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Identification of infants at risk for autism spectrum disorder and developmental language delay prior to 12 months

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Abstract

Studies have shown an increased head circumference and the absence of the head tilt reflex as possible risk factors for autism spectrum disorder, allowing for early detection at 12 months in typically developing population of infants. Our aim was to develop a screening tool to identify infants prior to 12 months at risk for autism spectrum disorder and developmental learning delay, not affected by literacy or primary parental language, and provide immediate determination of risk for autism spectrum disorder. An abrupt head circumference acceleration and the absence of head tilt reflex by 9 months were used to identify infants at risk for autism spectrum disorder. Stability of early findings was then investigated when compared to comprehensive standardized neurodevelopmental assessment results and complete neurological and genetics evaluations. A total of 1024 typically developing infants were enrolled by 9 months, with 14 identified as at risk for autism spectrum disorder and 33 for developmental learning delay. There was a good positive predictive value for the identification of autism spectrum disorder prior to 12 months. This study demonstrates an efficient means to identify infants at risk for autism spectrum disorder by 9 months of age and serves to alert primary care providers of infants who are vulnerable for autism spectrum disorder before symptoms are discernible by clinical judgment of primary care providers, parental concerns, or by screening questionnaires.

Keywords

autism spectrum disorder, developmental delays, developmental language delay, infant screening

The importance of early detection and treatment for children with autism spectrum disorder (ASD) has been well documented (Dawson, 2008; Dawson et al., 2010; Lord et al., 2012; Zwaigenbaum, 2010). Since 2006, the American Academy of Pediatrics has recommended routine screening measures for toddlers at risk for ASD at 18 and 24 months of age (American Academy of Pediatrics, 2006). Although numerous screening procedures have been developed, a reliable and effective mechanism to identify ASD prior to 12 months continues to be elusive, because of the variability of developmental progression in infancy and difficulty identifying reliable biomarkers and known variance in developmental trajectories of infants (Barbaro and Dissanayake, 2010; Kleinman et al., 2008; Luyster et al., 2011; Miller et al., 2011; Robins, 2008; Robins et al., 2001; Rogers, 2009; Wetherby and Prizant, 2002). Ascertaining children from impoverished, minority,

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and English-as-a-second-language (ESL) families at risk for ASD proves more challenging because of limited health care, low literacy, and difficulties completing screening questionnaires in nonnative languages for many ESL families (Begeer et al., 2009; Chaidez et al., 2012; Cuccaro et al., 1996; Liptak et al., 2008; Mandell et al., 2002; Valicenti-McDermott et al., 2012).

The Checklist for Autism in Toddlers (CHAT) was developed for toddlers at 18 months of age and was a landmark study on nearly 17,000 infants, but had low sensitivity and limited participation of 33% and 39% in two different studies (Allison et al., 2008; Baird et al., 2001; Baron-Cohen et al., 1996). The Early Screening of Autistic Traits Questionnaire was completed on 32,000 children with 98% participation (Dietz et al., 2006). Unfortunately, detection was reduced, with only 18 infants identified when prevalence rates suggested significant higher rates for infants at risk for ASD. The Modified Checklist for Autism in Toddlers (M-CHAT) was later created and has reported a positive predictive value (PPV) of 54%; however, it cannot be utilized prior to 16 months of age (Cheblowski et al., 2013). Recently, the Early Child Study screened 1000 infants using M-CHAT and the Infant Toddler Checklist (ITC) with telephone interview and in-person evaluations. Although detection results were very promising, it required a two-step screening process, which is often unrealistic in many pediatric settings (Miller et al., 2011).

To our knowledge, there are no screening questionnaires available specific to ASD prior to 16 months (Cheblowski et al., 2013). Symptoms of ASD are evident by 5 months of age illustrated from the results on the Baby Sibs Study. However, the development of questionnaires that captures these symptoms has been extremely difficult because there are both rapid as well as unpredictable developmental trajectories in all infants. This variance compounds the identification of potential risk factors versus the normal but *late blooming* infants. To date, a reliable and effective screening tool for ASD is not available prior to 16 months of age in the primary care setting (Miller et al., 2011). Recent research studies have also revealed that the clinical judgment of primary care providers (PCPs) may not be reliable for identification of ASD and may be even less likely to identify ethnic minority children (Begeer et al., 2009). There is a critical need to create a screening tool to assist PCPs with the identification of at-risk behavior in infants prior to 12 months so that therapeutic services on these vulnerable infants can be initiated.

