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A Case of Beare-Stevenson Syndrome with Unusual Manifestations

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Case series
Patient: —
Final Diagnosis: Beare-Stevenson syndrome
Symptoms: —
Medication: —
Clinical Procedure: Genetic analysis
Specialty: Pediatrics and Neonatology

Objective: Rare disease

Background: Beare-Stevenson syndrome (BSS) is an extremely rare genetic disorder, with fewer than 25 cases reported worldwide. This autosomal dominant syndrome has been linked to two mutations in the fibroblast growth factor receptor 2 gene (FGFR2), Tyr375Cys and Ser372Cys, both causing amino acid changes.

Case Report: BSS is characterized by a range of morphological features, some more classically associated than others, of which craniosynostosis has been almost uniformly present. Other common features include cutis gyrata, acanthosis nigricans, ear and eye defects, skin/mucosal tissue tags, prominent umbilical stump, and anogenital anomalies. This account reports what we believe to be the 25th case of BSS, and exhibits a constellation of the characteristic features similar to those previously described, including the presence of cutis gyrata, proptosis, a bifid scrotum, and hypospadias. However, craniosynostosis was not detected prenatally by ultrasound or at birth. Prenatal ultrasound may detect some dysmorphic features of BSS. Many of these features have also been associated with other genetic disorders with overlapping phenotypes.

Our case presented with the unusual features of a natal tooth and absence of craniosynostosis at birth. At birth, a diagnosis of BSS was suspected based on clinical features despite the absence of craniosynostosis. This was later confirmed with the use of molecular analysis, revealing a Tyr375Cys mutation of exon 9 of the FGFR2 gene.

Conclusions: We suggest that a normal antenatal ultrasound scan and the absence of craniosynostosis at birth should not preclude further workup for BSS if this possibility is clinically suspected.

MeSH Keywords: Acanthosis Nigricans • Congenital Abnormalities • Craniosynostoses • Receptor, Fibroblast Growth Factor, Type 2

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Background

Beare-Stevenson syndrome (BSS) is an extremely rare genetic disorder, with fewer than 25 cases reported worldwide. This autosomal dominant syndrome has been linked primarily to mutations in the fibroblast growth factor receptor 2 gene (FGFR2), especially Tyr375Cys or Ser372Cys [1]. BSS is characterized by a broad range of morphological features, some more classically associated than others, of which craniosynostosis, especially clover-leaf skull, has been almost uniformly present at birth. Other common features include cutis gyrata, acanthosis nigricans, skin tags, ear defects, and a prominent umbilical stump [1,2]. This article reports what we believe to be the 25th case of BSS, exhibiting a constellation of the characteristic features, but is one of the very few cases lacking craniosynostosis at birth, as well as having a natal tooth encompassed by a cyst.

Case Report

A male infant, twin B of monochorionic, diamniotic twins, was born at 33 weeks gestation via emergency cesarean section for preterm labor. The mother was 36 years old and the father's age was unknown. Her obstetric history was gravida 4, para 1, with a history of 2 elective terminations. Antepartum

Table 1. Comparison of clinical and laboratory findings of known cases with Beare-Stevenson syndrome*.

	Beare et al. (1969)	Stevenson et al. (1978)	Hall et al. (1992, Pt 1)	Hall et al. (1992, Pt 2)	Hall et al. (1992, Pt 3)	Hall et al. (1992, Pt 4)	Andrews et al. (1993)	Bratanic et al. (1994)	Ito et al. (1996)	Przylepa et al. (1996)	Krepelova et al. (1998)	Wang et al. (2002)
Case	1	2	3	4	5	6	7	8	9	10	11	12
Gender	M	F	M	M	M	F	M	F	F	NM	F	M
Craniofacial findings												
Craniosynostosis	–	–	+	+	+	+	-	+	+	+	+	+
Cranial shape	High forehead	Acroce-phalic	Acroce-phalic	Clover-leaf	Clover-leaf	Clover-leaf	Normal	Acroce-phalic	Clover-leaf	Clover-leaf	Clover-leaf	Clover-leaf
Palate	Cleft	Bifid uvula	Narrow	Narrow	Narrow	Narrow	High	High	NM	NM	NM	High
Head and neck												
Ocular hypertelorism	+	+	+	NM	+	+	+	+	NM	+	+	+
Ocular proptosis	–	+	+	+	+	+	+	+	+	+	+	+
Choanal atresia or stenosis	–	+	+	+	+	+	+	–	+	+	+	+
Dental												
Natal teeth	+	–	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Skin												
Cutis gyrata	+	+	+	+	+	+	+	+	+	+	+	+
Acanthosis nigricans	+	+	+	+	+	+	+	NM	NM	NM	–	+
Skin tag(s)	+	+	+	–	+	+	-	NM	+	+	NM	NM
Abdomen												
Prominent umbilical stump	+	+	+	+	–	+	+	+	+	+	+	+
Anogenital anomalies	NM	NM	NM	+	NM	+	+	NM	NM	NM	+	NM
Molecular Anaylsis	NT	Neither	Ser372Cys	NT	Neither	Tyr375Cys	NT	NT	NT	Tyr375Cys	Tyr375Cys	Tyr375Cys

