSA 340-A Doppler Color) at 24 weeks gestation, revealed a
single fetus with cloverleaf skull and depressed nasal bridge (Fig. 1a). Three-dimensional sonography (Kretz, Voluson 7300) showed ocular proptosis and depressed nasal bridge.

Delivery was by cesarean section due to an anterior cesarean section and diagnosis of fetal malformations. At birth, weight was 3,130 g (50th centile), length was 49 cm (50th centile), and head circumference was 31 cm (25th centile). Apgar score was 2 and 8 in the 1st and 5th min, respectively. Physical examination of the newborn showed craniofacial anomalies as cloverleaf skull, ocular hypertelorism, severe ocular proptosis, low nasal bridge (Fig. 1b,c), downsllanting palpebral fissures, midface hypoplasia, anteverted nares, bifid uvula, medial alveolar cyst, and rotated ears with preauricular creases. The umbilical stump was prominent. There was a sacral skin tag. The labia majora were hypoplastic and the labia minora were coarse and wrinkled and an anteriorly placed anus was noted. The hands had hypoplastic nails, palms and soles were furrowed, and the toe nails were narrow.

The signs of cutis gyrata became evident in the first week of life and consisted in deep vertical and diagonal creases extending across the forehead, anterior and posterior lobular area, preauricular furrows, and redundant skin on the nape of the neck.

Neonatally, because of respiratory distress she required intubation. At 7 days, she was extubated and required a tracheostomy because of intermittent high airway obstruction. Tone and activity were mildly decreased and she had continuous nasogastric tube feeding because of poor oral tolerance. Weight gain was slow but steady.

Karyotype with GTG banding and 550-band resolution was normal, 46,XX. Cranial radiographs and CT scan confirmed coronal and sagittal craniosynostosis. Lumbo-sacral ultrasonography reported anchored spinal cord. Nasolaryngoscopy revealed submucous fistula and bifid uvula.

Echocardiography showed permeable foramen ovale and mild left pulmonar stenosis.

This patient died at the age of 46 days because of cardio-respiratory arrest. No autopsy was allowed by the parents.

**Patient 2**

A female infant was the product of a 38-weeks gestation born in Porto Alegre (Brazil) to a 32-year-old African-Brazilian mother and a 30-year-old father. No history of prenatal teratogens was elicited and consanguinity was denied. Pregnancy was uncomplicated. In a previous marriage, the mother had a gestation of a female prematurely born that presented an abdominal wall defect. She died soon after birth. No more information is available. During her second marriage, she had a first-trimester spontaneous abortion before the gestation of the propositus. No history of prenatal teratogens was procured and there was no consanguinity. Onset of labor was spontaneous and delivery was by cesarean section due to failure of labor to progress. At birth, the weight was 3,090 kg (50th centile), length 47.5 cm (10th centile), and occipital-frontal circumference was

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*Fig. 1. a: Prenatal ultrasoundography of patient 1 at 24 weeks’ gestation. Note turricephaly, depressed nasal bridge, and prominent under lip. b: Facial characteristics of patient 1 at the age of 5 days. Note turricephaly, ocular proptosis, mildface hypoplasia, prominent under tip, preauricular and auricular creases. c: Frontal view of patient 1.*
31 cm (10th centile). Apgar scores were 4 and 7 at 1st and 5th min, respectively. Soon after birth, she presented cyanosis, respiratory distress and bilateral choanal atresia was diagnosed. Immediate intubation was necessary.

At clinical examination, a frontal and bilateral parietal prominence and wide anterior fontanel (6 × 5 cm) gave the appearance of a cloverleaf skull. Cutis gyrata in frontal and preauricular regions was observed (Fig. 2). Other craniofacial defects were ocular proptosis, ocular hypertelorism, low nasal bridge, large nasal root, bilateral choanal atresia, high and narrow palate, gum hypertrophy with some gingival tags (Fig. 3). The umbilical stump was prominent. The palms and soles were furrowed and hyperkeratotic. No acanthosis nigricans was detected at careful clinical observation.

The skull radiographs confirmed a cloverleaf skull with synostosis of coronal, sagital, and lambdoid sutures. Echocardiography was normal. The neurosurgeon performed a clinical evaluation and defined that there was no urgency in craniosynostosis correction. Chromosome analysis with GTG banding, was normal, 46,XX at 550-band resolution.

