Advanced parental ages and low birth weight in autism spectrum disorders—Rates and effect on functioning

Esther Ben Itzchak a,*, Eli Lahat b, Ditza A. Zachor c

a Department of Communication Disorders, Ariel University Center of Samaria, Israel
b Pediatric Neurology Unit, Assaf Harofeh Medical Center, Tel Aviv University, Zerifin 70300, Israel
c The Autism Center, Assaf Harofeh Medical Center, Tel Aviv University, Zerifin 70300, Israel

ABSTRACT

Objectives: (1) To assess the distribution of parental age and birth weight in a large cohort with autism spectrum disorder (ASD) and to compare them to Israeli national data. (2) To examine possible relationships between these risk factors and functioning.

Methods: The study included 529 participants diagnosed with ASD using standardized tests: the Autism Diagnosis Interview-Revised and the Autism Diagnosis Observation Schedule (ADOS). Medical, developmental and familial histories (gender, age, pregnancy and birth information, parental ages) were obtained. Autism severity was assessed using the new ADOS severity scale and adaptive skill using the Vineland Adaptive Behavior Scales.

Results: Advanced parental age was associated with ASD. In the older age range the percentages of mothers (35–44 y) and fathers (30–40 y) were significantly higher in the ASD cohort in comparison to the Israeli newborn data. The ASD cohort had significantly higher percentages of low birth weight (<2500 g) and very low birth weight (VLBW < 1500 g) in comparison to the Israeli newborn data. Of these risk factors, only VLBW was associated with lower adaptive functioning. The group with VLBW had lower scores in daily living, socialization and motor skills in comparison to the >1500 g group. Autism severity was not associated with advanced parental age or VLBW.

Conclusions: The shift in parental age distribution and birth weight in our ASD cohort suggests that the increase in ASD prevalence in recent years might be associated with novel prenatal insults. An adverse fetal course resulting in VLBW may represent a “second hit” phenomenon, causing a poorer outcome.

ARTICLE INFO

Article history:
Received 2 March 2011
Accepted 3 March 2011
Available online 17 April 2011

Keywords:
Autism spectrum disorder
Parental age
Low birth weight
Autism severity
Adaptive skills

1. Introduction

Autism spectrum disorders (ASD) are a group of neurobehavioral disorders defined by social and communication deficits and repetitive behaviors that are typically detectable in early childhood. ASD comprise a spectrum delineated by a set of observable dysfunctions and have wide variability with respect to the presence and intensity of the core symptoms, cognitive language and adaptive skills (Johnson & Myers, 2007). The current estimated prevalence of ASD in Europe and North America is approximately 1:100–150 (Kogan et al., 2009; Fombonne, 2005), which reflects a 15-fold increase from studies published a half-century ago. ASD are biologically based disorders that are highly heritable. Despite strong heritability, the lack of complete concordance in monozygotic twins (<70%), and the fact that the exact cause of ASD is still
unknown, suggest that non heritable prenatal and perinatal events may be risk factors for ASD or may modulate the phenotypic expression (Veenstra-VanderWeele & Cook, 2004).

Symptoms of autism can be identified as early as in the first two years of life. Therefore, pre-and perinatal events are now the focus of research into risk factors for ASD. Birth risk factors during the first and second trimesters of pregnancy play a role in the fetus via maternal factors and may cause many of the developmental brain abnormalities known to be associated with ASD. Several prenatal risk factors for autism were documented in previous studies. Two obstetric categories appeared to increase the risk of ASD: birth weight and duration of pregnancy, and intrapartum hypoxia [bleeding in pregnancy (Gardener, Spiegelman, & Buka, 2009; Hultman, Sparén, & Cnattingius, 2002), prolonged labor (Hultman et al., 2002), caesarian delivery (Gardener et al., 2009), low Appgar scores (Larsson et al., 2005)]. Advanced maternal and paternal ages were associated with ASD in numerous studies (Grether, Anderson, Croen, Smith, & Windham, 2009; Kolevzon, Gros, & Reichenberg, 2007). Research on parental ages as risk factors for autism yielded conflicting results regarding the contribution of each parent to the increased risk. Several studies found an increased risk for ASD with increasing paternal age (Larsson et al., 2005; Lauritsen, Pedersen, & Mortensen, 2005; Reichenberg et al., 2006). Shelton, Tancredi, and Hertz-Picciotto (2010) reported that father’s age increased the risk of ASD primarily for mothers under 30. Others described maternal age as a risk factor for ASD (Glasson et al., 2004) and several studies described both paternal and maternal ages as risk factors for ASD (Croen, Najjar, Fireman, & Grether, 2007; Durkin et al., 2008; King, Fountain, Dakhlallah, & Bearman, 2009).

