INTRODUCTION

Perspectives on the Care and Advances in the Management of Children With Trisomy 13 and 18

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The trisomy 13 and trisomy 18 syndromes are important and relatively common chromosome conditions each consisting of a recognizable pattern of multiple congenital anomalies, an increased neonatal and infant mortality, and a marked cognitive and motor disability in older children. Because of the medically serious nature of the outcomes, the traditional approach to management in the newborn and early infancy periods has been to withhold technological support and surgery. In the last decade a rich dialogue has emerged in the literature; one view makes the case for pure comfort care for the benefit of the child while the other view supports full intervention in appropriate situations. The principal aim of the series of articles in this issue of the Seminars in Medical Genetics is to enrich and continue this emerging dialogue. The papers include review articles, original research, and commentaries that discuss perspectives on the care and advances in the management of children with the trisomy 13 and 18 syndromes. © 2016 Wiley Periodicals, Inc.

How to cite this article: Carey JC, Kosho T. 2016. Perspectives on the care and advances in the management of children with trisomy 13 and 18. Am J Med Genet Part C Semin Med Genet 172C:249–250.

Trisomy 18 (Edwards syndrome) and trisomy 13 (Patau syndrome) represent the second and third most common autosomal trisomy syndromes after trisomy 21/Down syndrome. The combined total prevalence, that is, elective termination of pregnancies, stillbirths and live births, is approximately 1 in 1,800, making the occurrence of a fetus or baby with either of these conditions a relatively common event. In the US alone, over 2,000 families annually will have a pregnancy with one of these two disorders and experience their implications. The conventional approach to management of newborns and infants with both of the syndromes has traditionally been a withholding of technological support and surgery with the provision of pure comfort care. In this regard one of the authors (JCC) has indicated in a recent review paper that there is an active dialogue on this topic emerging primarily in the pediatrics, bioethics, and medical genetics literature [Carey, 2012]. In this discourse, various authors have suggested a more balanced view in the approach to initial and ongoing management of neonates and infants [Carey, 2012; Kosho et al., 2013; Bruns and Martinez, 2016; McCaffrey, 2016; Nelson et al., 2016]. Alternatively, other authors have made the case for holding off on intervention for various reasons including "the best interest of the child" [McGraw and Perlman, 2008; Merritt et al., 2012]. These contrasting views have created what was referred to by one of the papers in this series [Andrews et al., 2016] "a palpable tension."

The trisomy 18 and 13 syndromes are particularly unique among multiple congenital anomaly/intellectual disability syndromes for three reasons: The notably high frequency of medically significant congenital malformations, especially of the cardiovascular system but also other major congenital anomalies; the well-documented increased neonatal and infant mortality indicating that approximately 50% of newborns with these conditions die in the first week of life; and the occurrence in older children with the trisomy 13 and 18

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Conflicts of interest: The authors declare no conflicts of interest but do indicate that both are medical advisors for parent support groups for these syndromes.

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DOI 10.1002/ajmg.c.31527
Article first published online in Wiley Online Library (wileyonlinelibrary.com).

syndromes of a significant developmental disability. While by definition, all multiple congenital anomalies/intellectual disability syndromes exhibit the first and third of these components, the unique aspects of trisomy 13 and 18 are the particularly high frequency of major anomalies coupled with the high-infant mortality.

The main purpose of the series of articles in this issue of the Seminars in Medical Genetics is to continue and to ideally expand this emerging dialogue. The first group of papers in this series deals with perspectives on care and on research studying the issue of interventions in children with trisomy 13 and 18. The second group of papers documents advances in the management of specific medical manifestations, that is, seizures and tumors.

The Commentary by McCaffrey plunges immediately into the dialogue regarding the level of care in individuals with trisomy 13 and 18. Dr. McCaffrey suggests that care of the infants with the two syndromes "mirrors the evolution as a medical community caring for individuals with trisomy 21." He goes on to discuss and argue against the use of the terms "lethal" and "incompatible with life," still commonly applied labels after initial diagnosis. His essay summarizes the key works in recent years regarding interventions. He makes a "plea for truth, transparency, and recognition of our prejudices regarding patients" with the syndromes.

This dialogue regarding the "tension" in care is continued in the Commentary by Andrews and co-authors. These authors propose a model for care in the trisomy 18 and 13 syndromes that uses "shared decision making as a foundational principle" and the pathways approach as a method. The paper reviews the chronology of thought process that led us to the current controversy. The authors provide a detailed Table ("the centerpiece" of this work) that is designed to be a guide for applying the pathways approach and shared decision making.

The ensuing three papers involve interventions, procedures, and events in children with trisomy 13 and 18. Josephsen and colleagues perform a single center review of procedures performed in children with trisomy 13 or 18 over a 15-year period. These authors show an increasing rate of procedures per patient over this period of time. Townsend and co-authors utilize the Tracking Rare Incidence Syndrome (TRIS) database and examine medical interventions and survival rate in 82 children with full trisomy 18. The authors discuss their results and its implications for future research. The last paper in this group of studies on interventions is the questionnaire study of Janvier, Farlow, and Barrington. These authors invited parents to answer a survey online and 261 participated. Most of their children had full trisomy 18 and 13. Parents demonstrated "common hopes" when they received a diagnosis of one of these conditions. Parents wanted to "meet their child alive, take their child home, be a family and give their child a good life." The authors found that the single most important factor related to mortality before going home from the hospital or before 1 year was the presence of a prenatal diagnosis of the condition. The authors suggest that "rigorous transparency regarding specific interventions and outcomes may help personalize care for these children."

The last two papers add to our understanding of the natural history and management of infants and children with trisomy 18. The first of these by Matricardi and co-authors is a multicenter study of the clinical aspects, EEG features, and neuroimaging in children with full trisomy 18 and associated epilepsy. Among other important observations, the authors demonstrate that the patients with brain malformations have a more complex seizure history and are more frequently resistant to therapy. This is the first comprehensive study of seizures in children with full trisomy 18 and lays a foundation for arriving at the best strategy to approach the treatment of seizures in individuals with the syndrome.

The other paper on natural history and management is the article by Satge and co-authors, who reviewed the literature and present the occurrence of tumors in trisomy 18. The authors show that children with the syndrome are at increased risk for hepatoblastoma and Wilms tumor. Other tumor associations in trisomy 18 are presented. Carey and Barnes accompany this article with an Editorial that summarizes the evidence for the association of Wilms tumor in the trisomy 18 syndrome and uses a parent-reported outcome database to estimate the risk for a child with the syndrome to develop the tumor.

This Seminars series strives to enrich the existing dialogue on the care and management of children with the trisomy 13 and 18 syndromes. We look forward to more work on the analysis of the variables that affect outcome in these two important conditions.

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