During the neonatal period, the patient needed continuous ventilatory support. In the first days of live, choanal atresia was surgically corrected. She had a cardio-respiratory arrest at 21 days of life and died. Family denied autopsia.

MOLECULAR ANALYSIS

In patient 2, DNA was extracted from peripheral lymphocytes using standard protocols [Miller et al., 1988] while in patient 1 DNA was obtained from buccal cells using the QiAmp DNA mini kit (Qiagen, Inc., Valencia, CA).

We amplified exon 10 of the FGFR2 gene using the primer pair (Forward primer: 5’-TCAGTCTGTTGCTGC-TAACTCTATG-3’; Reverse primer: 5’-TCCGACGG-GATACGTGGTG-3’), and PCR conditions previously described [Przylepa et al., 1996]. PCR products were directly sequenced in both directions using an ABI 377 Prism Model 377 (Applied Biosystems, CA) and the Big Dye Terminator Cycle Sequencing Kit (PE Biosystems, Foster City, CA).

RESULTS

Sequencing of the PCR product revealed an A to G transition resulting in a Tyr to Cys substitution at codon 375 (Tyr375Cys).

Reference, sex, presence or absence of the characteristic findings of the physical examination of the patients with BSS, results of the cytogenetic study, age of death and results of the molecular analysis of our two patients and twelve previously described patients [Beare et al., 1969; Stevenson et al., 1978; Hall et al., 1992; Andrews et al., 1993; Bratanic et al., 1994; Ito et al., 1996; Przylepa et al., 1996; Krepelova et al., 1998; Hsu et al., 2001] are summarized in Table I.

DISCUSSION

Beare et al. [1969] described a boy with hypertelorism, alternating divergent strabism, reduced tear formation, corrugation of skin (defined as cutis gyratum), cleft soft palate, bifid uvula, gingival hypertrophy, pigmentation of skin (defined as acanthosis nigricans), hypertelorism in the axillas, groins, genitalia, upper thighs, and perineal area. The differential diagnosis included Donohue syndrome, Seip syndrome, and a case of variant “leprechaunism” described by Patterson and Watkins [Patterson and Watkins, 1962]. Later, Stevenson et al. [1978] published a similar case of an infant who presented cutis gyratum of the face and limbs, acanthosis nigricans, prominent eyes with hypertelorism, cleft palate, dental anomalies, umbilical protrusion, and bifid scrotum. The patient reported by Beare et al. was diagnosed at 4 years of age and died at 13 years of age after an anaesthetic procedure [Hall et al., 1992]. The one described by Stevenson died at 40 days of life because of septicemia [Stevenson et al., 1978].
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<th>Case</th>
<th>Sex</th>
<th>Craniofacial features</th>
<th>Ocular hypertelorism</th>
<th>Palate anomalies</th>
<th>Cutaneous skin tags</th>
<th>Ananthosis nigricans</th>
<th>Anogenital anomalies</th>
<th>Anteriorly placed anus</th>
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M, male; F, female; (+), present; (−), absent; NM, not mentioned; (abn pos), abnormal positioned; N, normal; ABN, abnormal.

*Mutation in FGFRII gene.*
Beare-Stevenson cutis gyrata syndrome needs to be
differentiated from conditions with cutis gyrata (cerebriform intradermal nevus, microcephaly and other CNS anomalies, inflammatory dermatosis, trauma), acanthosis nigricans (neoplasias, insulin-resistance, drug-induced type, other syndromes), abnormal umbilical area (Rieger syndrome, Robinow sequenc, and Aarskog syndrome), and skin tags (isolated, oculoauriculovertebral spectrum, autosomal dominant peri-follicular fibromas and skin tags, Pai syndrome, frontonasal dysplasia, and tuberous sclerosis) [Hall et al., 1992].

Hall et al. [1992] reviewed four cases of BSS and made a clinical comparison with two cases described previously by Beare and Stevenson. Andrews et al. [1993] described a case of a Brazilian-male-infant that presented several characteristic features of Beare-Stevenson syndrome. This patient did not have craniosynostosis or cloverleaf skull, but other anomalies such as absence of skin in several locations and dental anomalies were encountered. This is the only patient whose karyotype showed an abnormality, namely 46,XY,t(7,18)(q35,q21).

