A Prospective Study of Autistic-Like Traits in Unaffected Siblings of Probands With Autism Spectrum Disorder

Stelios Georgiades, MA; Peter Szatmari, MD; Lonnie Zwaigenbaum, MD; Susan Bryson, PhD; Jessica Brian, PhD; Wendy Roberts, MD; Isabel Smith, PhD; Tracy Vaillancourt, PhD; Caroline Roncadin, PhD; Nancy Garon, PhD

Context: The presence of autistic-like traits in relatives of individuals with autism spectrum disorder (ASD) is well recognized, but, to our knowledge, the emergence of these traits early in development has not been studied.

Objective: To prospectively investigate the emergence of autistic-like traits in unaffected (no ASD diagnosis) infant siblings of probands diagnosed as having ASD.

Design: Two groups of children unaffected with ASD were assessed prospectively—siblings of probands diagnosed as having ASD (high risk [HR]) and control subjects with no family history of ASD (low risk [LR]). Scores on a measure of autistic-like traits at 12 months of age were used in a cluster analysis of the entire sample.

Setting: A prospective study of infant siblings of probands with ASD from 3 diagnostic centers in Canada.

Participants: The study included 170 HR and 90 LR children, none of whom was diagnosed as having ASD at age 3 years.

Main Outcome Measures: The Autism Observation Scale for Infants was used to measure autistic-like traits and derive clusters at 12 months of age. Clusters were compared on ASD symptoms, cognitive abilities, and social-emotional difficulties at age 3 years.

Results: Two clusters were identified. Cluster 1 (n=37; 14.2% of total sample) had significantly higher levels of autistic-like traits compared with cluster 2. Within cluster 1, 33 children came from the siblings (19.4% of HR group) and only 4 came from the control subjects (4.5% of LR group). At age 3 years, children from cluster 1 had more social-communication impairment (effect size=0.70; P<.001), lower cognitive abilities (effect size=−0.59; P<.005), and more internalizing problems (effect size=0.55; P=.01). Compared with control subjects, HR siblings had a relative risk of 4.3 (95% CI,1.6-11.9) for membership in cluster 1.

Conclusions: Study findings suggest the emergence of autistic-like traits resembling a broader autism phenotype by 12 months of age in approximately 19% of HR siblings who did not meet ASD diagnostic criteria at age 3 years.

tino et al\textsuperscript{23} reported that roughly 20\% of siblings from families with more than 1 case of ASD showed elevated scores on the Social Responsiveness Scale, a measure of social impairment. This was not found in families with a single affected child. These traits were surprisingly common in female siblings, narrowing the sex ratio from that usually seen in ASD. Although informative in many ways, previous studies may be limited by participation bias because they were conducted in the context of genetic research. In such studies, families with more autistic-like traits in parents or siblings might tend to enroll more commonly than families without such characteristics. In addition to ascertainment bias, previous studies may also be limited by measurement issues. In studies that rely on retrospective or cross-sectional data from a parent, the rater may be especially attuned to, and therefore report more, autistic-like traits in a sibling after receiving the diagnosis of ASD for the proband. Alternatively, a parent may deny traits in a second child to experience a sense of reassurance about that child's development. In either situation, this bias may not occur in control subjects, leading to differential misclassification\textsuperscript{10} and a bias in the estimation of sibling risk.\textsuperscript{3} Furthermore, retrospective reports do not easily address the possibility that a child may have exhibited aspects of ASD in infancy but then lost those symptoms/trait with development. For example, individuals who exhibit the BAP as adolescents or adults may in fact have had more severe symptoms in early childhood, meeting criteria for ASD earlier but subsequently experiencing a resolution or reduction of symptoms owing either to development or intervention.

The baby siblings research paradigm has generated new knowledge about the early signs and symptoms of ASD and may be able to address many of these methodologic issues.\textsuperscript{24} In this high-risk research design, families of children with a confirmed diagnosis of ASD (ie, probands) are enrolled soon after the delivery of a new baby. That child (ie, the baby sibling) is followed longitudinally with regular evaluations of social-emotional reciprocity, communication and play, and cognitive skills. Siblings who are subsequently diagnosed as having ASD (usually by 36 months of age) can be compared with high-risk unaffected siblings and a low-risk comparison group (control subjects) to identify the nature and developmental course of the earliest signs of autism using measures independent of a parent.\textsuperscript{25} The combination of prospective data collection and a blinded objective assessment provides an important justification for the use of this design to study autistic-like traits in unaffected siblings of children with ASD.

