Management of Congenital Heart Disease Associated with Ellis-van Creveld Short-rib Thoracic Dysplasia

Devyani Chowdhury, MD[1], Katie B. Williams, MD, PhD[2], Aaron Chidekel, MD[3], Christian Pizarro, MD[4], Catherine Preedy, APN[5], Millie Young, RNC[2], Christine Hendrickson, RNC[2], Donna L. Robinson, CRNP[2], Portia A. Kreiger, MD[6], Erik G. Puffenberger, PhD[2], and Kevin A. Strauss, MD[2]

Objective To evaluate clinical outcome of patients with Ellis-van Creveld syndrome (EVC) in whom congenital heart disease (CHD) repair was delayed intentionally to reduce the risk of postoperative respiratory morbidity and mortality.

Study design This retrospective review of 51 *EVC* c.1886+5G>T homozygotes born between 2005 and 2014 focused on 18 subjects who underwent surgery for CHD, subdivided into early (mean, 1.3 months) vs delayed (mean, 50.1 months) repair.

Results Growth trajectories differed between control subjects and patients with EVC, and CHD was associated with slower weight gain. Relative to controls, infants with EVC had a 40%-75% higher respiratory rates (independent of CHD) accompanied by signs of compensated respiratory acidosis. Blood gases and respiratory rates approached normal values by age 4 years. Hemodynamically significant CHD was present in 23 children, 18 (78%) of whom underwent surgical repair. Surgery was performed at 1.3 ± 1.3 months for children born between 2005 and 2009 (n = 9) and 50.1 ± 40.2 months ($P = .009$) for children born between 2010 and 2014 (n = 9). The latter had shorter postoperative mechanical ventilation (1.1 ± 2.4 days vs 49.6 ± 57.1 days; $P = .075$), shorter intensive care duration of stay (16 ± 24 days vs 48.6 ± 44.2 days; $P = .155$), and no postoperative tracheostomies (vs 60%; $P = .028$) or deaths (vs 44%; $P = .082$).

Conclusion Among children with EVC and possibly other short-rib thoracic dysplasias, delayed surgical repair of CHD reduces postoperative morbidity and improves survival. Respiratory rate serves as a simple indicator for optimal timing of surgical repair. *(J Pediatr 2017;191:145-51).*

In 1940, Richard W. B. Ellis and Simon van Creveld described the constellation of short-limbed chondrodysplasia, polydactyly, ectodermal dysplasia, and congenital "morbus cordis" (heart disease), and coined the term *chondroectodermal* dysplasia for what is now commonly called Ellis-van Creveld syndrome (EVC; MIM# 225500).[1] McKusick et al[2] studied EVC among Old Order Amish populations during the 1960s, tracing the condition through 30 sibships and 10 generations to 1 of 4 Swiss Anabaptist founders who immigrated to the New World between 1744 and 1800. Amish pedigrees proved critical in mapping EVC to chromosome 4p16 and in 2000 the phenotype was finally linked to a homozygous splice-donor change in *EVC* (c.IVS13+5G>T).[3,4,5]

In 2015, a human phenocopy linked to *WDR35*[6] implicated aberrant sonic hedgehog (SHH) signaling in primary cilia as central to the pathogenesis of EVC.[7-13] This and other studies established EVC within the larger phenotypic series of short rib thoracic dysplasias (PS208500; SRTDs) caused by an array of genes (eg, *EVC, EVC2, WDR35, IFT172, DYNC2LI1, TTC21B, IFT80, TCTEX1D2, WDR19, NEK1, CEP120, WDR60, WDR34, DYNC2H1, KIAA0586, SRTD1, IFT140, IFT52*) that converge on the action of primary cilia and their intraflagellar transport system.[14,15] A number of these syndromes are also properly categorized as ciliary chondrodysplasias. For our purposes, we focus on the concept of the phenotypic series (ie, PS208500), because it emphasizes shared anatomic features of the shortened tubular bones, short ribs, and thoracic constriction (SRTDs) that predispose to cardiopulmonary morbidity.[16,17]

Sixty percent of neonates with EVC have congenital heart disease (CHD), especially atrioventricular septal defects, and all are born with short ribs and a long, narrow rib cage that decreases chest wall size and compliance.[2,18,19] The interplay between cardiac and respiratory pathology is the most vexing aspect of EVC and, despite advances in medical and surgical care, many affected infants still die of

CHD	Congenital heart disease
EVC	Ellis-van Creveld syndrome
Qp:Qs	Pulmonary to systemic blood flow ratio
SHH	Sonic hedgehog
SRTD	Shortened tubular bones, short ribs, and thoracic constriction

From the [1]Cardiology Care for Children, Lancaster; [2]Clinic for Special Children, Strasburg, PA; [3]Division of Pediatric Pulmonology; [4]Division of Pediatric Cardiothoracic Surgery; [5]Division of Neonatal Intensive Care, Nemours/duPont Hospital for Children, Wilmington, DE; and [6]Department of Pathology and Laboratory Medicine, The Children's Hospital of Philadelphia and Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

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respiratory failure.[19] In the report by McKusick et al,[2] 30 of 52 (58%) patients with EVC died from cardiopulmonary complications before age 6 months of age, two-thirds within the first 2 weeks of life. Little changed by 2010, when outcomes of 11 *EVC* c.IVS13+5G>T homozygotes born between 2004 and 2009 with hemodynamically significant CHD, 9 of whom underwent surgical repair within 5 months of life were reported.[19] Four (44%) died from respiratory failure by postoperative month 5 and 60% of survivors required tracheostomy.