Table 1 continued. Comparison of clinical and laboratory findings of known cases with Beare-Stevenson syndrome*.

	Wang et al. (2002)	Akai et al. (2002)	Izakovic et al. (2003)	Vargas et al. (2003, Pt 1)	Vargas et al. (2003, Pt 2)	McGaughran et al. (2006)	Eun et al. (2007)	Fonseca et al. (2008)	You-Chen et al. (2010)	Barge-Schaapveld et al. (2011, Pt 1)	Barge-Schaapveld et al. (2011, Pt 1)	Wenger et al. (2015, Pt 1)	Wenger et al. (2015, Pt 2)	Present Case
Case	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Gender	M	F	M	F	F	M	M	F	M	M	F	F	F	M
Craniofacial findings														
Craniosynostosis	+	+	NM	+	+	+	+	+	+	+	+	+	+	–
Cranial shape	Clover-leaf	Clover-leaf	NM	Clover-leaf	Clover-leaf	Clover-leaf	Clover-leaf	Clover-leaf	Clover-leaf	Clover-leaf	Clover-leaf	Clover-leaf	Clover-leaf	High forehead
Palate	High	NM	Bifid uvula	Bifid uvula	High narrow	High	NM	Normal	High, bifid uvula	Normal	NM	NM	NM	Normal
Head and neck														
Ocular hypertelorism	+	NM	NM	+	+	NM	+	+	+	+	+	NM	+	+
Ocular proptosis	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Choanal atresia or stenosis	+	NM	NM	NM	+	+	NM	NM	+	+	+	+	+	+
Dental														
Natal teeth	NM	NM	NM	NM	NM	NM	NM	NM	+	NM	NM	NM	NM	+
Skin														
Cutis gyrata	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acanthosis nigricans	+	NM	+	NM	-	NM	+	NM	+	NM	-	NM	NM	+
Skin tag(s)	NM	+	NM	+	+	+	+	NM	+	NM	NM	+	+	+
Abdomen														
Prominent umbilical stump	+	+	+	+	+	+	NM	+	+	NM	+	+	+	+
Anogenital anomalies	NM	NM	NM	+	+	+	NM	+	-	+	+	+	+	+
Molecular Anaylsis	Tyr375Cys	Tyr375Cys	NT	Tyr375Cys	Tyr375Cys	Tyr375Cys	Tyr375Cys	Ser372Cys	Neither	Tyr375Cys	Tyr375Cys	Tyr375Cys	Ser372Cys	Tyr375Cys

* M – Male; F –Female; '+' – present; '--' – mentioned absent; NM – not mentioned, NT – not tested. Adapted from You-Chen et al. (2010).

history included moderate polyhydramnios detected at the 26th week of gestation. Normal sequential maternal screen including normal nuchal translucency for both twin A and B was reported. The mother declined additional prenatal genetic testing. There was no evidence of antenatal craniosynostosis on a fetal sonogram at 31 weeks gestation.

Twin A was a still-born with severely macerated skin and an edematous body, at weight of 1945 gm (48th percentile) and length of 45.7 cm (78th percentile). Birth weight of twin B was 2470 gm (94th percentile), 44.4 cm in length (60th percentile) with a head circumference of 34 cm (99th percentile). Apgar scores were 1, 3, and 5 at 1, 5, and 10 minutes, respectively. The patient was transferred to our neonatal intensive care unit.

Table 2. Summary of clinical findings in known cases of BSS*.