In general, baby sibling studies have demonstrated that the onset of autism-specific symptoms is usually evident after 6 months of age, up to which point siblings who later develop ASD are either largely indistinguishable from control subjects or exhibit nonspecific delays (eg, in motor control).\textsuperscript{26,27} Cardinal symptoms of ASD (eg, reduced social communication) emerge by 12 to 18 months.\textsuperscript{28} For example, our group reported that several behavioral markers at 12 months (as assessed using the Autism Observation Scale for Infants [AOSI]\textsuperscript{29}) were predictive of subsequent ASD classification in a cohort of 65 high-risk infants. These markers included atypical/
CLINICAL BEST ESTIMATE DIAGNOSIS

At 3 years of age, an independent evaluation of each participant was conducted by an expert clinician blind to assessments from previous study visits. Autism spectrum disorder diagnoses were assigned using DSM-IV-TR criteria, based on the best judgment of the clinician (all with at least 10 years of diagnostic experience), taking into account current information from the Autism Diagnostic Interview—Revised (ADI-R) and Autism Diagnostic Observation Schedule (ADOS) and concurrent assessment of cognitive, language, and adaptive skills. The 3-year ADOS was completed blind to both prior visits and risk status for every participant. Parents were asked not to reveal prior diagnoses in the younger sibling or whether they had a child with ASD. In most cases, the ADI-R was also completed by the clinician responsible for the blind 3-year assessment, although in some cases, the ADI-R was completed by an experienced research assistant who was not blind to the child’s risk status. Even in those cases, the clinician reviewed the ADI-R blind to prior visits and risk status when establishing a best-estimate clinical diagnosis. Some children with a clinical best estimate (CBE) diagnosis of ASD had subthreshold algorithm scores on the ADI-R or ADOS but met DSM-IV-TR criteria based on expert review of all available data. This approach is consistent with current best practice, informed by a solid evidence base indicating that both a structured diagnostic interview (such as the ADI-R) and interactive assessment (such as the ADOS) are essential to ASD diagnoses, but neither, on their own or in combination, are an adequate proxy for clinical judgment, particularly in this age group.

For the purposes of this study, we excluded the 52 HR children and 1 LR child who were diagnosed as having ASD at age 3 years (based on the ADI-R; ADOS; and expert clinical assessment using DSM-IV-TR, blind to prior study assessments). Thus, the study sample consisted of 170 children from the HR siblings group (84 males; 49.4%) and 90 from the LR control group (45 males; 50%) for a total of 260 children, none of whom were diagnosed as having ASD at 3 years based on CBE (eTable, http://www.jamapsych.com).

ASSESSMENT INSTRUMENTS

ASD Symptoms/Traits

The AOSI is a semistructured direct observational measure developed within the context of our longitudinal study to identify behavioral markers of autism in infancy. Standardized activities are used to allow the examiner to observe and systematically rate the occurrence/nonoccurrence as well as the quality or severity of behaviors deemed to be informative of the earliest emergence of ASD. The assessment is designed to take 15 to 20 minutes, although administration times vary depending on the infant’s ability to engage with the examiner, as well as his or her temperament, state, and developmental level. Behaviors are rated on a scale from 0 to 2 or 3, where 0 implies typical function and higher values indicate increasing deviation. Behavioral markers rated on the AOSI include visual tracking and attentional disengagement, coordination of eye gaze and action, imitation, affective responses, early social-communicative behaviors, behavioral reactivity, and sensory motor development. Ratings on the 16 items are summed to generate a total score. Further details on AOSI items and scoring are available from Bryson et al. The AOSI has excellent interrater reliability at 12 and 18 months (0.94 for total score), good test-retest reliability at 12 months (0.61 for total score), and good predictive validity at 12 and 18 months for its original 16 items. One of the coauthors of this article (L.Z.) is co-first author on a study involving a different sample investigating the relationship between AOSI scores and ASD outcomes. In the context of that study, a random sample of 54 AOSI assessments were further assessed through video coding by examiners blind to the risk status of participants to assess for rater bias. There were no differences between blind and unblind AOSI total scores, regardless of risk status (A. M. Estes, written communication, May 2012). In our current study, the total AOSI score was used as an indicator of autistic-like traits in the cluster analysis.

