Infant predictors of autism spectrum disorder

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Abstract

The study of infants at familial risk for developing autism has revealed a variety of early brain and behavioural markers for this disorder. Brain connectivity, processing of gaze direction, attention shifting or reacting to sensory stimulation are all atypical during the first year of life in those high-risk infants who later develop symptoms of autism. Future research will have to determine whether these early signs are predictive of autism outside populations at risk and whether they are specific to autism.

Introduction

A diagnosis of autism spectrum disorder (ASD) is rarely made before 2 years of age (1) and behavioural signs emerge during this time (see Charman, in this issue (2)). Following evidence for moderate heritability (3) it is now widely accepted that ASD emerges as a result of genetic risk factors (inherited or de novo mutations) affecting processes of brain development and function. The study of infants at risk for ASD is motivated by both clinical and basic science considerations. From the basic science perspective, studying infants at risk allows us to characterise core brain function markers for this disorder, before they become compounded by the child's increasingly atypical interaction with his or her social and physical environment. From the clinical perspective, the discovery of early diagnostic markers heralds the opportunity to intervene before the full onset of symptoms.

Studying ASD in infancy

There are three approaches to studying infancy markers of later ASD symptoms. Retrospective studies of home videos of children diagnosed with ASD have helped to identify the behavioural "red flags", typically around one year, e.g. poor response to name and joint attention (5). However, these studies have major limitations, such as parents selecting positive behaviours. Prospective studies overcome these limitations but very large sample sizes are needed if they are to be carried out on the general population (as only 1% of cases will develop ASD). Population studies have provided information on demographic or prenatal risk factors (e.g. extreme stress during pregnancy (4)). The third approach is studies of high-risk populations (HR-ASD), such as infants at familial risk (often defined as having an older sibling with the disorder). About 20% of younger siblings develop ASD and another 20% will manifest other developmental atypicalities (6). Typically, a low-risk control group is also followed up, matched for having older siblings without ASD and no close relatives with ASD.

Methods used to study infant brain and cognitive development

Studies of infants at risk have become increasingly feasible in recent years due to the advent of new technology and methods for studying brain structure and function in infants (see Johnson 2010, (7) for review). The new methods allow us to address hypotheses about precursors of behavioural symptoms of ASD.

Brain imaging. Magnetic Resonance Imaging (MRI) can provide information about brain volume and brain structure (e.g. fibre integrity, white and grey matter volumes). Because this method is very sensitive to movement, in most of these studies infants are asleep or sedated.

Electroencephalography (EEG) and Near Infrared Spectroscopy. These methods can provide functional information on awake infants while they perform tasks.

Eye-tracking. Corneal reflections of infra-red light can be used to monitor naturally-occurring eye movements (saccades, fixations, smooth pursuit). Infant-friendly techniques are now available that require minimum set-up time.

Observational measures. Observations of naturalistic behaviours are still a rich source of early markers of ASD. Behaviours can be coded at different time scales (e.g. looking time, frequency of smiling).

ASD biomarkers within the first year of life

Three types of predictor of later outcome have been revealed through studies of infants at risk; markers of risk group, of later ASD diagnosis or of dimensional traits of ASD in childhood (e.g. severity scores of the ASD Diagnostic Observation Scale). We shall focus on the latter two types of association.

Brain structure. MRI measures have shown infants that later develop ASD symptoms tend to have larger brain volumes (and more frontal extra-axial fluid) from 12 months of age (8). Atypical (increased) brain connectivity is observed at 6 months of age in HR-ASD, compared to other high-risk infants (9).

Social orienting. While it has been hypothesised that poor orienting to social stimuli is a causal factor in ASD (21), the evidence is mixed. For example, during the first year of life, HR-ASD orient to faces (10) and seek social interaction (12) as much as controls. Scanning of faces measured using eye-tracking is typical at both 6 and 12 months of age in HR-ASD infants ((13); but see (11)). Decreased social orienting becomes apparent in the second year of life (14) and could be a secondary symptom.

Gaze processing. In typically-developing 6-9 month old infants, brain responses (EEG) differentiate gaze shifts away and towards the infant, but not in HR-ASD (15). Furthermore, this infant marker correlates with the severity of ASD symptoms at 2 and 3 years of age.

Attention disengagement. HR-ASD take longer to disengage their attention from a fixation stimulus to a target that appears in the periphery (16, 17).

Perception. Parents of HR-ASD rated them as being more sensitive to sensory stimulation from 6 months (18).

Motor skills. Six-month olds HR-ASD are less able to keep their head in line with their body when pulled to sit (19). This could reflect poor movement coordination but also difficulties with action anticipation.

Thus, while several factors have been identified as potential infant markers for later ASD, these come from a range of different sensory, motor and cognitive domains.

Modelling a multi-factorial developmental disorder

Predictive power. The expected continuous interplay between risk and protective genetic factors, and the child's environment may preclude strong predictive value for each individual infant marker. Where sensitivity and specificity have been calculated, as for example for total extra-axial fluid, the values are modest: 78% sensitivity (percentage of ASD cases above the threshold) and 79% specificity (percentage of non-ASD cases below the threshold). Prediction may increase with additional infant markers, and multi-variate statistical models can answer questions about how multiple markers interact to predict outcomes better.

Developmental trajectories. Sometimes developmental changes in ASD markers across ages are better predictors (e.g. an increase in disengagement latencies between 6 and 12 months; (16)). Different patterns of change are also used to identify subgroups of infants that develop ASD signs (e.g. slow

growth vs. regression (14)) and this will improve targeting of early intervention.

Limitations, unanswered questions and future directions

The genetics of children with ASD identified through high-risk family studies may be different from those of de novo cases. Thus, markers identified through HR studies will have to be validated in large population studies.

Currently, only a few markers have been identified before one year of age, and these tend to be measures of brain structure or function. This motivates a change of research focus towards a better understanding of early brain development and of the links between brain and behaviour. Finally, children with ASD often meet criteria for other developmental disorders (e.g. 20 % for ADHD (20)). It is not known whether the markers currently identified are specific to ASD. Studies of high-risk infants are underway for other developmental disorders, such as ADHD.

GP Comment.

What have I learned from this paper?

1. We found the paper to be a good educational resource for General Practitioners.

2. Autism spectrum disorder is a heritable condition with genetic risk factors affecting brain development and function.

3. We learnt that in early infancy there are potential markers in sensory, motor and cognitive domains that indicate later development of ASD.

4. When diagnosed early and with appropriate management, the outcomes will improve for the child and the family.

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