Title: Early Risk of Autism Spectrum Disorders in Infants with Down Syndrome

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Introduction: Despite strengths in social responsivity, children with Down syndrome (DS) are at elevated risk for an autism spectrum disorder (ASD), with 7% to 18% of persons with DS meeting DSM criteria (Diguiseppi et al., 2010; Kent et al., 1999; Lowenthal et al., 2007). The nature of the association of ASD in DS is of increasing interest in the field because it is common for there to be a delay in diagnosis or misdiagnosis of ASD in DS that may have deleterious effects on development (e.g., inappropriate interventions or school placements; Riley, 2009). However, no work has been carried out to identify potential prodromal features or identify risk factors (behavioral or biomarker), which is necessary for early diagnosis of ASD in DS. There is initial evidence that ASD symptoms do emerge early and remain stable in DS, but early emergence of ASD symptoms in infancy has yet to be examined. Potential early indicators of ASD suggested by Hepburn et al. (2008) include lower intellectual functioning, impairments in social and communication skills, and the temperamental areas of approach/withdrawal and rhythmicity. The presence of ASD in those with neurogenetic disorders allows for examination of the shared phenomenology between disorders (e.g., intellectual disability, which is present in 50-70% of individuals with ASD; Matson & Shoemaker, 2009). Thus, examining the emergence of ASD in DS as compared to fragile X syndrome (FXS) — another neurogenetic disorder at an elevated risk for ASD (30-74%) that is also associated with intellectual disability — can provide unique insight into the associations between ASD and intellectual disability. Therefore, the purpose of the present study is to examine differences in early ASD risk as measured by the Autism Observation Scale for Infants (AOSI; Bryson et al., 2008) between infants with DS as contrasted to infants with FXS, as well as describe the behaviors associated with elevated risk in infants with DS. In addition, the relationship between salivary cortisol — a physiological marker for stress and potential biomarker for ASD related behaviors — and ASD risk is explored.

Method: Participants were 11 infants with DS (9 males, 2 females) and 11 male infants with FXS matched on chronological age (range 7-17 months, \( t(20) = .27, p = .79 \)) and cognitive abilities as measured by the Mullen Scales of Early Learning (range 50-97, \( t(20) = -.44, p = .67 \)). As part of a larger assessment battery, all infants were administered the AOSI—a 15 to 20 minute semi-structured, play-based measure used to identify early signs of autism in high-risk infants between the ages of 6 and 18 months. The AOSI has 19 items that are rated throughout the administration from 0 to 3, where 0 indicates normal behavior and ratings of 1, 2 and 3 indicate increasing levels of abnormal behavior. The first 16 items are summed to create a Total Score, and the number of markers (i.e., number of items rated in the abnormal range) is determined. Seven or more markers are an indicator of later diagnosis of ASD. Cortisol stress levels were measured in three conditions: a pre-assessment baseline, a post-assessment cortisol level, and the change in cortisol between baseline and post-assessment.

Results: Infants with DS had significantly lower AOSI total scores (\( t(20) = -2.33, p = .03 \)) and number of markers (\( t(20) = -2.38, p = .03 \)) than infants with FXS. Specifically, 72% of infants with FXS and 36% of infants with DS were at an increased risk for ASD as measured by the AOSI. Infants with DS who were in the “at risk” category had lower cognitive abilities (\( M = 69, SD = 5.35 \)) than infants with DS not at risk (\( M = 76.57, SD = 10.72 \)). Examination of the AOSI items indicate that common risk markers (75-100% rated in the abnormal range) for infants with DS were disengagement of attention, orienting to name, imitation, social babbling, eye contact, reciprocal social smile, social interest and affect. Examination of the relationship between AOSI total scores and salivary cortisol in infants with DS indicated that increased baseline and reactant cortisol (\( r = .59, p = .05; r = 38, p = .25 \)), as well as, dampened cortisol change (\( r = -.62, p = .04 \)) was related to increased ASD risk.

Discussion: Consistent with studies of older individuals with DS and FXS, our preliminary findings indicate that infants with DS may have lower risk rates of ASD than infants with FXS. Similar to Hepburn et al. (2008), difficulties with social communication and lower intellectual abilities may be early indicators of ASD in DS. Unlike infants with FXS (Roberts et al., 2016), atypical motor behaviors do not appear to be an early marker of ASD risk in infants with DS. Thus, it is possible that there is some syndrome-specificity in early risk markers of ASD. Similar to previous studies in ASD and FXS (Corbett et al., 2009; Hall et al., 2008; Roberts et al., 2009), our results suggest that cortisol is also a potential biomarker of ASD behaviors in DS. Specifically, less modulation of cortisol, or change in cortisol in response from baseline to post-assessment, is associated with more ASD behaviors. Future research is needed to follow ASD risk in infants with DS into early childhood when a diagnosis can be reliably made, which will provide greater insight into what early markers of ASD predict a diagnosis. Such nuanced information regarding which social communication behaviors carry more or less ASD risk will aid clinicians in identifying earlier indicators of comorbid ASD in DS and inform treatment approaches.
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