Prospective Longitudinal Studies of Infant Siblings of Children With Autism: Lessons Learned and Future Directions

Peter Szatmari, MD, Katarzyna Chawarska, PhD, Geraldine Dawson, PhD, Stelios Georgiades, PhD, Rebecca Landa, PhD, CCC-SLP, Catherine Lord, PhD, Daniel S. Messinger, PhD, Audrey Thurm, PhD, Alycia Halladay, PhD

Objective: The objectives of this review are to highlight the impact of the first decade of high-risk (HR) infant sibling work in autism spectrum disorder (ASD) and to identify potential areas of translational focus for the next decade of research.

Method: A group of clinicians and researchers in ASD working both inside and outside of the HR design met on a regular basis to review the infant sibling research, and came to an agreement on areas that had changed clinical practice and areas that had the potential to change practice with further research. The group then outlined several methodological and translational challenges that must be addressed in the next decade of research if the field is to reach its potential.

Results: The review concluded that the HR design has yielded an understanding that ASD often, but not always, begins to emerge between 6 and 18 months, with early signs affecting social communication. Research using the HR design has also allowed a better understanding of the sibling recurrence risk (between 10% and 20%). Emerging areas of interest include the developmental trajectories of social communications skills in the early years, the expression of a milder phenotype in siblings not affected with ASD, and the possibility that early intervention with infant siblings may improve outcomes for those with ASD. Important challenges for the future include linking screening to intervention, collecting large sample sizes while ensuring cross-site reliability, and building in capacity for replication.

Conclusion: Although there are significant methodological and translational challenges for high-risk infant sibling research, the potential of this design to improve long-term outcomes of all children with ASD is substantial.

Key words: autism, longitudinal, sibling, development, opportunities

J Am Acad Child Adolesc Psychiatry 2016;55(3):179–187.

Prospective longitudinal studies of infant siblings of children with autism spectrum disorder (ASD) have provided important insights into the emergence of the disorder. In this high-risk (HR) design, younger siblings of an older child with ASD are typically followed from the first year of postnatal life through to at least 36 months, the age at which ASD diagnosis is both highly reliable and stable.[1] Although the use of the HR design to study ASD is a relatively new approach, it has already led to major discoveries, including estimates of the recurrence risk for the disorder in first-degree relatives[2,3] and of trajectories of different phenotypes that constitute the disorder.

The first paper reporting results of the HR infant sibling design was published in 2012, with an increasing number of published reports through 2015. With the first decade of findings now published, a reflection on the early discoveries arising from the HR infant sibling design is presented herein, along with suggested directions for the next decade of research that emphasize translational potential. This review is meant to be a selective and high-level synthesis. It was written by both contributors and noncontributors to the HR-infant sibling literature so as to provide a balanced review of the research. More systematic reviews of findings are available elsewhere.[4-6] We begin by providing a historical background, then highlight 2 findings to illustrate the power of the HR infant sibling design to change clinical practice. Three areas are then highlighted in which emerging findings also have the potential to improve clinical practice with further research and replication. We conclude with 2 design limitations inherent in HR-infant sibling studies, along with a summary of key methodological and translational challenges that must be addressed if the HR infant sibling design is to meet its full potential in the coming decade.

HISTORICAL BACKGROUND

Studies of infant siblings of children with ASD were, in large part, motivated by 2 important findings. First, several decades of research had noted that ASD was a disorder that ran in families, and that siblings of probands with autism were at risk for developing the disorder themselves.[7] The HR design provided an opportunity to estimate the sibling risk more precisely and to explore the full range of variable expressivity of the risk genotype from a longitudinal perspective. Second, many studies had reported on the disconcerting time lag between parents' concern about the onset of the disorder (usually between 12 and 18 months)[8,9]

and the average age of diagnosis (usually between 4 and 6 years of age).[10] This time lag is associated with considerable parental distress during the search for a diagnosis.[11] ASD affects many children[10] and is associated with considerable social and economic cost.[12] There is widespread acknowledgment of the urgent need to increase knowledge about the earliest signs and symptoms of ASD to promote earlier detection, earlier intervention, and hopefully improved long-term outcomes. Recent evidence suggests that the beneficial effects of early intervention may diminish with age,[13-15] underscoring the importance of detection as early as possible. It was hoped that the HR design would provide new knowledge about early signs and symptoms of ASD to facilitate earlier diagnosis than is currently seen.