The ADOS uses standardized activities and pressures to elicit communication, social interaction, imaginative use of play materials, and repetitive behaviors, allowing the examiner to observe the occurrence/nonoccurrence and severity of behaviors important to the diagnosis of ASD. Subscale scores for communication and social domains are based on a subset of items previously identified to best discriminate autism/ASD from other developmental disabilities, and they are summed to generate an overall diagnostic algorithm score. The ADOS consists of 4 modules, each of which is appropriate for individuals with differing language levels. A calibrated total severity metric that accounts for differences in age and module was used in our study.

The ADI-R is an investigator-directed interview used to elicit information about social development; verbal and nonverbal communication skills; and repetitive, stereotyped interests and behaviors required to make a diagnosis of autism. The questions were designed to distinguish qualitative impairments from developmental delays, identify behaviors that would be considered deviant at any age, and examine current and most abnormal behaviors for those strongly influenced by maturational age. The ADI-R discriminates well between autism/ASD and other forms of developmental disability, and inter-rater reliability is excellent. For this study, we used domain scores for social impairment; communication skills; and repetitive, stereotyped interests and behaviors.

Cognitive Skills and Abilities

The Mullen Scales of Early Learning consists of 4 scales: visual reception, receptive language, expressive language, and fine motor (a fifth gross motor scale is only administered with children younger than 30 months). An Early Learning Composite can be calculated based on scores from these 4 scales for children aged 0 to 69 months. Inter-rater and test-retest reliability are excellent.

Emotional and Behavioral Symptoms

The Infant-Toddler Social-Emotional Assessment (ITSEA) is a parent-report instrument, with subscales covering attachment status, task mastery, emotion regulation, and coping behaviors. The acceptability, internal consistency, test-retest reliability, and validity of the ITSEA are excellent, as assessed in a diverse sample of 214 parents of typically developing children between the ages of 12 and 36 months. The ITSEA scales
correlate well with laboratory measures of emotional regulation. Domain scores of externalizing behavior, internalizing behavior, dysregulation, and competence were used in our study to index variables previously found to be associated with ASD-related symptoms in very young children.39

DATA ANALYSIS

To explore the distribution of autistic-like traits, mean total scores from the AOSI at age 12 months were compared on 3 subsamples of interest: (1) HR siblings with a diagnosis of ASD at age 3 years (HR ASD; n = 52); (2) HR siblings without a diagnosis of ASD at age 3 years (HR non-ASD; n = 170); and (3) LR control subjects without a diagnosis of ASD (LR non-ASD; n = 90). Figure 1 depicts 2 findings: (1) the distribution of autistic-like traits appeared to lie on a continuum/gradient of severity across these 3 subsamples (HR ASD > HR non-ASD > LR non-ASD; all differences were statistically significant; P < .01) and (2) there was notable heterogeneity of autistic-like traits within the 3 subsamples, and the subsample distributions appeared to overlap.

Next, to better understand the observed heterogeneity of autistic-like traits in the non-ASD population (the focus of our study), mean total scores from the AOSI at age 12 months were used in cluster analysis (K means) to test for the existence of a distinct subgroup of children with elevated scores. Our primary hypothesis was that this group would contain more HR siblings (of probands with ASD) than LR control subjects and be associated with more ASD-like outcomes at 36 months. This method used the technique of Euclidean distance to the mean of the cluster and an algorithm to minimize within-cluster variance and maximize variability between clusters in an analysis of variance–like fashion. Specifically, analysis of variance F tests were conducted to examine differences between clusters on each variable used in the analysis; the magnitude of the F value was used to evaluate how well the variable discriminated between clusters. Cluster centers shifted with each iteration. The process continued until cluster means did not shift more than a given cutoff value or the iteration limit was reached.40