We took a novel approach to screening infants for ASD based on recognized neurodevelopmental disturbances, earlier research findings, and the overlooked but critical role of motor proficiency and neuromotor development in ASD. The acceleration of head growth and increased head circumference (HC) have been documented as weighted risk factors for ASD in several research studies (Courchesne et al., 2003; Dawson et al., 2007; Elder et al., 2008). Unfortunately, the presence of accelerated HC in infants often does not prompt further query into ASD by medical providers (unpublished data, 2013).

Postural control, early motor development, and motor proficiency have been under-investigated as possible and plausible factors in the early detection of ASD until very recently (de Bildt et al., 2012). Mostofsky et al. (2006) found that children with ASD lack appropriate praxis abilities with delayed development of skilled motor movements at school age (Flanagan et al., 2012; Mulligan and White, 2012). Older studies by Teitelbaum et al. (1998, 2004) demonstrated that head tilt reflex (HTR) was atypical in infants with ASD by their first birthday in two retrospective studies. Recent research studies have documented that low muscle tonus and persistent head lag are present in infants with ASD at 6 months of age (Flanagan et al., 2012). These findings support the probability that a possible early indicator of ASD may be in the neuromotor domain and linked to early motor development disturbances that have not been well investigated as of yet. We believed that if we linked HC growth with a salient neuromotor factor we could be more effective in the early identification of infants at risk for ASD prior to 12 months from infants with global developmental delay (DD) or developmental language disorders.

Although older studies completed by Philip Teitelbaum (1998) and Osnat Teitelbaum (2004) revealed a link between HTR and children with ASD, the HTR has not been utilized as a screening measure in a large normative sample of infants. We hypothesized that HTR could be a quick and easy mechanism to identify the early manifestations of the decreased muscle tonus, motor delay, and praxis deficits that are more common in older children with ASD (Teitelbaum et al., 1998, 2004). We further postulated that together HTR and accelerated HC could be more effective in separating the infant at risk for language-based learning disorders from the infant at risk for ASD in the first year of life. The principal focus of this study was to determine whether two novel and salient factors could provide an efficient means to identify infants at low risk for ASD prior to 12 months of age regardless of the family's socioeconomic status (SES), primary language, or ethnicity.

Methods

Three large pediatric practices participated with six pediatricians (MD) and two pediatric nurse practitioners (PNP) in this study. All pediatric providers administered the M-CHAT at 16 months and/or ages and stages at well baby visits (WBVs) prior to the onset of the study and throughout the duration of the study, in their

respective practices. During their pediatric training, medical providers, both PNPs and MDs, are trained to assess the presence or absence neonatal primitive reflexes. The HTR is one of these reflexes that is present as early as 4 months with 99% of all infants demonstrating it by 9 months of age. The measurement of HC is a standard part of every pediatric practice until 24 months of age.

At the commencement of the study, the administration and scoring of the HTR was discussed with each provider so that there was reliability and cohesion among all providers on the administration and scoring of HTR. Each provider was shown how to administer the HTR and what a typically developing infant looked like on the maneuver as well as what an abnormal result looked like. The measurement of HC was also reviewed so that measurements were consistent across all providers.

The fidelity of the protocol was maintained through monitoring the PCP's completion of forms and the administration of HTR and HC periodically. Institutional Review Board (IRB) approval for the study was given and updated yearly.

Patient population

PCPs were asked to discuss the study with all families who had full-term infants and had no known neurogenetic disorders (such as Down syndrome, Fragile X) or with known neonatal complications of severe hypoxia, newborn seizures, or more than 5 days in the neonatal intensive care unit (NICU). A total of 1024 infants were enrolled in the study. Families were given a packet of information at the WBVs, explaining the purpose of the study and the informed consent.

Screening protocol

HTR and HC were completed by providers at the 4-, 6-, and 9-month WBVs. The HTR was performed by holding the infant in axillary suspension (holding the infant under the upper extremities), and tilting the infant 45° slowly and laterally to each side for 3–5 s. The HTR was scored present when the infant's head tilted toward the midline and absent if there was no head movement back to midline. HTR was completed at the 6- and 9-month WBVs, if not present at 4 months (Dubowitz and Dubowitz, 1981; Prechtl, 1977).

HC was routinely measured in conjunction with weight and height as a part of the WBVs. HC and other anthropometric measurements were monitored for advanced growth, specifically HC growth (above or equal to the 75%) or rapid acceleration (an increase of over 25% resulting in HC above the 75%) that was not proportionate. Greater than 25% difference between HC and height and weight was deemed disproportionate.