Low birth weight with or without prematurity is a risk factor for many neurodevelopmental disorders, including cerebral palsy and mental retardation (Johnson & Breslau, 2000; Veen et al., 1991). Inconsistent results were documented regarding the association of low birth weight (LBW) of <2500 g with ASD (Kolevzon et al., 2007; Schendel & Bashin, 2008). The studies differed in their methodology, size of the sample and control of confounding variables.

Great variability has been documented in the clinical presentation in ASD. Differences have been noted in autism core symptoms, expression and severity, cognitive level, language abilities and adaptive skills (Fein et al., 1999). Research so far has focused on identifying risk factors for ASD but not on the effect of these risk factors on behavioral manifestations in ASD.

The current study focused on the association between environmental risk factors (parental ages and child’s birth weight) and ASD in a large cohort diagnosed with ASD. This study had two main aims. The first aim was to assess the distribution of parental ages and child’s birth weight in a cohort with ASD and to compare them to Israeli national data. The second aim was to examine possible relationships between the risk factors (parental ages; very low birth weight) and functioning (autism severity; adaptive skills).

2. Methods

The study was conducted at The Autism Center at Assaf Harofeh Medical Center, Tel Aviv University, in Israel. The Autism Center is a national center that provides diagnosis and treatment services and is involved in research in the field of ASD. The children were referred to the Autism Center for a comprehensive assessment of possible diagnosis of autism by pediatricians, teachers, paramedical professionals and parents. The comprehensive evaluation included a neurological assessment by a pediatric developmental neurologist, and behavioral and cognitive evaluations by a skilled interdisciplinary team. Assessment of ASD was obtained using standardized tests, the Autism Diagnosis Interview–Revised (ADI–R) (Le Couteur, Rutter, & LeCouteur, 2003) and the Autism Diagnosis Observation Schedule (ADOS) (Lord, Rutter, DiLavore, & Risi, 1999), and meeting criteria for autism/ASD based on DSM-IV criteria (APA, 1994). Autism severity was assessed by using the new ADOS severity scale. Assessment of adaptive skills was made using the Vineland Adaptive Behavior Scales (Sparrow, Balla, & Cicchetti, 1984).

Medical, developmental and familial histories were obtained from the parents, including data on child’s gender, age, pregnancy and birth information, perinatal history, familial history and parental ages. Data was collected between February 2002 and April 2010.

2.1. Participants

The study included 637 participants, 529 of whom (M:F 6.8:1) received a diagnosis within the autism spectrum and 108 of whom (M:F 2.8:1) received other diagnoses, including developmental delay, language disorder, ADHD, behavioral problems, mental retardation and others. In the current study, only the ASD cohort was included. The ethnic origin of the ASD cohort was homogenous as at least one of the parents was Jewish in 99.8% and only 0.2% was of another ethnicity.

