

Can Asperger Syndrome Be Diagnosed at 26 Months Old? A Genetic High-Risk Single-Case Study

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ABSTRACT

Asperger syndrome, a heritable condition entailing empathy deficits together with unusually narrow interests in individuals of normal or even above-average intelligence, was recognized only recently. Here we report the first-ever prospective study of a child born to two adults with a formal diagnosis of Asperger syndrome. The child's parents are both scientists (a mathematician and a chemist). The aim of study 1 was to test if the child also developed Asperger syndrome, given the heritability of the condition, and if Asperger syndrome can be detected at 26 months. At 18 months, the child was given the Checklist for Autism in Toddlers, and at 26 months, she was assessed diagnostically for autism spectrum conditions using the Autism Diagnostic Interview-Revised and the Autism Diagnostic Observational Scale. The child failed the Checklist for Autism in Toddlers at 18 months and met the criteria for Asperger syndrome at 26 months. This single case is consistent with the hypersystemizing, assortative mating theory of autism. This theory requires further testing with large samples. This study also demonstrates that Asperger syndrome can be diagnosed by age 26 months. The aim of study 2 was to test if dyadic eye contact in infancy is intact in a child later diagnosed with Asperger syndrome. The same child's eye contact was measured at three time points (3, 6, and 9 months) over her first year of life and compared with that of age-matched controls. Although the child had low rates of eye contact at 6 months, it was within the normal range at all three points in the first year of life. We conclude that low levels of eye contact are not predictive of later development of Asperger syndrome. (*J Child Neurol* 2006;21:000–000; DOI 10.2310/7010.2006.00072).

Autism spectrum conditions affect 1 in 200 children.^{1,2} The causes are neurobiologic, including differences in brain function and structure,^{3,4} arising for genetic reasons.^{5–7} The key symptoms are difficulty in social relationships and communication and an obsessional, detailed style of information processing.^{8,9} The earliest

point that detection of classic autism has been possible is age 18 months.¹⁰ Asperger syndrome is a subgroup on the autistic spectrum with a normal IQ and normal language development. It is typically detected later and rarely before 6 years of age.¹¹ In this study, we tested if Asperger syndrome can be detected at a much younger age (26 months) than has hitherto been reported (study 1) and if eye contact in the first year of life is impaired in Asperger syndrome (study 2).

We employed a single-case, family genetic design for three reasons. First, to demonstrate that Asperger syndrome can be identified early requires only a single case. One positive demonstration is sufficient to prove that it can be done, even if issues of reliability of diagnosis at this age would require larger samples to be studied. Second, the hypothesis that eye contact in the first year is impaired in Asperger syndrome can be disproved by demonstrating in a single case that eye contact is intact. Finally, testing both the principle of early detection and the development of eye contact in a child later diagnosed with Asperger syndrome is facilitated by studying a child at high risk of developing Asperger syndrome. In the two studies reported here, we took advantage of the

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opportunity to study the development of a baby born to a couple, both of whom have Asperger syndrome and who agreed to let their baby be observed for research from birth. Such a baby was expected to be at maximum genetic risk of developing Asperger syndrome, and such a natural experiment has not previously been reported.

STUDY 1: EARLY DIAGNOSIS AND HERITABILITY OF ASPERGER SYNDROME

Although the detection of classic autism has been possible by 18 months of age,¹⁰ Asperger syndrome is rarely detected before 6 years of age.¹¹ Studies of home movies of children later diagnosed with autism spectrum conditions report abnormalities in social responsiveness as young as 12 months.¹² Assessing the child of two parents with Asperger syndrome provides the opportunity to test for Asperger syndrome at 26 months, and this opportunity is premised on Asperger syndrome being heritable. It is well established that classic autism is heritable, from both twin studies⁵⁻⁷ and molecular genetic studies.^{13,14} The evidence for Asperger syndrome being heritable is more recent. Although there has not been a twin study of Asperger syndrome, family genetic studies show that Asperger syndrome runs in families,⁶ and there has been one molecular genetic study of Asperger syndrome showing significant linkage peaks that suggest genes for Asperger syndrome.¹⁵ A twin study of quantitative Asperger syndrome traits using the Childhood Asperger Syndrome Test¹¹ also shows that such traits are heritable.¹⁶ On this basis, one might predict that a child born to two parents with Asperger syndrome would be at increased genetic risk of developing Asperger syndrome.

