INTRODUCTION

Introduction to the American Journal of Medical Genetics Part C on Holoprosencephaly

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Holoprosencephaly (HPE) is a severe condition that results from failed or incomplete forebrain cleavage early in gestation. HPE occurs at the incredible frequency of approximately one in 250 conceptions, making it the most common structural brain malformation in humans. Virtually all geneticists (and many non-geneticists involved in medical care) will encounter patients with HPE in some capacity, whether it be counseling a pregnant couple suspected to have an affected fetus, diagnosing an infant, performing cytogenetic or molecular testing in a reference laboratory, or trying to understand complex questions regarding forebrain development in the research environment.

Max Muenke, one of the editors of this issue of the American Journal of Medical Genetics Part C, encountered his first patient with HPE on Rosh Hashanah in 1986, in his first on-call shift covering the clinical genetics service during his fellowship training at the Children's Hospital of Philadelphia. Little did he know that the beginning of this New Year would also mark the beginning of the next decades of research on HPE. This male newborn had semilobar HPE and an initial karyotype of 45,X. Molecular work showed a de novo translocation t(Y;18) with a deletion of the short arm of chromosome 18. Within 4 weeks, he saw two additional patients with HPE, one with a deletion del(2)(p21), and one born to a mother with diabetes mellitus, and he thought that HPE was the most common genetic condition of all.

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Sylvie Odent, the French co-editor of this issue, began to work on HPE in 1995 because of the interest in brain malformations of the genetic team of Rennes (France), the observation of several familial cases of HPE, and because of encouragement by Arnold Munnich, a geneticist at the Hospital Necker-Enfants Malades in Paris. Knowledge about the genetics of this severe malformation was still poor at the time, and an epidemiological study had provided the early basis for genetic counseling. It was also the beginning of a fruitful collaboration between USA and Europe on this subject.

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As the first patients seen by Dr. Muenke demonstrate, HPE is an extremely complex condition—clinically and etiologically—which deserves detailed study from the molecular to the population-based level. In this issue of the American Journal of Medical Genetics Part C, we have collected reviews on many aspects of the condition. We hope to provide detailed information that will be imme-

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diately helpful to practitioners engaged in diverse areas of clinical and research genetics. These analyses are written by experts representing numerous fields of study, enabling us to examine HPE through different and complementary lenses. For example, the perspectives of molecular scientists, embryologists, radiologists, clinical geneticists, genetic counselors, and affected families, all take on related topics from different perspectives. Compiling these different viewpoints can help us understand the condition as a whole, and through this collaborative effort, we can continue to shed light on the various aspects of HPE.

In this issue, we thus attempt to present a comprehensive and cohesive overview about what is known about HPE in 2010. However, we also try to highlight the many questions that need to be addressed, and endeavor not to avoid controversial or difficult subjects. While we have learned a staggering amount about this disease in the last two decades, no facet of HPE is completely understood. We cannot yet provide a satisfactory explanation for the causes of HPE in all patients. However, we continue to search for optimal methods to predict and prevent this devastating condition, and we strive to develop better treatments for affected patients and families. Much work is required to offer a better understanding of the complex pathogenesis of HPE, and we hope that this issue will demonstrate the progress that has been made, as well as act as a call to action for future work. As in all medical science, the ultimate goal of increased knowledge is to translate discoveries into patient care.

Our presentation on HPE is divided into five overlapping subject areas: history, epidemiology, embryology and molecular biology, diagnosis, and clinical management and genetic counseling. Many articles cover many of these areas as they relate to a particular component feature of HPE. Specific topics covered in this issue include the history of HPE and issues of nomenclature, which includes a discussion of some of the challenges in defining features of the condition. We also provide several articles focusing on aspects of the epidemiology of HPE. These articles consider data from a number of studies performed in diverse regions of the globe, focus on different types of etiologies, and highlight key epidemiological trends. Along these lines, the causes of HPE are extremely heterogeneous, and include cytogenetic anomalies, teratogenic exposures, and aberrant signaling in pathways of forebrain development. These discussions describe the situation from both theoretical and practical levels, and offer guidance for clinical practice as well as nuanced hypotheses pointing to future research directions.

HPE arises very early in gestation, and our articles on embryology focus on both humans and animal models in order to detail what is known about the embryology and developmental biology of HPE. We include several detailed analyses of key molecular pathways that play critical roles in the pathogenesis of HPE. These reviews are designed both to outline what is known about the genetic causes of HPE and also to present pressing questions that demand further scientific study.

In the clinical realm, we present articles that address many general aspects of the condition, and additionally provide a number of specific articles reviewing conditions that include HPE as well as other features. The causes of these conditions are overall not yet well delineated, though tantalizing clues are beginning to emerge, which may act as springboards from which new genetic discoveries can be made.

Overall, HPE is an extremely challenging condition for the clinician, both in terms of ensuring a complete diagnostic work-up and also as relates to management of the many difficult medical aspects facing affected patients and families. In order to shed light on problematic and controversial topics, we present detailed discussions so as to provide concrete and valuable information for the clinician. These discussions have been written by the clinicians from all over the world who have the most experience with HPE. We are very pleased that we have been able to collaborate with affected families, especially as relates to the topics of counseling and management.

In summary, we are confident that this issue will be useful to many individuals who encounter HPE, regardless of experience level. We hope that the reader will come away with a better understanding of the condition, which will benefit any future encounter with this syndrome and we equally hope that this issue serves as an inspiration to all who care for patients and families with holoprosencephaly.

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