Two specialists who had clinical expertise in the evaluation of muscle tonus and motor movements independently assessed muscle tonus. Together, both specialists developed criteria for abnormal muscle tonus, but scored independently on each infant. Both specialists have published extensively on children with common as well as rare neurodevelopmental disorders that have atypical motor development and abnormal muscle tonus. They are both recognized as clinical experts on ASD and have provided care in a pediatric tertiary care setting for more than 20 years.

Evaluation process (Figure 1)

After the 9-month WBV, infants who had an HC above or equal to 75% or an increase in HC of 25% or more in conjunction with a 10% discrepancy to height between 4 and 9 months of age and/or failed the HTR were considered at risk for ASD or developmental learning delay (DLD). Registered nurses (RNs) contacted parents of high-risk infants and arranged an appointment with a neurodevelopmental specialist and the neurologist. The *Mullen Scales of Early Learning, Preschool Language Scale–Fourth Edition* (PLS-4), and the *Early Language Milestone Scale-2* (ELM-2) were completed on all at-risk infants to determine neurodevelopmental function. The *Infant/Toddler Sensory Profile Caregiver Questionnaire* and the *MacArthur-Bates Communicative Inventory* were completed by the parents. Repeated attempts via mail and telephone were made to schedule any parents who were not responsive for the scheduling of neurodevelopmental and/or neurological testing.

All infants determined at risk were evaluated by a physician who is board certified in neurology, clinical genetics, and developmental pediatrics. Since the mean age of assessment, and age when the final clinical diagnosis was made, for the at-risk infants was 37.7 months, the two specialists developed a list of several salient characteristics commonly observed in young children with ASD who were also associated with the diagnostic criteria for ASD as specified in the *Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition* (*DSM-IV*) (American Psychiatric Association, 1994). This was necessary since the *DSM-IV* is not deemed appropriate for infants under the age of 2 years, but similar symptoms are present in infancy (Barbaro and Dissanayake, 2010).

These characteristics include impaired ability to direct attention to others, poor eye contact, delayed nonverbal communication, lack of integration between verbal, facial, and gestural communication, lack of response to name, poor imitation of gestures and sounds, repetitive use of objects, atypical response to other's attempts to engage with them or direct their attention and significant sensory dysfunction. All children were formally diagnosed as having ASD, DLD, or as typically developing, based on the

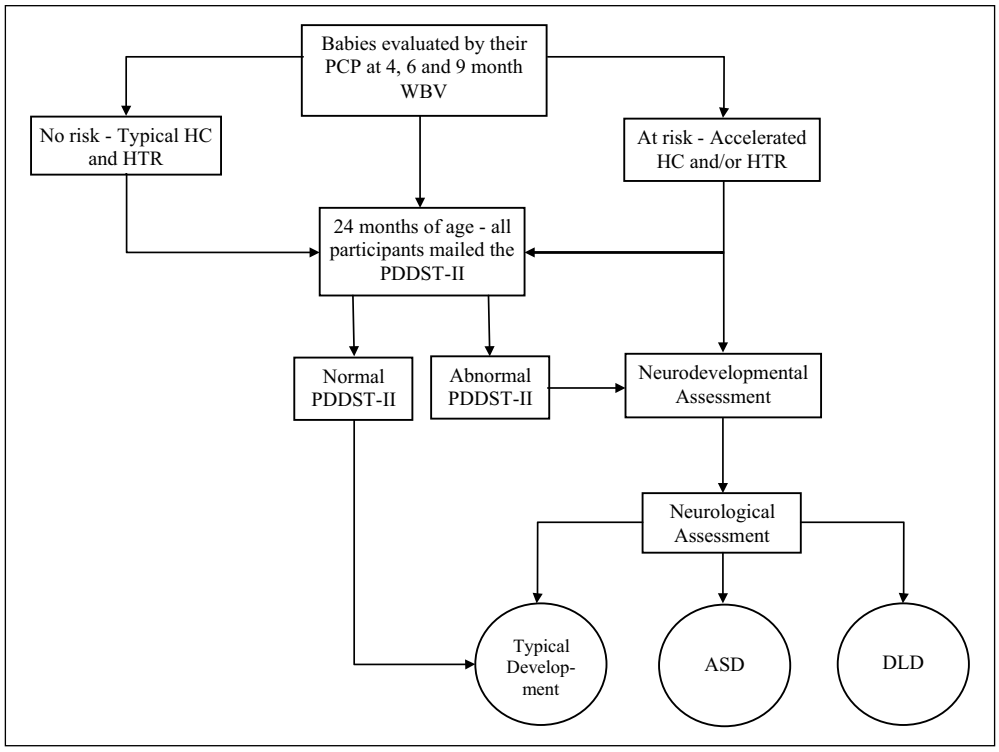

Figure 1. Flow chart of evaluation process.
PCP: primary care provider; WBV: well baby visit; HC: head circumference; HTR: head tilt reflex; PDDST-II: Pervasive Developmental Disorders Screening Test–II; ASD: autism spectrum disorder; DLD: developmental learning delay.