To increase knowledge about the emergence of ASD, researchers first used retrospective study designs in which data were obtained from home videotapes, medical records, and/or parent recall that focused on the early development of children already diagnosed with ASD. Studies of home videotapes of infants who later were diagnosed with ASD revealed that many of those infants displayed symptoms before or at age 12 months, including a failure to orient to name, reduced eye contact, pointing, and motor abnormalities.[16-19] Although retrospective studies generated important information about the early signs of ASD, limitations of this approach include recall bias that may affect parents' report of the onset and timing of symptom emergence. Parental recall may be influenced by many factors such as the number of previous children in the family, the time lag between the parent interview and the years being recollected, and general knowledge about child development. Furthermore, home videotapes prohibited the use of more experimental measures, such as neurophysiological and eye-tracking methods, to reveal more subtle patterns of atypical development, and could not describe patterns of developmental change (e.g., regressing, slowing, plateauing, accelerating). These limitations stimulated the implementation of longitudinal designs in which infants who were at genetic risk for ASD due to having an older sibling could be systematically followed. In the next section, an overview of some of the key findings to emerge from this HR infant sibling design that have informed clinical practice is provided.

HR INFANT SIBLING DESIGN REVEALS NEW FINDINGS THAT INFORM CLINICAL PRACTICE

Defining the Early Behavioral Markers of ASD

Some of the key initial questions that the HR infant sibling design addressed focused on the earliest age at which ASD can be reliably detected and the types of behavioral markers that may reliably differentiate siblings who eventually develop ASD from those who do not. Theoretical considerations and retrospective reports initially suggested that some of the core behavioral symptoms observed in infants with ASD, such as limited eye contact or lack of social smiling, would be present in the first year of life and would therefore enable identification of affected children earlier than previously possible. However, evidence from the infant sibling studies suggests that, on a group level, frank behavioral symptoms in the social-communication domain do not become pronounced until 12 months of age or even later.[17,18,20] Therefore, the presence of typical dyadic social-communicative behaviors such as good eye contact and socially directed smiling and vocalizations before age 12 months does not necessarily rule out the possibility of developing symptoms of ASD later on. Moreover, although it is plausible that HR siblings who are later diagnosed with ASD exhibit delays in, and atypical patterns of, social-communicative skills in the first year of life,[20,21] the deficits may be subtle and difficult to detect using existing observational methods.[22]

Two large multisite studies have focused on examining stability of early ASD diagnosis in infant siblings.[23,24] Ozonoff *et al.* examined the stability of clinical best estimate (CBE) diagnosis of ASD assigned at 18 and 24 months.[23] The study suggested that a diagnosis of ASD in an infant sibling at 18 or 24 months was extremely stable, but that many siblings who received a diagnosis at 36 months were not picked up earlier. This level of stability of the CBE diagnosis was comparable to that reported in clinic-referred samples.[25-27] In another large, multisite study, Chawarska *et al.*[24] focused more specifically on identification of behavioral signatures of ASD at 18 months. The researchers applied a decision tree learning algorithm to an array of behaviors recorded at 18 months. This analysis suggested that at 18 months, a large proportion of infant siblings who go on to develop ASD cannot be reliably identified. Among those who were identified correctly by the data mining approach, there were 3 subgroups of infants with ASD, each characterized by a different pattern of change in symptom severity over time. One of the groups was characterized by marked symptoms by 18 months that were maintained through 3 years. In the second group, relatively mild symptoms intensified by the age of 3 years, and in the third group, moderate level of symptoms was maintained from 18 to 36 months. Siblings with ASD who were missed at 18 months by expert clinicians or by the data mining algorithm showed not only lower levels of autism symptom severity but also significantly higher levels of verbal and nonverbal skills than children who were identified positively at 18 months.[24,28] Taken together, these studies suggested that around 40% of siblings with eventual ASD become symptomatic by 18 months, and in these children, stability of a diagnosis based on a comprehensive assessment is very high (93%). Based on these findings, toddlers who present with frank symptoms of ASD at 18 months should be referred for treatment, whereas the remaining siblings should be monitored. These findings also highlight the variability in the developmental trajectories of the affected children with familial risk factors and reinforce the need for monitoring development of all high-risk siblings over multiple time points in the first 3 years of life. This has important implications for screening protocols that target a single time point, and may