A 2-cluster solution was specified to test our hypothesis that the sample consisted of 2 distinct groups/clusters: those with high and those with low levels of autistic-like traits as measured by high and low total AOSI scores. As a second step, each participant was assigned to 1 of the 2 clusters based on probability scores. Cross tabulation with χ² test was used to describe the count of individuals from the 2 clusters within the HR sibling and LR control groups and to see whether there was differential distribution of HR siblings and LR control subjects in the 2 clusters. The relative risk for cluster membership was calculated for the HR and LR groups.

Finally, t tests were used to compare cluster mean scores on independently determined (1) ASD symptoms (indexed by the ADOS severity metric and ADI-R domain scores); (2) cognitive ability (indexed by the Mullen Early Learning Composite); and (3) emotional and behavioral symptoms (indexed by the ITSEA domain scores) 29 months later at 3 years of age. Bonferroni correction for multiple comparisons was applied separately within the ASD symptoms domain (P > .01) and the emotional and behavioral domain (P > .01). Effect size (ES) was calculated for cluster mean differences on these variables using the formula:

\[ ES = \frac{\text{mean } [\text{cluster 1}] - \text{mean } [\text{cluster 2}]}{\text{standard deviation (SD)} [\text{cluster 2}]} \]

Two distinct clusters with statistically significantly different scores on the AOSI at 12 months were derived. Cluster 1 (51.4% male) had more autistic-like traits, with a total mean AOSI score of 10 (SD = 3.0) and consisted of 37 children (14.2% of total sample). Cluster 2 (49.3% male) had a total mean AOSI score of 2 (SD = 2.0) and consisted of 223 children (85.8% of total sample). The relative proportion of HR and LR infants differed between the 2 clusters (χ² = 10.8; P < .01). Within the HR group, 33 of 170 children were assigned to cluster 1 (19.4%) and 137 to cluster 2; only 4 of 90 (4.5%) of the LR group were assigned to cluster 1. Compared with LR infants, HR infants had a relative risk of 4.3 (95% CI, 1.6–11.9) for membership in cluster 1. There was no difference in the distribution of sex across clusters (P > .05).

Mean comparisons (t tests) showed that, at age 3 years, children in cluster 1 (identified at 12 months) had significantly higher scores (ie, more autistic-like behaviors) than children in cluster 2 on measures of social (ES = 0.86) and communication (ES = 0.72) impairment, as indexed by the corresponding ADI-R domains (P < .001). Children in cluster 1 also had lower cognitive levels, as indexed by the Mullen Scales of Early Learning–Early Learning Composite (ES = −0.59; P < .005). Children in cluster 1 scored higher on the internalizing problems domain of the ITSEA (ES = 0.55; P = .01). Finally, children in the 2 clusters did not differ significantly on the ADOS severity metric, although the effect was in the expected direction, with cluster 1 trending toward higher scores (ES = 0.35; P = .06) (Table).

Using prospective data, our study examined the presence of autistic-like traits at age 12 months among HR siblings (of probands with ASD) who did not go on to receive a diagnosis of ASD by age 3 years in comparison with LR control infants. A cluster/subgroup of children had elevated levels of autistic-like traits at 12 months but did not meet CBE criteria for an ASD diagnosis at 36 months. This cluster comprised approximately 19% of the HR unaffected siblings, or 15% of the entire HR group.
Table. Cluster Comparison on the ADOS, ADI-R, MSEL, and ITSEA Scores at Age 3 Years