pediatric specialist's clinical expertise, and the above characteristics. The physician was blinded to the risk status of the infants at the time of the evaluation.

All infants participating in the study, regardless of screening outcome, were mailed the Pervasive Developmental Disorders Screening Test–II (PDDST-II) at 24 months of age in order to identify those infants who may not have been detected by the two biomarkers and could have been at risk. This scale has good reliability and was chosen to further facilitate the identification of infants who could be ASD and/or more mildly effected. Those infants determined at risk from the PDDST-II then proceeded through the identical procedure for neurodevelopmental and neurological assessments as the at-risk infants identified by HC or HTR.

Statistical analysis

Neurodevelopmental data were bifurcated into two groups based on diagnosis of ASD or DLD. Statistical procedures were utilized to measure neurodevelopmental differences between the two groups and test of significance between the means of the infants with ASD and those with DLD. A test of significance was performed using the nonparametric Wilcoxon–Mann–Whitney Test for independent samples when the variable was not normally distributed and the *t*-test for independent samples when the variable was determined to be normally distributed.

Additionally, logistic regressions were run to determine the odds of predicting the final diagnosis with the initial diagnosis, with the final diagnosis as the dependent variable and initial diagnosis as the independent variable.

Results

Of the 1024 patients enrolled, 18 later declined participation in the study and 282 patients were lost to follow-up or did not show for evaluations (Figure 2). There was concerted effort to locate the families lost to follow-up in three ways. Repeated telephone calls were placed to families in various times of the day in an effort to locate them. Three separate mailings were sent to each family. Additionally, we contacted each child's primary physician and they were asked to stress the importance of the study and the follow-up appointments.

A total of 49 of the infants showed abnormal results. None of the 49 infants had previous diagnoses, nor were there any caregiver concerns or clinical suspicions by the medical providers. Ages and stages did not identify infants with ASD prior to our detection; however, one infant was detected by the M-CHAT at 18 months of age. Follow-up PDDST-II questionnaires were sent out to the 700 infants who had turned 24 months of age at the time of this article.

All infants formally diagnosed with either ASD or DLD had negative family histories for ASD with the exception