2.2. Measures

1. Autism Diagnostic Interview – Revised (ADI–R). A semi-structured interview administered to parents, designed to make a diagnosis of autism according to DSM-IV criteria (Le Couteur et al., 2003).
2. Autism Diagnosis Observation Schedule (ADOS). A semi-structured, interactive schedule designed to assess social and communicative functioning (Lord et al., 1999). The new ADOS diagnostic algorithm that classifies children into categories of autism, ASD or non-spectrum is used (Gotham et al., 2008). To assess autism severity, the new ADOS severity score is used (Gotham, Pickles, & Lord, 2009).
2.3. Data analysis

The distributions of birth weight and parental ages in the ASD cohort were calculated and compared to national data on the Jewish population collected by the Israeli Central Bureau of Statistics (2004). Data on very low birth weight (VLBW < 1500 g) was obtained from the database published by the Women and Children’s Health Research Unit, The Gertner Institute for Epidemiology and Health Policy Research, The Israeli National for Disease Control, and The Israel Neonatal Network (Reichman, Lewitzky, Boyko, & Lerner-Geva, 2009). For comparisons between the ASD cohort and the Israeli population, Chi² goodness-of-fit tests were used. In addition, within the ASD cohort, we defined groups according to birth weight (<1500 g), maternal age (<34 y) and paternal age (<34 y). For comparisons between the defined groups for autism severity, one-way ANCOVAs were used, and for adaptive skills measures, one-way MANCOVAs were used, controlling for the child’s age in all analyses.

3. Results

Risk factors for ASD including, parental ages and birth weight were investigated.

3.1. Parental ages

To investigate parental age as a risk factor for ASD, maternal and paternal age distribution in the ASD cohort was compared to Israeli newborn data. Significant differences in maternal age distribution were found between the ASD cohort and the Israeli newborn data [$\chi^2(5) = 39.8, p < .001$]. The percentage of mothers in the older age range of 35–44 y was significantly higher in the ASD cohort, while the percentage of mothers in the younger age range of 20–29 y was lower than in the Israeli newborn data (Table 1).

Investigating the impact of maternal age on functioning did not yield significant differences between the older (>34 y) and younger (<34 y) maternal age groups in VABS scores ($F(4,310) = .81, p = NS, \mu^2 = .010$), and in autism severity scores ($F(1,466) = 1.5, p = NS, \mu^2 = .003$).

Significant differences in paternal age distribution were found between the ASD cohort and the Israeli newborn data [$\chi^2(3) = 48.8, p < .001$]. The percentage of fathers in the older age range of 30–40 y was significantly higher in the ASD cohort, while the percentage of fathers in the younger age-range of 20–29 y was significantly lower than in the Israeli newborn data (Table 2).

Investigating the impact of paternal age on functioning did not yield significant differences between the older (>34 y) and younger (<34 y) paternal age groups in VABS scores ($F(4,300) = .61, p = NS, \mu^2 = .008$), and in autism severity scores ($F(1,447) = .70, p = NS, \mu^2 = .002$).

3.2. Birth weight

The distribution of birth weight in the ASD cohort was compared to Israeli newborn data. Using chi² goodness-of-fit test, significant differences were found between these two groups [$\chi^2(3) = 40.2, p < .001$]. The ASD cohort had a significantly higher percentage of low birth weight (<2500 g) and a lower percentage of birth weight in the range of 2500–3990 g (Table 3).

We further investigated a subgroup within the ASD cohort of very low birth weight (VLBW) <1500 g. The frequency of VLBW in the ASD group was 4%, significantly higher than the frequency in the Israeli newborn (1%) data. To examine whether older parental age affected the occurrence of VLBW in the ASD cohort, we compared the percentage of parents with advanced age (>34 y) in the ASD-VLBW cohort and the Israeli national VLBW data. The percentage of mothers >34 y did not differ