	Known cases (if mentioned) **	Percentage	Our case
Craniofacial findings			
Craniosynostosis	20/23	87	–
Cloverleaf shape	22/23	96	–
Head and neck			
Ocular hypertelorism	18/18	100	+
Ocular proptosis	23/24	96	+
Choanal atresia	17/19	89	+
Natal teeth	2/22	9	+
Abdomen			
Prominent umbilical stump	21/23	91	+
Anogenital anomolies	21/23	91	+
Skin			
Cutis gyrata	24/24	100	+
Acanthosis nigricans	13/15	87	+

* '+' – Present, '–' – absence; ** summary of mentioned findings in 24 BSS cases previously reported.

Physical examination revealed craniotabes with a widely separated sagittal suture, an enlarged anterior fontanelle extending over the nasal bridge, and frontal bossing with cutis gyrata over the forehead and bilaterally in the preauricular areas. The infant's mid-facial region showed severe proptosis bilaterally and ocular hypertelorism, a flattened nasal bridge, and low-set anterior and posterior hairlines. He was also noted to have hypoplastic nipples, a bifid scrotum, and hypospadias. The palms and soles bilaterally had thickened skin with deep creases, and the fingers were short. The back was intact with bogginess over the lower lumbosacral area of the spine. The patient was intubated immediately after birth due to respiratory distress. On day two of life, otolaryngology was consulted due to difficulty passing a suction catheter through both nostrils. Suspected bilateral choanal atresia was confirmed with a CT scan, which also revealed bilateral intraventricular hemorrhage but no evidence of craniosynostosis.

The patient was subsequently transferred to another facility for specialized surgery for repair of choanal atresia. However, this was unsuccessful due to mid-face hypoplasia. Tracheostomy was placed and the baby was transferred back to our NICU for further management. The patient was discovered to have a natal tooth encompassed by a cyst, which required extraction. Pathology revealed normal human tooth histology. The remainder of his course was significant for development of hydrocephalus secondary to aqueductal stenosis. Due to these findings, the patient was transferred for neurosurgical evaluation.

BSS was suspected clinically and confirmed by sequence analysis of the FGFR2 gene, which revealed a heterozygous Tyr375Cys missense mutation of exon 9. This mutation has been reported in other cases of BSS (Table 1). The mutation was not tested for in twin A because further testing and autopsy was declined by the parents. Genetic counselling was then provided to the parents in regards to screening for future pregnancies.

Discussion

Beare-Stevenson syndrome (BSS) was first described in 1969 in an infant who displayed a unique constellation of features [3]. This constellation included craniosynostosis, cutis gyrata, hypertelorism, choanal atresia, cleft palate, premature eruption of teeth, acanthosis nigricans, hypoplastic nipples, and bifid scrotum. In 1986, D.W. Smith Workshop delineated the features from the six cases reported at that time, and named the condition Beare-Stevenson cutis gyrata syndrome [1,2]. Defined features of the syndrome included craniofacial anomalies (particularly craniosynostosis), cutis gyrata, acanthosis nigricans, skin/mucosal tissue tags, ear defects, prominent umbilical stump, and anogenital anomalies. BSS has been linked to mutations in the fibroblast growth factor receptor 2 (FGFR2) gene, most commonly Tyr375Cys but also Ser372Cys, although other mutations in FGFR2 have been reported [4–6]. Both are missense mutations that are thought to cause constitutive activation of FGFR2 isoforms. This ultimately results in upregulation of signal transduction pathways involved in skeletal and skin development [6]. Here, we report a case of BSS that exhibits all

of the classic features seen in the original cases that defined this genetic disorder except for the absence of craniosynostosis at birth and the unusual manifestation of a natal tooth [7]. These uncommon findings are compared with the findings in previously reported cases in Tables 1 and 2. Although BSS has not been classically associated with advanced parental age, this possible association can be investigated in future cases as data is not readily available from previous cases.

Conclusions

Since the delineation of BSS in 1986, the pattern of anomalies described in reported cases has remained notably similar. Since these clinical characteristics have also been associated with a variety of other genetic disorders with overlapping phenotypes, and there is some variation in the presentation of BSS (Tables 1 and 2), clinical suspicion of BSS should be confirmed using molecular mutation analysis. This is especially true in the absence of typically reported features such as craniosynostosis at birth. Given the relatively small number of reported cases, it is difficult at this time to make definitive phenotypic/genotypic correlations for BSS.

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