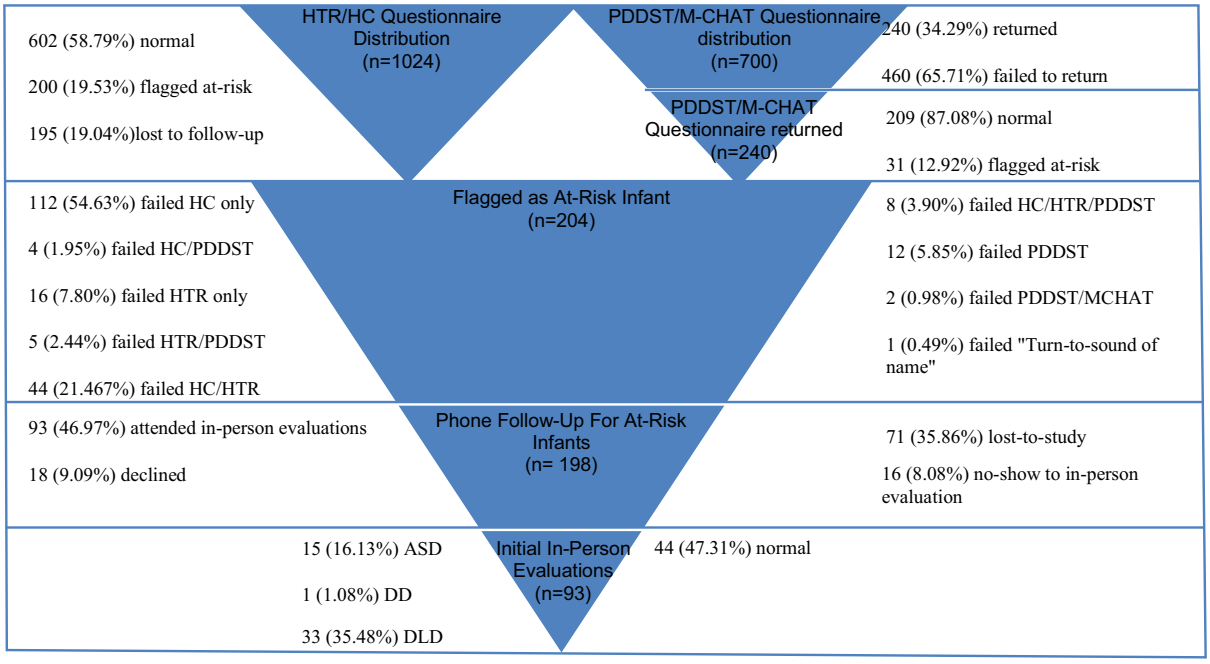

Figure 2. Study process for infants at risk.
HTR: head tilt reflex; HC: head circumference; PDDST-II: Pervasive Developmental Disorders Screening Test–II; M-CHAT: Modified Checklist for Autism in Toddlers; ASD: autism spectrum disorder; DD: developmental delay; DLD: developmental learning delay.

Table 1. Parental age of at-risk infants.

Diagnosis	Father		Mother	
	Mean age (years)	Range (years)	Mean age (years)	Range (years)
ASD	36.92	26–45	32.85	23–41
DLD	35.84	27–47	34.10	25–41

ASD: autism spectrum disorder; DLD: developmental learning delay.

of four. One male infant had an older sibling diagnosed with ASD at 3 years, but parents did not suspect ASD at the time of this infant's evaluation. One female at risk for ASD had a paternal uncle with Asperger syndrome. The father and paternal grandmother of the second male infant with ASD exhibited phenotypic characteristics consistent with the broader autism phenotype (BAP) (Piven et al., 1997).

ASD

Patient demographics

The mean age for the fathers of the ASD infants was 36.92 years and the mothers' mean age was 32.85 years (Table 1). (Note: Parents' ages were recorded at the time of birth of the infant.) The ethnicities of the ASD group were well representative of the population and had all racial and ethnic groups: 10 infants deemed at risk for ASD were Caucasian, 4 African-American, and 1 Hispanic (Table 2). Of the 15 infants diagnosed as having ASD, 8 (53.33%) were male and 7 (46.67%) female. Seven of the eight males and five of the seven females were identified with the two biomarkers. The mean age at diagnosis for the ASD infants was 37.6 years (Table 3).

Examiner inter-reliability

Examiner inter-reliability was only calculated on those infants seen by neurodevelopmentalist and neurologist (Table 4). Examiner agreement on the assessment of ASD and DLD infants was 87.50% on children with a diagnosis of ASD. There was 100% concurrence of the presence of hypotonia in the infants at risk for ASD between the two specialists.

Screening measures

A total of 15 infants were recognized as at risk for ASD: 12 using the HTR and HC biomarkers and 3 using the

Table 2. Race of at-risk infants.

Race	%	Study protocol	PDDST-II
ASD			
African-American	26.67	4	0
Caucasian	66.67	8	2
Hispanic	6.67	0	1
DLD			
African-American	15.15	5	0
Caucasian	81.81	23	4
Hispanic	3.03	0	1

PDDST-II: Pervasive Developmental Disorders Screening Test–II; ASD: autism spectrum disorder; DLD: developmental learning delay.

Table 3. Gender of at-risk infants.

Gender	%	Study protocol	PDDST-II
ASD			
Female	46.67	5	2
Male	53.33	7	1
DLD			
Female	27.27	8	1
Male	72.73	21	3

PDDST-II: Pervasive Developmental Disorders Screening Test–II; ASD: autism spectrum disorder; DLD: developmental learning delay.

Table 4. Examiner inter-reliability between neurodevelopmentalist and neurologist.

Assessments	ASD (n = 8/%)	DLD (n = 13/%)
At-risk status	7 (87.5)	9 (69.23)
Hypotonia	8 (100)	9 (75)

ASD: autism spectrum disorder; DLD: developmental learning delay.

Table 5. Screening measures for at risk infants.