<table>
<thead>
<tr>
<th>Age/years</th>
<th>Maternal age</th>
<th>Israeli cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ASD</td>
<td>Israeli cohort</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>&lt;19</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20–24</td>
<td>37</td>
<td>7.4</td>
</tr>
<tr>
<td>25–29</td>
<td>145</td>
<td>29.2</td>
</tr>
<tr>
<td>30–34</td>
<td>178</td>
<td>35.8</td>
</tr>
<tr>
<td>35–39</td>
<td>107</td>
<td>21.5</td>
</tr>
<tr>
<td>40–44</td>
<td>26</td>
<td>5.2</td>
</tr>
<tr>
<td>&gt;45</td>
<td>4</td>
<td>.8</td>
</tr>
<tr>
<td>Total</td>
<td>497</td>
<td>100</td>
</tr>
</tbody>
</table>

* $p < .05$.
** $p < .01$.
*** $p < .001$. 

---

Table 1
Maternal age distribution in the ASD and the Israeli newborn data.
significantly between the ASD-VLBW group (25.0%) and the Israeli VLBW data (22.8%) \( x^2 (2) = 2.3, p = \text{NS} \). Similarly, the percentage of fathers > 34 y did not differ significantly between the ASD-VLBW group (35.7%) and the Israeli VLBW data (36.9%) \( x^2 (1) = .01, p = \text{NS} \).

To investigate the impact of VLBW on functioning, we compared the ASD-VLBW group to the ASD > 1500 g group in autism severity and adaptive skills. Autism severity scores did not differ significantly between the ASD-VLBW (\( M = 7.1, SD = 2.5 \)) and the ASD > 1500 g (\( M = 7.1, SD = 1.8 \)) groups. VABS scores were compared between the two ASD birthweight groups using one-way MANCOVA controlling for age. The ASD-VLBW group showed significantly lower scores \( F(4,267) = 3.8, p < .01, \mu^2 = .054 \) than the ASD > 1500 g group. Analyzing each developmental domain separately using ANCOVAs while controlling for age revealed significant differences between the groups in three domains: daily living skills, socialization and motor skills (Table 4).

4. Discussion

This study found that advanced maternal and paternal ages and low birth weights were more frequent in the ASD cohort than in the Israeli newborn national data. Of these risk factors, only very low birth weight was associated with lower adaptive skills.

In our study, advanced parental age at birth of both genders appears to be associated with ASD. Generally, the ASD cohort included fewer young mothers (<30 y) and higher rates of older mothers (35–45 y) than the Israeli newborn cohort. In the paternal age distribution, a similar trend was noted; the Israeli newborn cohort included a larger number of young fathers (<30 y) than the ASD cohort. However, higher rates of older fathers in the ASD cohort were noted only in the 30–40 y range, but not in the most advanced ages (>40 y). These findings suggest that advanced maternal age is a more dominant risk factor.
in ASD. The results of the current study support and complement previous population-based studies reporting that both advanced maternal and paternal ages (Croen et al., 2007; Durkin et al., 2008; King et al., 2009; Shelton et al., 2009) or only advanced maternal age (Glasson et al., 2004) were associated with ASD risk. Our study results are in accordance with the findings of Shelton et al. (2009), that advancing maternal age increased the risk of autism. In addition, Shelton et al. found that advanced paternal age conferred an increased risk for ASD when mothers were <30 y but had little effect when mothers were >30 y.

In the current study, the effect of paternal age also seemed limited, but in our cohort we did not find combinations of fathers >40 y with young mothers <30 y that could be further examined. Our findings were in contrast to previous studies that found only advanced paternal age as a risk factor for ASD (Lauritzen et al., 2005; Reichenberg et al., 2006). Reichenberg et al. (2006) examined a large Israeli cohort derived from draft board registry data on parental ages and diagnoses outcomes using ICD-10 criteria. Although, both Reichenberg and our study looked at the Israeli population, the ASD cohorts were different. Reichenberg’s cohort was born in 1989, before the DSM-IV criteria were in use (1994). Therefore, one can assume that a diagnosis of autism in the Reichenberg study was made according to old criteria, while our cohort was diagnosed using standardized tests and based on DSM-IV criteria. Although our study results suggested that advanced parental age is a risk factor for ASD, the findings did not support an association between parental age groups (30-40 y) and autism severity or adaptive behavior functioning. Our findings suggest that, while parental age might be a risk factor for ASD, this factor was not related to a unique clinical phenotype in ASD.