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Cluster 1 (n = 37)b</th>
<th>Cluster 2 (n = 223)b</th>
<th>ESc</th>
<th>P Valued</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADOS Severity Metric</td>
<td>2.62 (1.86)</td>
<td>2.06 (1.62)</td>
<td>0.35</td>
<td>.06</td>
</tr>
<tr>
<td>ADI-R</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social domain score</td>
<td>3.76 (3.56)</td>
<td>1.86 (2.20)</td>
<td>0.86</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Communication domain score</td>
<td>3.22 (3.33)</td>
<td>1.66 (2.17)</td>
<td>0.72</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Behaviors domain score</td>
<td>1.24 (1.42)</td>
<td>0.84 (1.44)</td>
<td>0.28</td>
<td>.11</td>
</tr>
<tr>
<td>MSEL-ELC score</td>
<td>105.27 (20.50)</td>
<td>115.37 (17.15)</td>
<td>−0.59</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>ITSEA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Externalizing domain score</td>
<td>0.41 (0.29)</td>
<td>0.42 (0.26)</td>
<td>−0.04</td>
<td>.83</td>
</tr>
<tr>
<td>Internalizing domain score</td>
<td>0.49 (0.28)</td>
<td>0.38 (0.20)</td>
<td>0.55</td>
<td>.01</td>
</tr>
<tr>
<td>Dysregulation domain score</td>
<td>0.48 (0.30)</td>
<td>0.43 (0.25)</td>
<td>0.20</td>
<td>.32</td>
</tr>
<tr>
<td>Competence domain score</td>
<td>1.50 (0.34)</td>
<td>1.59 (0.27)</td>
<td>−0.33</td>
<td>.18</td>
</tr>
</tbody>
</table>

Abbreviations: ADI-R, Autism Diagnostic Interview–Revised; ADOS, Autism Diagnostic Observation Schedule; ELC, Early Learning Composite; ES, effect size; ITSEA, Infant-Toddler Social-Emotional Assessment; MSEL, Mullen Scales of Early Learning.
a Cluster 1 (n = 37) included 33 high-risk siblings and 4 low-risk control subjects.
b Cluster 2 (n = 223) included 137 high-risk siblings and 86 low-risk control subjects.
c Effect size = (mean [cluster 1] – mean [cluster 2]) / SD (cluster 2).
d P value cutoff set at .01 based on a Bonferroni correction for multiple testing (significant values are in bold).

Figure 2. Total mean Autism Observation Scale for Infants (AOSI) scores with standard deviation bars at 12 months of age for high-risk (HR) autism spectrum disorder (ASD), cluster 1, and cluster 2 groups. The HR ASD group scores are shown for descriptive purposes so that the cluster analysis results can be placed within the distribution/context of autistic-like traits in all HR siblings. All differences between groups are statistically significant (P < .01 for all).

Study findings suggest that autistic-like traits emerge very early (by 12 months), although children in cluster 1 ultimately experienced different outcomes than those HR siblings who were subsequently (ie, at age 3 years) diagnosed as having ASD. However, it is important to note that, with currently available data, we cannot yet confirm that these are the same children who present with the BAP at later ages (at least, as it is currently understood). For example, rigidity, pragmatic language deficits, and circumscribed interests are a prominent part of the BAP but are not relevant traits to be measured at 12 months. Moreover, we cannot say that some of these siblings will not eventually (ie, say at age 5 years) be diagnosed as having ASD. However, it would be reasonable to suggest that children within cluster 1 present with features that could reflect the earliest manifestations of a BAP; whether this phenotype is the same (qualitatively and/or quantitatively) as the one defined in older populations remains an empirical question. Our continuing follow-up investigation of this sample will address these critical issues.

The question then that arises is whether HR unaffected siblings from cluster 1 (n = 33; used in our study) and HR affected/diagnosed siblings (n = 52; not used in our study) started (at 12 months of age) with similar or different levels of autistic-like traits. As depicted in Figure 2, post hoc analysis showed that at 12 months of age, the AOSI scores for the 2 groups were significantly different (unaffected siblings from cluster 1: mean [SD] = 9.7 [2.5] vs siblings with an ASD diagnosis: mean [SD] = 7.6 [5.1]; P < .01; ES = 0.46). We believe this finding (higher score in the unaffected siblings) is owing to a statistical artifact (ie, the cluster analysis applied only to unaffected siblings data derives a subgroup with extreme scores). Nevertheless, the finding that both HR children diagnosed as having ASD at 3 years and a subgroup not diagnosed as having ASD have elevated symptom scores at 12 months relative to control subjects raises interesting questions about what factors might influence...
variation in subsequent trajectories and outcomes among the combined group of 12-month-old symptomatic HR siblings.