Screening measures	n (%)	Incomplete data (ID)	IC with hypotonia
ASD (n = 15)			
HC acceleration >25%	7 (46.67)	–	–
HTR absent	2 (13.33)	7	5/7
Both HC and HTR	2 (13.33)	–	–
DLD (n = 33)			
HC acceleration >25%	20 (60.6)	–	–
HTR absent	2 (.06)	6	1/6
Both HC and HTR	2 (.06)	–	–

ASD: autism spectrum disorder; HC: head circumference; HTR: head tilt reflex; DLD: developmental learning delay.

PDDST-II (Table 5). HC was accelerated on 9 of the 15 (60%) infants identified as at risk for ASD by more than 25 percentiles between 4 and 9 months. HTR was absent in 4 of the 15 (26.67%) at-risk infants for ASD; however, 7 infants had incomplete data since PCPs had inadvertently neglected to record the findings on the HTR. Five of these seven infants exhibited hypotonia, suggesting that the HTR was likely to be absent at 9 months. Thus, the possibility is that 9 of 15 (60%) infants with ASD could have failed HTR.

When the medical evaluation was completed at 36 months, one infant previously identified as at risk for ASD improved to normal and one infant diagnosed with DD regressed to a diagnosis of ASD. One infant regressed from normal to an undetermined diagnosis of either DLD or ASD since the neurodevelopmentalist and physician

differed in their clinical suspicions. This infant was not included in the data analysis.

DLD

Patient demographics

The mean fathers' age for the DLD at-risk infants was 35.84 years and the mothers' mean age was 34.10 years (Table 1). (Note: Parents' ages were recorded at the time of birth of the infant). Of the 33 infants at risk for DLD, 27 were Caucasian, 5 African-American, and 1 Hispanic; and 24 (72.73%) of the 33 DLD infants were male and 9 (27.27%) were female, with the majority identified using both the HC and HTR biomarkers (Tables 2 and 3). The mean age at diagnosis for the ASD infants was 37.8 years.

Examiner inter-reliability

Examiner inter-reliability (Table 4) was only calculated on those infants seen by both the neurodevelopmentalist and the neurologist. Examiner agreement on the assessment of those with DLD was 69.23%. Of the DLD patients seen by both specialists, there was 75% inter-reliability on the presence or absence of abnormal muscle tonus.

Screening measures

Examinations by neurodevelopmental and neurological specialists deemed 33 infants at risk for DLD (Table 5). A total of 29 infants were initially identified by using the HTR and HC biomarkers and 4 infants using the PDDST-II. One infant was identified as developmentally delayed using the biomarkers. Of the 33 infants, 20 (60.6%) had accelerated HC—more than 25 percentiles between 4 and 9 months. The majority of the DLD infants (89%) had the HTR by 9 months of age. HTR was only absent for 3 of the 33 (11.11%) at-risk DLD infants. Six infants had incomplete data on HTR, and of these six infants, only one had hypotonia, suggesting that this infant's reflex was truly absent. Therefore, the HTR was very selective in the identification of ASD versus DLD in infancy since HTR was present in 89% of at-risk DLD infants.

Neurodevelopmental assessments

There was a significant difference between infants at risk for ASD and those at risk for DLD on the receptive language domain ($p = 0.0037$) of the Mullen Scales of Early Learning, as well as, within the auditory comprehension ($p = 0.0006$) domain of the PLS-4 (Tables 6 and 7). There were significance differences between the ASD and DLD groups in the Gross Motor Skills ($p = 0.0301$). Infants with both DLD and ASD had delays in expressive language skills (Tables 6 and 7).

PPV

The PPV (true positives/all screen positives) of the screening measures, biomarker, and questionnaires was calculated based on the child's initial categorization as at risk for ASD or DLD after failing the HTR/HC biomarkers and/or the PDDST-II and subsequent diagnoses, during the neurodevelopmental and neurological examinations, by the specialists.

Of the 15 children who were diagnosed as at risk for ASD, 14 sustained the ASD diagnosis, yielding a PPV of .93. One child failed the screening measures of HTR and HC only to be categorized as typically developing, thus showing our only false negative. The diagnostic category of DLD had a PPV of .97 as 32 of the infants diagnosed as at risk for DLD remained in the DLD diagnostic category of the original 33. When examining all infants brought in for neurodevelopmental evaluations after failing HTR, having an accelerated HC of more than 25%, PDDST-II, or M-CHAT, or combination thereof, our study produced a PPV of .51 for children diagnosed as at risk for ASD and DLD who upheld their respective diagnosis. The combination of the two screening measures proved more reliable than separately; when looking solely at HTR, a PPV of .36 was observed, and when looking at just HC, a PPV of .39 was found.

