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Higher prevalence of autism in Taiwanese children born prematurely: A nationwide population-based study

Yea-Shwu Hwang [a], Shih-Feng Weng [b], Chiung-Yu Cho [c], Wen-Hui Tsai [d,*]

[a] Department of Occupational Therapy, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[b] Department of Medical Research, Chi Mei Medical Center, Tainan, Taiwan
[c] Department of Physical Therapy, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[d] Division of Neonatology, Department of Pediatrics, Chi Mei Medical Center, Tainan, Taiwan

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ABSTRACT

The reported prevalence of autism in preterm and full-term children varies partially because of small sample sizes. Moreover, little is known about the specific factors that contribute to the risk of autism in preterm children. We aimed to compare the prevalence of autism in preterm and full-term children and to identify neonatal risk factors for autism in preterm children using a large national health system database. We analyzed data from 1078 early preterm (<28 weeks of gestation or birth weight < 1000 g), 28,947 later preterm (28–36 weeks), and 1,104,071 full-term (≥37 weeks) children who were 8–11 years old in 2009. The descending order of prevalence was early preterm (2.2%), later preterm (1.3%), and full-term (0.6%). The prevalence of autism was approximately 2–4 times higher in preterm children than in children born at full-term. The male–female ratio (4:1) in preterm and full-term children was not significantly different. Most of the children were first diagnosed with autism between 3 and 6 years old. Preterm children with autism were not diagnosed earlier than were full-term children. Regression analysis showed that male gender, a very low birth weight, and neonatal cerebral dysfunction were risk factors for autism in the preterm group. We conclude that autism is more prevalent in preterm children. Preventing extremely preterm birth and significant early brain insults may be helpful in reducing the risk of autism in preterm children.

1. Introduction

Infantile autism is analogous to the childhood autism characterized in The International Classification of Mental and Behavioral Disorders, 10th Edition (ICD-10) (World Health Organization, 1992) by markedly impaired function in social interaction, and communication, and by restrictive and repetitive behavior. This disorder is called autistic disorder in the Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition, Text Revision (DSM-IV-TR) (American Psychiatric Association, 2000). The term *autism spectrum disorders* (ASD) has, for the past few decades, generally been used to describe a broader autistic category: infantile autism (autistic disorder), Asperger's disorder, pervasive developmental disorder not otherwise specified, childhood disintegrative disorder, and Rett's disorder (Chien, Lin, Chou, & Chou, 2011; First & Tasman, 2004). In this study, we use the term autism to refer only to infantile autism.

* Corresponding author at: Division of Neonatology, Department of Pediatrics, Chi Mei Medical Center, 901 Chung Hwa Road, Yong Kang District, Tainan 710, Taiwan. Tel.: +886 6 281 2811x57109; fax: +886 6 282 8928.
E-mail address: whys.tsai@msa.hinet.net (W.-H. Tsai).

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Preterm children are at high risk for developmental problems, including autism (Hack et al., 2009; Indredavik et al., 2004). Limperopoulos et al. (2008) reported that up to 25% of 91 very preterm infants (gestational age < 32 weeks) at the age of around 24 months demonstrated autistic behaviors from the Modified Checklist for Autism in Toddlers. However, their results may be confounded by significant sensory, motor, or cognitive disabilities (Luyster et al., 2011; Moore, Johnson, Hennessy, & Marlow, 2012). Using diagnosis-based evaluations, researchers have consistently indicated a higher prevalence of ASD in preterm children. Furthermore, preterm children with a younger gestational age (GA) or a lower birth weight seem at a higher risk for ASD. For example, compared with a 0.6–1.6% prevalence of ASD in the general population (Baron-Cohen et al., 2009; Fernell & Gillberg, 2010; Kadesjo, Gillberg, & Hagberg, 1999; Nicholas, Carpenter, King, Jenner, & Charles, 2009), one study with a sample of hundreds of low-birth-weight (LBW) adolescents (96.3% born ≤ 36 weeks) reported that the prevalence of ASD was 3.7% in adolescents with a birth weight of 1500–2000 g and rose to 10.6% for those born weighing <1500 g (Pinto-Martin et al., 2011). In a study of 219 extremely preterm children (<26 weeks gestation), researchers also found that the prevalence of 6.5% with autism and 8% with ASD at 11 years (Johnson et al., 2010).