There are similarities between EVC and other asphyxiating thoracic dystrophies within the SRTD family.[16,17,20] Although respiratory morbidity of SRTD is commonly attributed to mechanical aspects of the chest wall, murine data indicate that Evc protein, through downstream actions on Shh targets (eg, Gli2, Gli3, Foxf1), might also influence lung embryogenesis.[21-23] Whether such findings pertain to humans is unknown, but life-threatening respiratory complications associated with EVC and other SRTDs often dissipate with age, and evidence suggests that adults with EVC have normal pulmonary function.[24-26] To accommodate this distinctive pattern of early ribcage and lung development, we intentionally delayed thoracotomy for Amish patients with EVC born between 2010 and the present.

Methods

The Institutional Review Board of Lancaster General Hospital approved the study and parents consented in writing on behalf of their children. Over the last decade (2005-2014), 51 children homozygous for *EVC* c.IVS13+5G>T who had the characteristic phenotype were treated. We conducted a retrospective chart review of growth, pulmonary maturation, and clinical outcome. The same Clinic for Special Children nurse measured and recorded growth and respiratory indices during each outpatient encounter. Respiratory rates were recorded for a full minute in relaxed or sleeping subjects; children on chronic supplemental oxygen remained so during respiratory measurements.

Thirty children (59%) were born with CHD and 18 (35%) underwent surgical repair. The latter were divided into 2 temporal cohorts (**Figure 1**): 1 born between 2005 and 2009 (n = 9) and the second born between 2010 and 2014 (n = 9; mean age, 5.4 ± 3.1 years; range 0.9-12.5; 47% female). We used the Student *t* test and Fisher exact test (Prism 6, GraphPad, La Jolla, CA) to compare them.

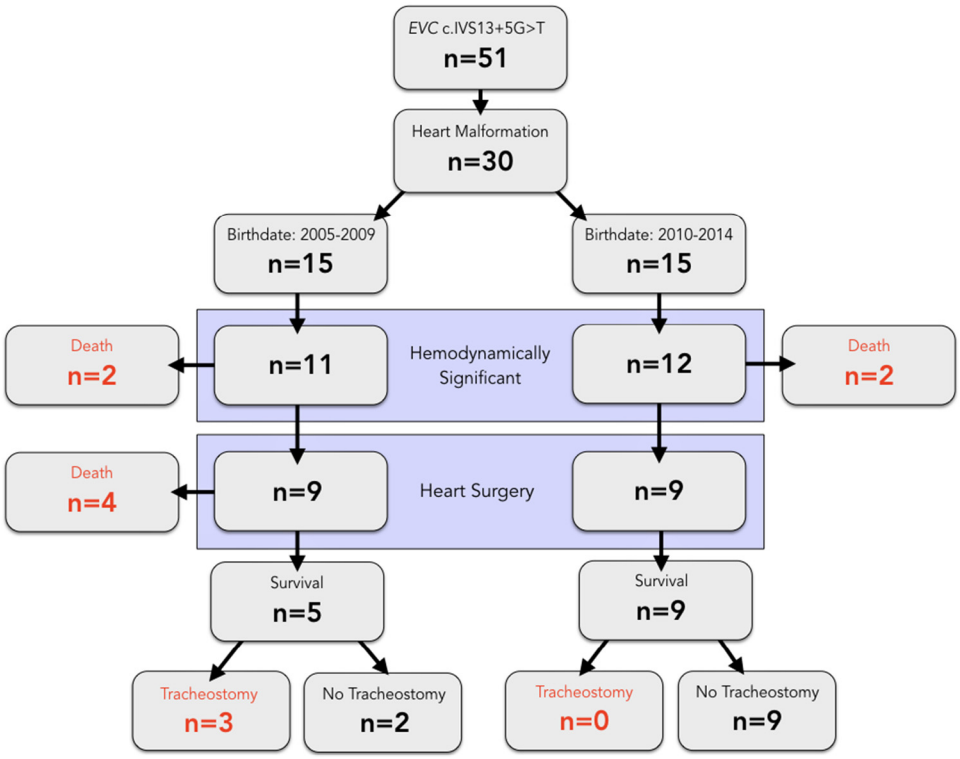

Figure 1. Fifty-one *EVC* c.IVS13+5G>T homozygotes were diagnosed at a single center (Clinic for Special Children) and divided into 2 cohorts based on the strategy for managing hemodynamically significant CHD. Affected children born between 2005 and 2009 were managed using conventional guidelines for the timing of surgical repair, which occurred at an average of 1.3 ± 1.3 months and was associated with high postoperative respiratory morbidity (78%) and mortality (44%). For affected patients born between 2010 and 2014, surgery was delayed an average of 50.1 ± 40.2 months, and there were no postoperative deaths or tracheostomies.