Discussion

Our study demonstrates a novel, efficient, and easy means to identify infants at risk for ASD and DLD as early as 9 months of age in a low-risk population of infants, regardless of their primary language, parental literacy, or SES. These biomarkers afford a mechanism for medical providers to identify infants at risk for ASD using immediately accessible information during WBV prior to 12 months of age and before ASD-specific questionnaires are available and appropriate to use.

The results on HC support previous findings by Courchesne and others that increased HC may be a common biomarker for some children with ASD as well as the DLD due to the overlap in symptomology (Courchesne et al., 2003; Dawson et al., 2007; Herbert et al., 2004; Lord et al., 2012). HC alone is not sufficient to identify the infant at risk for ASD based on our findings and others (Elder et al., 2008). However, it does serve as a biomarker associated with neurodevelopmental disturbances in the speech and language domain in infancy. Accelerated HC serves as good biomarker to identify the infants at risk for speech dysfunction from neurotypical infants, but alone it does not sort the DLD infant from the ASD infant.

The underlying mechanism for accelerated head growth, the effect on neural pathways, and the differences in the development of language between infants at risk for ASD versus DLD is a complex issue that is not well

Table 6. Neurodevelopmental assessment results.

Assessment	M	SD	*p*-value
PLS-4[a]			
Auditory comprehension			
ASD	75.00	12.78	0.0006
DLD	84.77	13.02	
Expressive communication			
ASD	75.09	15.64	NS
DLD	79.97	15.64	

SD: standard deviation; PLS-4: Preschool Language Scale–Fourth Edition; ASD: autism spectrum disorder; DLD: developmental learning delay.

Table 7. Mullen scales of early learning results (*t*-scores).

Assessment	M	SD	*p*-value
Gross motor			
ASD	39.36	13.31	0.0301
DLD	51.44	13.09	
Visual receptive			
ASD	33.72	13.80	NS
DLD	43.81	12.44	
Fine motor			
ASD	40.27	16.86	NS
DLD	47.84	14.31	
Receptive language			
ASD	30.09	15.20	0.0037
DLD	49.74	11.92	
Expressive language			
ASD	40.73	16.52	NS
DLD	37.43	12.43	

SD: standard deviation; ASD: autism spectrum disorder; DLD: developmental learning delay.

understood. However, in a seminal article, Kuhl (2010) postulates that social cognition is an integral component to the development of language as well as to sensory motor development. We hypothesize that despite accelerated HC, DLD infants had more intact social cognition and receptive language skills. This, coupled with the appropriate sensory motor development, partially explains the differences in these two different infant populations. Accelerated HC serves as good biomarker to identify the infants at risk for speech dysfunction from neurotypical infants, but alone it does not sort the DLD infant from the ASD infant.

With our additional parameter of the HTR, the diagnoses of infants at risk for ASD and DLD became more evident and easily differentiated. Since 60% of both the ASD and DLD groups failed the HC measure, however, 26.67% of the ASD group failed the HTR measure in comparison to only 11.11% of the DLD group. Our study expands on Flanagan et al.'s (2012) findings that early motor function may be a very valuable means to discern infants at risk for ASD prior to 12 months especially when coupled with the additional biomarkers. Our study also amplifies the findings of Lloyd et al. (2013) that motor development is atypical not only in toddlers with ASD but also infants with ASD as early as 9 months of age.

Atypical motor development and developmental dyspraxia have been described in children with ASD (de Bildt et al., 2012; Mulligan and White, 2012). Our recent findings further support the importance of the assessment of early motor function in infants at high risk for ASD. The majority of infants with ASD did not demonstrate HTR by 9 months in comparison to the infants with DLD. This is a very important finding because HTR may be a salient biomarker that reflects the inadequate development of the central nervous system and it can be easily identified during a WBV (Dubowitz and Dubowitz, 1981).

A recent study by Cheblowski et al. (2013) found a PPV of .54 using the M-CHAT and M-CHAT Follow-Up Interview (M-CHAT/F) for children 16 months of age or older. Using the combined screening biomarkers, we were able to produce a PPV of .51 for children at risk for ASD and DLD by 9 months of age. Using these combined measures of HTR and HC, infants at risk for ASD were detected at 9 months, earlier than this recent study. It is very encouraging that these maneuvers had a similar positive predictability rate. Additionally, our factors are independent of literacy, language, and SES, which have been impediments to the early identification of impoverished and minority families.