There is a second reason to expect this particular child to be at risk of developing Asperger syndrome, based on the hypersystemizing, assortative mating theory of autism.¹⁷ According to this theory, autism is the result of hypersystemizing in both parents. This can be referred to as the $A = S^2$ theory (where A = autism spectrum conditions and S = systemizing). (The squared operation is chosen by convention because in genetics, the genotype of the offspring is conventionally denoted by using a multiplication symbol between the genotype of each parent.) In the case of the child reported in the studies below, her parents are both scientists and therefore strong systemizers. The $A = S^2$ theory itself extends the E-S theory of autism spectrum conditions, which argues that the core features of the phenotype are impaired empathizing (E) alongside intact or superior systemizing (S).¹⁸

Empathizing is the drive to identify others' mental states and to react with appropriate affect to another person's mental state. Evidence for the empathizing impairment is now well established.¹⁹⁻²⁵ Systemizing is the drive to analyze or construct a system using input-operation-output rules. When we systemize, we look for structure, pattern, rules, laws, or periodicity in data. The evidence for intact or hypersystemizing in autism spectrum conditions includes the following: (1) obsessions in autism cluster in the domain of systems²⁶; (2) people with Asperger syndrome score higher than average on the Systemizing Quotient²⁷; (3) people with Asperger syndrome perform at a normal or high level on tests of systemizing²⁸⁻³¹; and (4) people with Asperger syndrome can achieve extremely high levels in systemizing domains such as mathematics, physics, or computer science.³² Normal or hypersystemizing can explain the nonsocial features of autism, such as the obsessions,

islets of ability, narrow, detailed attention, and the need for sameness or repetitive behavior.³³ There is also evidence that degrees of autism characterize hypersystemizers. Thus, scientists (who by definition are hypersystemizers) score higher than nonscientists on the Autism Spectrum Quotient.³⁴ Within the sciences, mathematicians score highest of all on the Autism Quotient.³⁴ The link between hypersystemizing and autism is likely to be genetic in origin. This is evident in two studies of students in the natural sciences (engineering, mathematics, physics) who had a higher number of relatives with autism than did students in the humanities.^{35,36}

There are four lines of evidence for the assortative mating ($A = S^2$) theory. First, both mothers and fathers of children with Asperger syndrome have been found to be strong in systemizing on the Embedded Figures Test.³⁷ This study suggests that both parents can be contributing their systemizing genotypes. Second, both mothers and fathers of children with autism or Asperger syndrome have elevated rates of systemizing occupations among their fathers.³⁸ Third, both mothers and fathers of children with Asperger syndrome show extreme male patterns of brain activity while performing a systemizing task.³⁹ Fourth, both mothers and fathers of children with autism score higher on the Autism Spectrum Quotient.⁴⁰ For these reasons, we predicted that a child born to two hypersystemizing parents would go on to develop Asperger syndrome. The single case reported allows a test of these predictions.