In addition, two studies of hundreds of preterm children indicated that the risk of ASD in very preterm children was about twice that of their full-term peers (Buchmayer et al., 2009; Schendel & Bhasin, 2008). Schendel and Bhasin also reported that the higher risk of ASD in very preterm infants might apply only to girls: although boys born very preterm and at term had a similar magnitude of risk of ASD, girls born very preterm had a risk of ASD five times higher than did girls born at term. However, because of their small sample size ($n = 30$), their findings need to be confirmed by additional studies.

The specific causes for the higher prevalence of autism and ASD in preterm children are still unclear. Buchmayer et al. (2009) reported that after controlling for a group of maternal, pregnancy-related, and neonatal factors, the magnitude of risk of ASD in very preterm children became no higher than for full-term children. Two recent studies (Indredavik et al., 2010; Johnson et al., 2010) indicated a significant association between higher symptom scores in ASD screening questionnaires and some neonatal factors in preterm children and adolescents. Those factors included male gender, low GA at birth (≤24 weeks), not being breast fed, abnormal cranial ultrasound scan results, vaginal breech delivery, and a lower 1-min Apgar score. However, whether those factors are also associated with the prevalence of autism or ASD in the preterm population has not yet been demonstrated.

Because of the diversity of disorders comprising ASD, and to reduce potential confounding effects from the heterogeneity of the study population, we chose infantile autism rather than ASD as the target disorder. However, a low prevalence of autism may lead to insufficient statistical power to identify the differences between preterm and full-term children with autism and the risk factors for autism in preterm children. Taiwan's National Health Insurance (NHI) program began in March 1995. By the end of February 1996, it covered 19.2 million Taiwanese residents (92% of the population) (Chiang, 1997). In 2007, the insured population increased to 22.6 million, more than 98% of Taiwan's population. The annual NHI research database (National Health Insurance Research Database, 2012) was launched in 2000. Using this large nationwide database, we aimed to reliably estimate and then compare the prevalence of autism in preterm and full-term children, and to identify specific neonatal risk factors for autism in the preterm population.

2. Methods

2.1. Data sources

Since 1996, patient registration files and original claim data have been collected, anonymized (name and identification code deleted), and entered in the Taiwan National Health Insurance Research Database (NHIRD). We used the NHIRD registration files, monthly claim summaries for inpatient claims, and details of ambulatory care orders from 1998 to 2009. All data were coded based on The International Classification of Diseases, 9th Revision, Clinical Modified (ICD-9-CM) (Buck, 2003).

2.2. Study population

Children born between 1998 and 2001 (i.e., 8–11 years old in 2009) were selected as the sample population for this study. The ICD-9-CM divides preterm children into two groups: early preterm: GA < 28 weeks or birth weight < 1000 g (ICD code: 765.0), and later preterm: GA 28–36 weeks (765.1). Full-term children (GA ≥ 37 weeks) were those without a code of 765.x. Children with autism were diagnosed and coded by their doctors based on ICD-9-CM definitions. The children with autism included in this study were those with a code of 299.0 (infantile autism). Children without any medical records since 2 years old (i.e., those who died or moved out of Taiwan) were excluded.

2.3. Neonatal factors predicting the autism risk in preterm children

Birth weight (765.x1–765.x9), gender, hyperbilirubinemia (774.2), intraventricular hemorrhage (772.1), bronchopulmonary dysplasia (770.7 and 518.89), significant cerebral dysfunction in newborns (779.0, 779.1, 779.2), respiratory distress syndrome (769), birth asphyxia (768.x), hypothyroidism (243, 244.x), and patent ductus arteriosus (747.0) were selected to examine their relationship with the risk of autism in prematurely born children.