Our findings of atypical receptive language skills support previous studies on the neurodevelopmental profile of the infant with ASD (Ozonoff et al. 2010). Receptive language skills were preserved in the infants at risk for DLD and significantly different from infants at risk with ASD. Yet, these receptive language deficits were not appreciated by PCPs, parents, or standardized questionnaires provided at WBVs. Our study suggests that early markers of receptive language dysfunction are present before 12 months of age, but not easily discerned and most importantly not identified by commonly used screening tools. This study expands our understanding of speech and language deficits in infants with ASD from low-risk population and augments our understanding of the early phenotypic presentation of these infants.

Identification of females with many neurodevelopmental disorders has always been more challenging. Females are often underdiagnosed in attention deficit hyperactivity disorder (ADHD), dyslexia, and language-based learning disorders (Bruchmuller et al., 2012; Derks et al., 2007; Hawke et al., 2009; Ramtekkar et al., 2010; Willcutt and Pennington, 2000). Early research studies on ADHD revealed a male predominance until screening measures were more refined, only then did females became more representative in ADHD (Biederman and Faraone, 2004; Biederman et al., 2002; Ramtekkar et al., 2010; Sclar et al., 2012).

In contrast to previous research studies, we observed a more evenly distributed female-to-male ratio (7:8) with ASD, which is extremely rare at all ages for ASD and especially in the youngest population of children. This preliminary finding proposes that females with ASD may be more prevalent than thought and are more difficult to identify with ASD at this early age with traditional measures. Our results are consistent with other recent research findings where an increased prevalence of females with ASD has been reported but not easily identified (Kopp and Gillberg, 2011; Zwaigenbaum et al., 2012).

Identification of a more representative population of females at risk for ASD is an important finding that merits further exploration. Our diagnostic criteria may provide an opportunity to identify female infants with ASD who have been missed previously as well as enhance our understanding of the early symptomology of gender differences and brain development of at-risk infants. These findings improve our ability to identify females with ASD as well as our ability to develop targeted treatment and potentially modify outcomes for female infants with ASD.

There were some limitations to our study. Infants were lost to follow-up for a variety of reasons and this has been a common finding in other large screening studies of infants at risk for ASD (Allison et al., 2008; Baird et al., 2001; Baron-Cohen et al., 1996; Miller et al., 2011). The lack of recognition of early signs of DLD or ASD on the part of caregiver and/or medical providers may have contributed to the decreased compliance despite our efforts to provide appropriate training for medical providers and support for the families. Ages/stages did not identify any infants prior to 24 months and M-CHAT only identified one of our 14 infants with ASD prior to 18 months, which highlights the importance for an effective screening tool prior to 12 months of age.

Although the Autism Diagnostic Observation Scale (ADOS) was not administered to the infants who were identified at risk for ASD and DLD and this is a recognized limitation, infants at risk were seen by the senior clinical researcher who is a pediatric neurologist/geneticist with 25 years experience and extensive training in the evaluation of infants at risk for ASD and other genetic disorders. Diagnosis of ASD at this age is quite challenging and additionally developmental progression often confounds the stability of diagnosis. Yet, in our study, only 1 infant out of 14 identified at risk for ASD progressed onto normal development. This strongly suggests that our findings were highly reliable at the identification of the infant at risk for ASD prior to 12 months of age. Despite recognized challenges in developmental variance in at-risk infants, our biomarkers propose a mechanism for early detection and treatment in a cost-effective, stable, and reliable manner that is not available via general developmental screenings and before ASD-specific questionnaires are reliable. Our diagnosis had a high degree of stability between 12 months and 36 months.

Our study documented that there were significant differences in several developmental domains commonly reported between infants with ASD and DLD at 12 months of age on comprehensive developmental testing. This strongly suggests that these biomarkers have merit in the identification of infants at risk for ASD at an early age in a manner that is impervious to literacy level, primary language, and SES of the families. Our study discerned deficits present in infants at risk for ASD who are not typically flagged based on clinical judgments of PCPs, parents, or general screening measures at 12 months of age.

Conclusion

Our study reveals two plausible biomarkers that are quick and easily administered during WBV with good reliability and predictability at 36 months. Our results provide an innovative format that may be extremely helpful in identifying infants at risk for ASD before 12 months of age who are not discernible by standard questionnaires or screening tools. Further investigation is underway to determine the efficacy of HTR and HC in conjunction with several novel findings identified from this study and to develop a screening tool that can be implemented prior to 9 months of age and lead to earlier identification of male as well as female infants at risk for ASD in typical pediatric setting on infants who are at low risk.

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Declaration of conflicting interests

There are no conflicts of interest.

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