Low birth weight has been strongly considered as a high risk factor for various neurodevelopmental disorders. In our study the distribution of birth weight in the ASD cohort was significantly different from that of the Israeli newborn population. Significant high frequencies of low birth weight (<2500 g) and very low birth weight (<1500 g) were noted in the ASD cohort. Since parental age is a known risk factor for ASD, parental age distribution in those with VLBW from the ASD cohort was compared to the Israeli VLBW cohort. The distribution of parental age in these two cohorts was not different, emphasizing the role of birth weight itself and not parental age in this group as a risk factor for ASD. Low birth weight may be an indicator of fetal growth problems originating from different etiologies. Previous studies reported conflicting results concerning low birth weight as a risk factor for ASD. The methodologies used in different studies were highly variable and can explain the inconsistencies among the results. A review by Kolevzon et al. (2007) of seven epidemiological studies from a Medline search focused on risk factors that were found in at least two studies and were associated with at least a 50% increase in the risk for autism. Being small for gestational age or having LBW was associated with a twofold increase in risk in two studies (Eaton et al., 2001; Hultman et al., 2002). Schendel and Bashin (2008) found that low birth weight (<2500 g) was associated with an approximately twofold increased risk for autism. The magnitude of the risk was higher for girls and for having autism combined with other developmental disabilities. Of note, the authors found that the prevalence of other developmental disabilities in low birth weight was higher than the rate of autism.

To examine whether having very low birth weight and ASD represent a distinct clinical group, autism severity and adaptive skills were compared in the ASD population with and without a history of VLBW. Autism severity was not different in these two groups, suggesting no specific effect of VLBW on core autism symptoms. However, the ASD/VLBW group did show more deficits in various developmental areas, including daily living skills, socialization and motor skills, than ASD without a history of poor fetal growth. Very low birth weight represents a nonspecific marker of an adverse prenatal course or of an abnormal fetus who is more susceptible to environmental exposures. Very low birth weight has been associated in a substantial number of studies with myriad developmental problems, including a variety of cognitive, speech and language learning disabilities and attention problems (Veen et al., 1991). It is possible that autism and other developmental disabilities share the same pathological mechanisms affecting outcome in different developmental domains. Our study supported this possibility. Having an adverse fetal course resulting in very low birth weight in children with a genetic susceptibility to develop ASD may represent a “second hit” phenomenon that can lead to a poorer outcome.

The strengths of this study were the large cohort with ASD and the case ascertainment. In addition, the cohort was well-defined, diagnosed using stringent criteria based on standardized tests, and had comprehensive evaluations of behavioral functioning. Many previous studies used chart review to identify ASD cases, which could lead to many unidentified cases or misdiagnoses.

This well-characterized ASD cohort was compared to national Israeli newborn data published by the Israeli Central Bureau of Statistics in 2004. This year was used for the comparisons because the average age of the cohort in 2009 corresponded to the age of children born in 2004. Unfortunately, this was also a limitation since the data did not reflect the entire age range of the ASD cohort. Most previous studies were population-based cohort studies that looked at risk factors for ASD. The current study had a different methodology, focusing on the frequencies of known risk factors specifically in a large ASD cohort. Using this methodology limited the possibility of calculating the contribution of the investigated risk factors to the occurrence of ASD in the general population.

The shift in parental age distribution and birth weight in our ASD cohort suggests that the increase in ASD prevalence in recent years might be associated with novel prenatal insults. Trends in the general population for more advanced parental ages and the recent advances in neonatal technologies and prenatal care resulting in increased survival of premature infants may increase the risk for ASD. Further research is needed to investigate the rate of ASD in large advanced parental age range and in low birth weight populations.
References