Participants

The child (T.A.) has two parents. Her father is British born and has a degree that spans mathematics and psychology. He is currently studying for the Med and was a remedial mathematics teacher at the college level. He has also worked as a technician in a medical physics department in a district hospital. This work included mathematical modeling. T.A.'s mother is a Finish born woman with an FM (equivalent of MSc) in plant physiology (genetics) and the equivalent of an AdvCertSci in genetics. She also holds a PgDipSpEd. Both parents have Asperger syndrome. It is rare for two adults with a confirmed diagnosis of Asperger syndrome to marry. They were diagnosed by experts in the United Kingdom and Finland, respectively, using standard internationally recognized criteria.⁸ As an additional check on diagnosis, they were given the Autism Spectrum Quotient, a self-report instrument. Eighty percent of people with Asperger syndrome score above 32 of 50 on this instrument.³⁴ The father scored 49, whereas the mother scored 37. They met via an e-mail list for adults with Asperger syndrome and became a couple. Because both parents have a university degree in a science, we can assume that they are both strong systemizers. However, we tested this by administering the Systemizing Quotient.²⁷ This is an 80-item scale. Normal men score a mean of 30.3 (SD = 11.5), whereas normal women score a mean of 24.1 (SD = 9.5). On the Systemizing Quotient, the father scored 49, whereas the mother scored 37. Both of these are more than 1 SD above the population means for typical men and women. This confirms that both adults are hypersystemizers. The parents contacted us when the mother had just become pregnant. Their consent was sought for a prospective study of their unborn child.

Method

At 19 months, the child was sent the Checklist for Autism in Toddlers.^{10,41} The Checklist for Autism in Toddlers is a screen for autism spectrum conditions but is not diagnostic. At 26 months, the Autism Diagnostic Interview-Revised⁴² and the Autism Diagnostic Observation Schedule⁴³ were administered in person.

Table 1. Subject's Algorithm Scores on the Autism Diagnostic Interview-Revised and the Autism Diagnostic Observation Schedule, with Cutoff Scores for Autism

| Test | Communication | Social Interaction | Repetitive/Stereotyped Behaviors |
|----------|---------------|--------------------|----------------------------------|
| ADI-R | 18 (8) | 16 (10) | 4 (3) |
| ADOS (1) | 9 (4) | 7 (7)* | NA [†] |

ADI-R = Autism Diagnostic Interview-Revised; ADOS = Autism Diagnostic Observation Schedule; NA = not applicable.

*The Autism Diagnostic Observation Schedule also has a combined score in which communication and social interaction totals are added. The combined score must exceed a cutoff of 12 for module 1. The child has a combined score of 16.

[†]The Autism Diagnostic Observation Schedule does not include the presence of repetitive behaviors as necessary for a diagnosis of autism because the observation is not long enough to guarantee that such behaviors would be reliably observed.

RESULTS

Checklist for Autism in Toddlers at 19 Months

T.A. showed a partial failure on the Checklist for Autism in Toddlers at 19 months, placing her in the moderate-risk group for an autism spectrum condition. On Section A of the Checklist for Autism in Toddlers, she showed three abnormalities: an absence of pointing (protodeclarative and protoimperative), an absence of showing behaviors, and a partial failure on pretend play (the parents suggested that they were uncertain as to whether the child had ever really pretended). Section B confirmed these abnormalities: T.A. did not use a pointing gesture to indicate objects or direct attention. She also showed a partial failure on response to pointing by another: she looked first at the adult's arm and then followed along the length of the arm to the finger tip and from there to the object of focus. Thus, she did not use another's point spontaneously to direct her attention. Finally, there was a partial failure on pretend play, in which the child was asked to make a cup of tea with a pretend tea cup. Reports state only a "tentative yes" to whether she was able to pretend to pour out the tea and drink it, etc. Total failure on the Checklist for Autism in Toddlers (high-risk group) is associated with classic autism, but a partial failure of this nature might indicate Asperger syndrome.

