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Transient QT Interval Prolongation in an Infant With Simpson–Golabi–Behmel Syndrome

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TO THE EDITOR:

Simpson–Golabi–Behmel syndrome (SGBS, OMIM #312870) is a rare X-linked overgrowth syndrome resulting from mutations in the *GPC3* gene [Pilia et al., 1996]. SGBS is characterized by pre- and post-natal macrosomia, coarse facial features, varying degrees of intellectual impairment, cardiac and hand abnormalities, and an increased risk of embryonic cancers. Diagnosis in these patients can be challenging due to variability in clinical presentation, a small number of known patients, and overlap with other syndromic conditions. Timothy syndrome (OMIM #601005), also known as type 8 long QT syndrome (LQT8), is one of many syndromes that shares some common features with SGBS. Timothy syndrome is a cardiac channelopathy caused by a mutation in the *CACNA1C* gene of 12p13.3 resulting in marked QT interval prolongation and risk for sudden death [Splawski et al., 2004]. Additional clinical findings in Timothy syndrome include syndactyly, congenital heart disease, immune deficiency and cognitive abnormalities. We report on a male infant who presented elsewhere with transient QT interval prolongation and syndactyly that prompted an initial diagnosis of Timothy syndrome rather than the subsequent clinically suspected and genetically confirmed diagnosis of SGBS. We also describe the phenotype of his carrier mother and his prenatal findings that may be characteristic of SGBS and could potentially help in prenatal diagnosis.

The white male infant was born to a 35-year-old gravida 1 para 0 mother. First trimester screening revealed increased nuchal translucency, and subsequent chorionic villus sampling at 12 weeks gestation revealed a normal 46,XY karyotype. Fetal macrosomia and an enlarged abdominal cavity were noted on prenatal ultrasound at 20 weeks gestation, and maternal alpha-fetoprotein level was elevated. No other fetal anomalies were noted, and a fetal echocardiogram at 25 weeks gestation was unremarkable.

The male infant was born via cesarian due to fetal macrosomia at 38 1/7 weeks gestation. Both weight and length at birth exceeded the 97th centile for gestational age. Multiple anomalies were noted at birth, including hypoplastic index fingers bilaterally, post-axial

polysyndactyly of the right hand, a submucosal cleft palate and bifid uvula. Complete physical findings are listed in Table I. A post-natal rhythm strip on a cardiac monitor showed intermittent sinus bradycardia and suspicion for prolonged QT interval. A 12-lead electrocardiogram (ECG) confirmed QT prolongation during the first week of life. Post-natal echocardiogram was unremarkable.

Because of the prolonged QT interval and hand abnormalities, a diagnosis of Timothy Syndrome (TS1 or LQT8) was rendered elsewhere and the parents were counseled regarding the high risk of sudden cardiac death stemming from the possibility of TS1/LQT8-triggered ventricular arrhythmias. Accordingly, in the context of this diagnosis, an implantable cardioverter-defibrillator (ICD) was placed at 7 days of age. The patient was dismissed home on oral beta-blocker therapy. Genetic testing shortly after birth revealed a normal array CGH. Subsequently, genetic testing for the Timothy syndrome-susceptibility gene (*CACNA1C*) was negative as was genetic testing for the canonical LQTS-susceptibility genes.

At 6 months of age, the infant's parents sought a second opinion at the Mayo Clinic from one of its LQTS specialists. Here, continuous, electronic QTc monitoring revealed QTc values between 440–510 msec and serial, 12-lead ECGs (Fig. 1) demonstrated QTc values <460 msec, left axis deviation, and Q waves in leads II, III, and aVF, electrocardiographic features atypical for Timothy syndrome. Additionally, his dysmorphic features in general and his hand anomalies (Figs. 2 and 3) particularly were also thought to be atypical for Timothy syndrome.

Accordingly, a genetics consult was obtained to explore alternative etiologies for the patient's constellation of findings. Rather than the typical syndactyly seen in Timothy syndrome, the patient's hand anomalies consisted of post-axial polysyndactyly of the right hand, with hypoplasia of both index fingers having extra bony components causing ulnar deviation. Clinically, Timothy syndrome was replaced with a suspected diagnosis of SGBS and DNA testing of the X-linked, SGBS-susceptibility gene, *GPC3*, subsequently confirmed this clinical suspicion. In *GPC3*, the patient had a hemizygous mutation in exon 2 (c.256 C>T) resulting in a nonsense mutation annotated as p.Arg86X.

Because of this revised diagnosis, his parents opted for removal of all ICD and lead hardware and this operation was performed at 9 months of age. He is currently doing well at 19 months of age with no cardiac problems noted.