Our study has methodologic strengths that enhance the validity of the results compared with previous studies that retrospectively assessed the BAP in unaffected siblings recruited largely through genetic studies. We had the advantage of following up these siblings prospectively and using a reliable and valid observer-based assessment of autistic-like traits designed for infants, the AOSI. The assignment to clusters was based on information gathered prior to outcome assessments at age 3 years (which were blind to 12-month data), and we used a data-driven approach to assign children into clusters rather than using AOSI scores arbitrarily to divide the sample.

This study also has limitations that need to be taken into account. Most importantly, the assessors administering and scoring the AOSI at 12 months were on occasion not blind to HR sibling or LR control status. For example, some parents lacking a child care arrangement brought the affected older child to the appointment. In addition, the sample sizes of the clusters (especially cluster 1) were small. The fact that the ASD diagnosis at age 3 years was based on the CBE procedure means that some HR siblings (especially from in cluster 1) might in fact have had true ASD at age 3 years but may have been missed by the CBE. A descriptive analysis showed that of the 33 children in cluster 1, 4 met the ADI-R cutoff for ASD and 10 met the ADOS cutoff for ASD at age 3 years; however, none of these children met both ADI-R and ADOS criteria for ASD.

Although the cluster difference on the ADOS severity score (at 36 months) was not statistically significant (\( P = .06 \)), the ES (0.35) was in the expected direction. Several measurement issues may have influenced this result. One possible explanation is that because the ADOS severity metric used in our analyses reflects a combined score from all ASD symptom domains, it cannot distinguish children from cluster 1 who had elevated severity only on social-communication symptoms but not repetitive behaviors (Table). An alternative explanation is that some children from cluster 1 had more severe autism symptoms during infancy, but that those symptoms may have resolved by the time these children were 3 years of age. One final explanation for the lack of statistically significant cluster differences on the ADOS severity metric could be that the variability of the severity metric is (by definition) reduced in unaffected children (the metric was developed such that non-ASD scores range from 1-3, whereas ASD scores range from 4-10).

Despite the limitations just noted, results from our study, if replicated, could have important clinical and research implications. First, the results imply that genetic liability in these families is more normally distributed than restricted only to those with the disorder. Even children who do not go on to develop ASD could potentially benefit from surveillance and early intervention should there be impairment. Second, genetic, epigenetic, and environmental studies of these children might help us understand the mechanisms leading to variation in familial aggregation of ASD and related traits. Third, it will be important to follow these siblings to see whether they develop other forms of psychopathology (such as internalizing disorders), and/or whether persistent social and communication difficulties, despite being subthreshold for an ASD diagnosis, affect functional outcomes or quality of life.

The fact that the overall risk for ASD and these milder autistic-like traits now reaches almost 40% (based on a study by Zwaigenbaum et al and our study) with an equal sex ratio has implications for our understanding of the genetic architecture of the disorder. It appears as if roughly 40% of infant siblings of autistic probands have autistic-like traits at 12 months. Traits persisted in half of the group who received a diagnosis of ASD at age 3 years. In the other half, those traits attenuated to some extent so that at age 3 years, mild ASD-like traits, lower cognitive scores, and more internalizing symptoms were seen relative to LR control subjects, but these individuals fell below the diagnostic threshold for ASD. One unanswered question is, “Why do autistic-like traits persist in one group and attenuate in the other?” This question will require further research and provides a focus on studying potential modifying mechanisms that might explain the variable expressivity between the cluster 1 siblings and the ASD probands. These modifying factors might provide an opportunity for intervention in all children at risk for ASD and autistic-like traits. This study supports previous recommendations of continuous monitoring of all HR siblings of probands with ASD.

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Correspondence: Peter Szatmari, MD, Offord Centre for Child Studies, McMaster University, Chedoke Site, 1280 Main St W, Patterson Bldg, Hamilton, ON, L8S 4K1, Canada (szatmar@mcmaster.ca).

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Online-Only Material: The eTable is available at http://www.jamapsych.com.
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