Autism Diagnostic Interview-Revised and the Autism Diagnostic Observation Schedule at Age 26 Months

The child met the criteria for autism on both the Autism Diagnostic Interview-Revised and the Autism Diagnostic Observation Schedule at age 26 months. Algorithm scores for the Autism Diagnostic Interview-Revised and the Autism Diagnostic Observation Schedule are shown in Table 1. On the Autism Diagnostic Observation Schedule, it was difficult to get the child to look at the experimenter (F.S.) or at her mother when she was engaged in another activity, even when F.S. placed her face directly in front of the child's face, close up, and touched her physically. It was not possible to initiate joint-attention behaviors with the child, nor did she show any toys or objects to her mother at any point. The child responded to her name being called by the interviewer on the second attempt, turning to look, and engaged in eye contact and face-to-face expression if she was interested in what the interviewer was doing. However, these social orienting behaviors were inconsistent. Parental reporting from the Autism Diagnostic Interview-Revised stated that the child had poor eye contact, did not use it communicatively, and it was "sporadic." They confirmed that she did not attend to her parents unless they specifically called her name, and even then she would often not turn without them taking her face in their hands and physically turning her to look at them. The

child showed no pointing or response to a point for joint attention. Developmental milestones were all normal. On the basis of both the Autism Diagnostic Interview-Revised and Autism Diagnostic Observation Schedule scores, as well as clinical interview, a diagnosis of Asperger syndrome was made.

DISCUSSION

This single-case study confirms that Asperger syndrome can be diagnosed at 26 months of age. This warrants a larger-scale study to establish the stability and reliability of such an early diagnosis. Study 1 found that a child born to two parents with Asperger syndrome herself went on to develop Asperger syndrome. This is consistent with Asperger syndrome being heritable but by itself is not proof of heritability, only familiarity. It warrants a family-genetic or a twin study of Asperger syndrome to calculate the degree of heritability of Asperger syndrome. Finally, this study found that a child born to two hypersystemizing parents went on to develop Asperger syndrome herself. This is consistent with the $A = S^2$ theory, which needs to be tested further by surveying if autism occurs more commonly in carefully selected parent groups: parents who are both hypersystemizers (eg, two physicists who have a child) compared with couples in which there is either only one systemizer or couples in which neither parent is a systemizer). Such a study is under way in our laboratory.

The prospective videotaping of this child every 3 months in the first year of life allowed us the opportunity to test if the development of dyadic eye contact is intact or not in a child who develops Asperger syndrome. This is reported for study 2.

STUDY 2: DYADIC EYE CONTACT IN INFANCY IN ASPERGER SYNDROME

The fact that in study 1, the child's eye contact was sporadic and at times difficult to establish during the Autism Diagnostic Observation Schedule raises the possibility that eye contact was abnormally low in infancy. This is possible only to establish comparison with a control group of infants at the same ages. Study 2 reports normative data on the frequency of eye contact. Normal neonates not only show a face preference effect⁴⁴ but can also distinguish direct versus averted eye contact.⁴⁵ Dedicated areas of the brain in the temporal-occipital region subservice both face processing in general and gaze detection in particular.^{46,47} It is known that there are individual differences in the frequency of eye contact. For example, girls make more eye contact than boys at 12 months of age.⁴⁸

Eye contact has long been thought to be abnormal in classic autism. Clinical accounts report that children with autism can

Table 2. Subject's Looking Times During a 160-Second Face-to-Face Interaction

| Control Group Age (mo) | n (N = 55) | Sex Ratio (M:F) | Frequency of Eye Contact, Mean (SD) | Child's Age (mo) | Frequency of Eye Contact |
|------------------------|------------|-----------------|-------------------------------------|------------------|--------------------------|
| 3 | 25 | 12:13 | 12.68 (5.42) | 3 | 11 |
| 6 | 15 | 10:5 | 11.27 (6.42) | 6 | 7 |
| 9–12 | 15 | 9:6 | 8.67 (5.98) | 9–12 | 5 |