Bratanic et al. [1994] described a girl born from an in vitro fertilization procedure from a 30-year-old primipara and 43-year-old husband with clinical description of Beare-Stevenson syndrome. This patient presented a mild cloverleaf configuration of the skull on X-ray. She died at 3 months of age after a craniofacial surgery. Ito et al. [1996] reported a case of BSS presenting with craniosynostosis and cloverleaf shaped skull in association with Chiari malformation. Roscoli et al. [2001] described a female infant with severe premature craniosynostosis (turricephaly, ocular proptosis, shallow nasal bridge), and a prominent umbilical stump. Cutis gyrata, deep creasing of palms and soles, and acanthosis nigricans developed later at about 6 weeks of age [Roscoli et al., 2001].

The most important features of the syndrome were present in our two patients, cloverleaf skull due to coronal and sagittal sutures synostosis, ocular proptosis and hypertelorism, palate anomalies, cutis gyrata, characterized by skin furrows with a wrinkled appearance in facial and auricular areas, and acanthosis nigricans (hyperkeratotic areas varying in color from slight discoloration to brownish) primarily in genital region. Moreover, our patient 2 showed bilateral choanal atresia.

Our patient 1 demonstrates that the prenatal diagnosis in Beare-Stevenson syndrome is difficult. With the ultrasound craniofacial images, the diagnosis of Antley-Bixler syndrome was suggested. The intraterine growth was normal as in all described cases. Hsu et al. [2001] reported the first case with prenatal two- and three-dimensional ultrasonographic findings at 32 weeks gestation with polyhydramnios and cloverleaf skull, high forehead, ocular proptosis, and prominent umbilical stump (case L). Wang et al. [2002] described the Tyr375Cys mutation at FGFR2 gene in this patient reported by Hsu.

Craniosynostosis has been present in 11 out of 14 cases including the two present patients. Hydrocephalus was encountered in three of the cases reported by Hall et al. [1992]. Acrocephalic cranial shape was described in 3 and cloverleaf skull in 9 cases. Craniosynostosis seems to be related to an unfavorable prognosis, as most patients died during or soon after the neonatal period.

Cutis gyrata was present in all patients and seems to be a very particular clinical sign of BSS. It is characterized by skin furrows with corrugated appearance. In our cases the cutis gyrata was noted in frontal and preauricular regions. There were also excessive furrows in soles and palms. It is also relevant to consider that signs of cutis gyrata get more prominent with age of the infant as in our patient 1.

Acanthosis nigricans was absent in these patients. This is one of the most striking clinical findings in BSS, and was observed in eight patients previously described. It is possible that it becomes more evident with aging.

Another finding that has been often noticed is choanal atresia. It was present in 10 cases including our patient 2, and is as common as cutis gyrata and acanthosis nigricans.

Umbilical modifications are another characteristic finding of this syndrome. It is represented by a protuberant cutaneous outgrowth of the umbilical stump. Of cases referred to in the literature, just one in Hall’s review did not show this clinical sign [Hall et al., 1992]. This author emphasizes that this feature could be found also in Rieger, Robinow, and Aarskog syndromes.

Anogenital anomalies were present in 8 of the described cases. Our patients showed an anteriorly placed anus with excessive tissue molding as it was encountered in six patients in the literature.

The chromosome studies of our patients were normal. The karyotypes were normal in all those described except from the case of Andrews et al. [1993] that showed 46,XY,t(7,18)(q35,q21).

The mutation in FGFR2 gene, Tyr375Cys, found in our patients is identical to that detected previously in four patients (cases F, J, K, and L). Przyplea et al. [1996] also found an Ser372Cys mutation in a fifth patient (case B), the original patient of Stevenson et al. [1978]. They did not find a mutation in FGFR2 gene nor in FGFR3 gene in patients C and E. They suggest that the creation of the new cysteine residue at the N-terminal end of the transmembrane domain probably severely alters the function of the receptor [Przyplea et al., 1996]. Roscoli et al. [2001] describe a P250R missense mutation in FGFR3 gene in a father and his daughter affected with premature calvarial synostosis and epidermal hyperplasia, what they call Beare-Stevenson-like anomalies, suggesting that activated FGFR receptors stimulating common downstream developmental pathways, result in overlapping clinical features.

Study of additional patients will validate the clinical phenotype and confirm the association with mutations in FGFR2 gene, clarifying if involvement in FGFR3 gene is a true alternative for BSS. It is important to note that the mutation P250R in FGFR3 gene has already been associated with a wide spectrum of clinical phenotype [Passos-Bueno et al., 1998].
REFERENCES


