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


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.

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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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