A Cohort Study of Autism Spectrum Disorders: a Multidisciplinary Approach to Exploring Social Origin in Atypical and Typical Development

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Autism Spectrum Disorders (ASD) represents developmental disorders characterized by social and communication impairments and repetitive/stereotyped behaviors. The standard diagnostic criteria of ASD are based on clinical observations of children aged 3 to 4 years and older, and as such they cannot be applied to children under 3 years of age. However, a growing body of literature indicates that children with ASD can be reliably diagnosed as young as age 2 on the basis of various social abnormalities. Although the general consensus is that some type of early abnormal neural development of prenatal origin underlies the disorder, the behavioral abnormalities can be observed only several months after birth. The behavioral features persist throughout and beyond childhood but vary according to developmental stage. In older children or adults, co-occurring psychiatric problems, such as depression or anxiety in addition to the core social abnormalities including an inability to be aware of or understand others' feelings and intentions reduce social adaptation and quality of life (QOL) in everyday life. Although early detection and early intervention is suggested not only to facilitate the development of children with ASD but also to improve their social adaptation and QOL, it is at present difficult in Japan for public health workers and clinicians in their daily practice to detect early symptoms of ASD in toddlerhood and thus intervention is likely to be delayed. One of the ways to understand the complex social behavior of individuals with ASD is to detect the earliest markers and monitor the children prospectively. By doing so, will get an insight into the nature-nurture interactions involved in developing later complex and diverse clinical manifestation.

The aims of the present study were five-fold:

1) to delineate the developmental trajectories from 1 to 3 years of age in children with ASD as well as children with typical development
2) to identify the early marker (s) of ASD if any

3) to identify risk factors and protective factors for developing ASD
4) to explore neurocognitive abnormalities behind the diverse behavioral features of ASD over the lifespan, and
5) to explore gene expression abnormalities which are common to the probands for ASD and mothers of individuals with ASD.

Toward these aims, we used an epidemiological approach to identify children suspected of having ASD, and prospectively monitored them in collaboration with a local health agency and related professionals in the community. This approach aimed at initiating the necessary support for vulnerable children and their families at 2 years of age whenever possible. Screening involved the completion of a checklist inquiring about preverbal social behaviors and repeated clinical evaluations conducted by our research team. In addition to this cohort study, we reviewed developmental information from birth, and also conducted neuro-cognitive behavioral experiments conducted with children and adults with or without ASD. As a result, the following conclusions were reached.

First, by using the checklist which examines the early symptoms of ASD in toddlerhood (the Modified Checklist for Autism in Toddlers: M-CHAT), the sensitivity of the 18-month health check-up was improved. This enabled larger numbers of children and their families to access the various forms of support available. The detailed clinical evaluations of 38 children revealed that the severity and the number of autistic symptoms were found to change from 2-3 years of age: although the majority of the children remained in the clinical category of ASD, a few moved on the autism spectrum from the severer end to the milder end, or vice versa.

Second, a set of preverbal social behaviors, which were also confirmed to emerge before 17 months of age in the general infant population, were identified as an early behavioral marker for toddlers with ASD at 18-24 months of age, irrespective of developmental functioning, although there was no single early behavioral marker.

According to clinical samples reported in the literature, macrocephaly and early atypical brain growth appears to be the single most consistent physical characteristic of children with autism. Therefore, among our epidemiological sample (n=2146),

we examined whether this characteristic is a clinical marker for ASD. Our cohort data confirmed that there is a higher rate—about 10% of the total population— who showed macrocephaly before age 3. To determine head growth in ASD from birth to 3 years, the growth trajectory of head circumference (HC) for each child was estimated controlling for height and weight (hierarchical linear model). Although the HC and growth rate of children with ASD (n=40) was not different from that of the local population as a whole, HC was negatively correlated with the severity ratings and the growth pattern varied by subtype within ASD.

Third, advanced parental age at childbirth has often been reported as a potential risk factor of ASD, suggesting possible nature-nurture interactions in the development of the disorder. Our cohort data revealed that advanced maternal age was significantly associated with atypical social development at 18 months; children of mothers in the oldest age group (≥35 years) were 1.58 (1.08-2.32) times more likely to fail on the M-CHAT than the reference group. Another finding was that the association between maternal age and ASD diagnosis was marginally significant.

Fourth, the neuro-cognitive behavioral experiments conducted with children and adults with ASD and matched controls with typical development produced various findings which add new evidence to controversial hypotheses of autism. The domains studied ranged from low-level perceptual processing (including imitation) to higher-level social perception, language, and decision-making. The neuro-cognitive dysfunction seen in these domains in individuals with ASD is likely to arise when a task requires integrative processing, whether automatically or intentionally. Consistently with these findings, our diffusion tensor imaging (DTI) findings on children with ASD demonstrated abnormal white matter microstructure in the areas where intrahemispheric as well as interhemispheric transfer of information is important for integrative processing.

Taken together, the earliest behavioral manifestations that children with ASD show may reflect some maturational delay. The ill-timed maturational events might result in insufficient neural organization in most cases, although some children might compensate somehow and thus move outside the clinical diagnosis range of ASD. Such

insufficient neural circuitry will affect higher-order processing as a downstream effect in addition to the basic lower-order processing abnormalities. Exploring the earliest developmental origin and the developmental trajectories will help us to develop therapeutic intervention strategies along the life course as social policy for ASD. It is expected that further research combined with longitudinal and multidimensional approaches will reveal the underlying mechanisms of the developmental diversity leading to various social impairments and will help to design optimal prevention and intervention.