Subsequently, the patient's mother was tested and found to be a heterozygous carrier of *GPC3*-Arg86X. She was generally healthy at 35 years of age except for a history of Raynaud's phenomenon and subclinical hypothyroidism. She had generalized joint laxity and a history of multiple shoulder dislocations and forearm fractures. She was considerably taller than the other women in her immediate family but had normal body proportions including a normal arm span-to-height ratio (Fig. 4). She had dolichocephaly, a high-arched palate, macrostomia, hoarse voice, and pectus excavatum. No arachnodactyly, polydactyly or other digital anomalies were noted. Overall, her features were reminiscent of a connective tissue disorder. She gave a history of having previous abnormal ECGs, and our evaluation revealed nonspecific T-wave abnormalities with a normal echocardiogram. Her father (the proband's maternal grandfather) was of normal stature and healthy at age 76 with no clinical manifestations of SGBS, and, therefore, was not tested for the mutation. Her mother (the proband's maternal grandmother) did not harbor a mutation when tested on peripheral blood. Therefore, we assume that the patient's mother had a de novo mutation, although gonadal mosaicism or low level somatic mosaicism in either of her parents cannot be ruled out.

Prenatal findings of increased nuchal translucency and high AFP levels have been previously described with SGBS [Hughes-Benzie et al., 1994; Li and McDonald, 2008] but may remain under-recognized. Similar findings in our patient confirm that increased nuchal translucency and elevated maternal AFP levels are associated with SGBS and can be important clues to the diagnosis. Findings in the patient's mother highlight the fact that female carriers can have a recognizable phenotype, but that clinical diagnosis may be challenging due to a number of symptoms overlapping with connective tissue dysplasias. Previous reports mention carrier females having "mild" manifestations of SGBS [Golabi et al., 1984; Behmel et al., 1988; Hughes-Benzie et al., 1996], but detailed phenotypic descriptions of female carriers are sparse. It is unlikely that her nonspecific ECG abnormalities hold any clinical significance. One previous report mentions that a carrier mother had a ventricular tachyarrhythmia [Hughes-Benzie et al., 1996]. As skewed X-inactivation may result in expression of X-linked disorders in carrier females, it is possible that clinical manifestations in our patient's mother are caused by such a mechanism. However, these studies have not been pursued.

Although cardiac abnormalities including arrhythmias are a known feature of patients with SGBS, transient QT prolongation has never been described in SGBS. Lin et al. [1999] in their review of 101 cases reported that 12% of cases had any ECG abnormalities, 25% of whom had an underlying cardiovascular malformation. Out of the 29 deaths in this review, 9 (31%) were associated with a structural cardiac abnormality, and only one was associated with an ECG abnormality (partial right bundle branch block). Although previous reports indicate neonatal mortality in affected males with SGBS to be as high as 50% [Neri et al., 1988], there is no clear evidence that arrhythmias have a role in neonatal mortality without the presence of a major cardiac malformation.

In contrast, neonatal mortality due to persistent QT prolongation is high for Timothy syndrome and aggressive therapy with an ICD is not only appropriate but can be life-saving for a Timothy syndrome patient. As opposed to the myriad of prenatal and postnatal features exhibited by this patient, the key features of Timothy syndrome/LQT8 are QT prolongation and syndactyly [Splawski et al., 2004]. However, the QT prolongation seen in Timothy syndrome is usually extreme and persistent, and the syndactyly is typically bilateral cutaneous syndactyly between the 3rd, 4th, and 5th fingers or 2nd and 3rd toes, with absence of bony fusion [Marks et al., 1995a,b]. Our patient exhibited complex polysyndactyly, with bony fusion, that is not a feature of Timothy syndrome. As exemplified in this case, distinguishing SGBS from Timothy syndrome is of paramount importance.

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FIG. 1.
ECG of patient with SGBS at 9 months showing normal QT interval. Heart rate = 150 bpm
and QTc = 423.

FIG. 2. Patient with SGBS at 6 months of age. A: Note hypertelorism, epicanthal folds, coarse facial features, prominent philtrum, grooved lower lip, and macroglossia. B: Note bifid uvula and submucosal cleft. C,D: Note the X-shaped crease on foot. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

FIG. 3.

A,B: Syndactyly seen in patient with SGBS. Note post-axial polysyndactyly of right hand with bilateral extra bony prominences and ulnar deviation and hypoplasia of index fingers. C: Typical syndactyly seen in Timothy syndrome (©A.D.A.M.). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

FIG. 4. Patient's mother and maternal grandmother. A: Note maternal tall stature. B: ECG of mother showing nonspecific T-wave abnormalities. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE I**Physical Findings in Our Patient With Simpson–Golabi–Behmel Syndrome**

Physical findings in our patient with SGBS
Accessory nipple
Bifid uvula
Broad thumbs
Coarse facial features
Epicanthal folds
Grooved tongue and lower lip
Hypertelorism
Long fifth toes ^a
Macrocephaly
Macroglossia
Macrosomia
Notching of ear helices ^a
Post-axial 5–6 right-sided polysyndactyly
Short index fingers with only 2 phalanges and ulnar deviation
Submucosal cleft
Truncal hypotonia
Wide hands
X-shaped crease on palmar aspect of feet near metatarsal joints ^a

^aNot previously noted in patients with SGBS.