make too little eye contact or too much.^{49–51} Such abnormalities are thought to reflect deficits in the pragmatics of nonverbal communication.⁵² Neuroimaging (functional magnetic resonance imaging) studies report that in autism, the fusiform face area might not be activated by faces to the normal extent⁵³ and that whereas the superior temporal sulcus can be overactive, the amygdala and medial frontal areas can be underactive during the interpretation of mental states from another person's eyes.³ In terms of the functional use of eye contact, experimental studies of autism report deficits in the triadic use of eye contact for joint attention.^{20,21,54,55} Recent gaze-tracking studies confirm that people with autism might not track triadic joint attention to the same extent as controls.⁵⁶ Cognitive studies also show that even adults with high-functioning autism or Asperger syndrome do not use the eyes to infer complex mental states or emotions in others.^{22,23,57} In theoretic terms, Baron-Cohen argued that during the perception of others' eyes, dyadic mechanisms (eg, the eye direction detector) are intact, but triadic mechanisms (eg, the shared attention mechanism) are impaired.^{19,58} In study 2, we tested if the child's eye contact was significantly worse than that of age-matched controls during the first year of life as a test of the hypothesis that dyadic eye contact in infancy is intact in a child who later goes on to develop Asperger syndrome.

Participants

The same child (see study 1) was compared with a control group that was also videotaped to establish normative developmental data for the growth of eye contact. These were 55 randomly selected babies at ages 3, 6, and 9 to 12 months born at the Rosie Maternity Hospital, Cambridge. Their sex ratio and sample size are given in Table 2. All were attending follow-up clinics at the postnatal unit for minor concerns and were free of medication or clinical diagnosis. Preterm babies or those with specific chromosomal abnormalities (eg, Down syndrome) were excluded.

Method

The child was filmed prospectively to record eye contact with her mother at 3, 6, and 9 months of age. The children in the comparison group were filmed in cross-sectional studies at the same three ages while engaged in a one-to-one, face-to-face interaction with their mother. The child was either sitting in a child seat with the mother kneeling in front or was sitting on the mother's lap. The interactions lasted for 160 seconds in each case. During this period, the mother attempted to engage the child by talking, cooing, pulling faces, and making sounds. The child's attention was not forced by physically turning the head at any point. Each videotaped interaction by the child and by the control participants was coded, and the frequency of looks toward the mother's face during the interaction was recorded. Interrater reliability was calculated by having a second, independent rater code 33 of the 55 videotapes, and agreement was good (Cohen's kappa = 0.75).

RESULTS

The frequency of eye contact by controls (and standard deviations) at each of the five time points is given in Table 2. Analysis of variance across the three age groups showed that there was no difference in the frequency of eye contact across the three age groups ($F(2,52) = 2.2, P = .12$). The child's frequency of eye contact, although appearing to be lower than that of controls, was within 1 SD of that of typical controls at each age point.

Discussion of Study 2 and General Discussion

Study 2 confirms that frequency of eye contact is within normal limits in the child, despite the fact that she is on a developmental trajectory to a diagnosis of Asperger syndrome. The eye contact measured was limited to dyadic interactions with her mother and can be said to be intact. From the Autism Diagnostic Observation Schedule and from the Checklist for Autism in Toddlers, it is clear that she shows triadic deficits in joint attention, suggesting a profile of dissociation between (intact) dyadic and (impaired) triadic eye contact. This is in line with findings from studies of classic autism at 18 months of age.⁵³ This result, although from a single case, suggests that eye contact is not a clear predictor of Asperger syndrome. The results from the control group are also of interest in showing very little (if any) growth in eye contact over the first year. Although these low rates of eye contact at each age studied might indicate that, under experimental conditions (with a video camera present), typically developing children make relatively low rates of eye contact (between 8 and 12 times in 120 seconds), it is under such artificial conditions that clinical observations might also be carried out and as such give an indication of how useful eye contact might be as a marker of abnormality.

We conclude that Asperger syndrome can be diagnosed early, although it remains a challenge as to how to screen and detect Asperger syndrome in the first 2 years of life. Finally, the child's own development of Asperger syndrome was predicted on the basis of both of her parents having Asperger syndrome and being hypersystemizers. The $A = S^2$ theory warrants further testing with a larger sample of hypersystemizing parents.

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