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Descriptive epidemiology of cerebellar hypoplasia in the National Birth Defects Prevention Study

Meredith M. Howley[1], **Kim M. Keppler-Noreuil**[2], **Christopher M. Cunniff**[3], **Marilyn L. Browne**[1,4], and **for the National Birth Defects Prevention Study**

[1]Congenital Malformations Registry, NYS Department of Health, Albany, NY;

[2]Medical Genomic & Metabolic Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD;

[3]Department of Pediatrics, Weill Cornell Medical College, New York, NY

[4]Department of Epidemiology and Biostatistics, School of Public Health, University at Albany, Rensselaer, NY

Abstract

Background: Cerebellar hypoplasia is a rare disorder of cerebellar formation in which the cerebellum is not completely developed, smaller than it should be, or completely absent. The prevalence of cerebellar hypoplasia at birth is unknown, and little is known about epidemiological risk factors. Using data from the National Birth Defects Prevention Study (NBDPS), a population-based, case-control study, we analyzed clinical features and potential risk factors for non-syndromic cerebellar hypoplasia.

Methods: The NBDPS included pregnancies with estimated delivery dates from 1997–2011. We described clinical features of cerebellar hypoplasia cases from the study area. We explored risk factors for cerebellar hypoplasia (case characteristics, demographics, pregnancy characteristics, maternal health conditions, maternal medication use, and maternal behavioral exposures) by comparing cases to non-malformed live born control infants. We calculated crude odds ratios and 95% confidence intervals using logistic regression models.

Results: We identified 87 eligible cerebellar hypoplasia cases and 55 mothers who participated in the NBDPS. There were no differences in clinical features between interviewed and non-interviewed cases. Cerebellar hypoplasia cases were more likely than controls to be from a multiple pregnancy, be born preterm, and have low birthweight. Cerebellar hypoplasia cases were more likely to be born in or after 2005, as opposed to earlier in NBDPS. We found elevated ORs that were not statistically significant for maternal use of vasoactive medications, non-Hispanic black mothers, and mothers with a history of hypertension.

Conclusions: While unadjusted, our findings from a large, population-based study can contribute to new hypotheses regarding the etiology of cerebellar hypoplasia.

Address correspondence to: Meredith M. Howley, Congenital Malformations Registry, New York State Department of Health, Corning Tower, Room 1264, Albany, NY 12237; 518-402-7771 (phone); 518-402-7769 (fax).

Conflict of Interest Statement

The authors have no conflicts of interest or financial disclosures relevant to this manuscript.

Keywords

cerebellar hypoplasia; birth defects; risk factors; epidemiology

Introduction

Cerebellar hypoplasia cerebellar hypoplasia is a disorder of cerebellar formation in which the cerebellum is not completely developed or is smaller in volume than it should be (Hunter, 2006; Patel & Barkovich, 2002; Poretti, Boltshauser, & Doherty, 2014; Poretti, Prayer, & Boltshauser, 2009). Cerebellar hypoplasia can range from mild or partial underdevelopment to complete absence. Neuroimaging is critical for the diagnosis of cerebellar hypoplasia, and the defining features include a small vermis and/or hemispheres with small fissures that are of normal width compared to the folia (Hunter, 2006; Poretti et al., 2014). Because of the often subtle anatomic variation and the broad spectrum of cases, studying cerebellar hypoplasia can be extremely challenging. Cerebellar hypoplasia can occur in isolation, but is a component of Dandy-Walker malformation, a feature of several malformation syndromes, and associated with several metabolic disorders and neurodegenerative disorders (Parisi & Dobyns, 2003; Poretti et al., 2014; Wassmer et al., 2003). Cerebellar development begins early in embryogenesis, before most brain structures, but cerebellar maturation continues throughout pregnancy and through 20 months of postnatal life for complete cellular differentiation (Goldowitz & Hamre, 1998; Hunter, 2006; Koning et al., 2016; Parisi & Dobyns, 2003; Patel & Barkovich, 2002; Rodriguez & Dymecki, 2000).

Recent studies of the causes of cerebellar hypoplasia have explored genes and signaling molecules involved in the organizing and early patterning of the midbrain and anterior hindbrain during early pregnancy. Animal studies have shown that certain molecules that guide brain development, such as the *Wnt* family of signaling molecules, also play a role in cerebellar development (Goldowitz & Hamre, 1998; Rodriguez & Dymecki, 2000; Subashini et al., 2017). Others have revealed that targeted knockouts of murine genes (En1 and En 2) have produced cerebellar abnormalities in mice (Davis & Joyner, 1988). A recent case report suggested that *WDR73* is a candidate gene involved in cerebellar hypoplasia (Jiang et al., 2017). Additionally, chromosomal aberrations (trisomy 9, 13, and 18) and metabolic conditions have been linked to cerebellar hypoplasia (Poretti et al., 2009; M. Steinlin, Blaser, & Boltshauser, 1998). Yet, the specific etiology of most cerebellar hypoplasia cases remains unknown (Hunter, 2006).

Because it is rare, few studies have been able to identify non-genetic, epidemiological risk factors for cerebellar hypoplasia (Koning et al., 2016). The majority of evidence for potential prenatal risk factors comes from animal studies or case reports (Koning et al., 2016; Poretti et al., 2009), although Zika virus infection has drawn attention to the posterior fossa, including cerebellar hypoplasia. Maternal exposures linked to cerebellar hypoplasia include smoking (Ekblad et al., 2010), alcohol use (Norman, Crocker, Mattson, & Riley, 2009), cocaine use (Bellini, Massocco, & Serra, 2000), valproic acid use (Main & Kulesza, 2017; Squier, Hope, & Lindenbaum, 1990), mifepristone use for failed termination (Afadapa &

Elsapagh, 2006; Sitruk-Ware, Davey, & Sakiz, 1998), family history (Hunter, 2006; Murray, Johnson, & Bird, 1985), and congenital infections (Silasi et al., 2015) such as cytomegalovirus infection (Ceballos, Ch'ien, Whitley, & Brans, 1976; Patel & Barkovich, 2002; Poretti et al., 2009; M. I. Steinlin, Nadal, Eich, Martin, & Boltshauser, 1996) and Zika virus infection (Araujo Junior, Carvalho, Tonni, & Werner, 2017; de Fatima Vasco Aragao et al., 2016; Hazin et al., 2016; Melo et al., 2016; Meneses et al., 2017; Schuler-Faccini et al., 2016). Additionally, gestational age at birth has been associated with cerebellar hypoplasia and several studies have focused on postnatal risk factors for the maturation of the cerebellum after preterm birth, including glucocorticoid exposure and brain injury (Brossard-Racine et al., 2017; Limperopoulos et al., 2014; Tam, 2013; Tam et al., 2011). We sought to use data from the National Birth Defects Prevention Study (NBDPS) to explore potential epidemiologic risk factors for cerebellar hypoplasia.

Methods

The NBDPS was a large, multi-site, population-based, case-control study designed to investigate risk factors of major structural birth defects that began collecting data in 1997 (Reefhuis et al., 2015). Briefly, cases with one or more of 30 different categories of major structural birth defects were ascertained through birth defect surveillance programs in ten states (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah). Cases with a known chromosomal or single-gene abnormality were excluded. Clinical information of each case was reviewed by a clinical geneticist at each site to ensure standard case classification (Reefhuis et al., 2015). Controls were live born infants without birth defects randomly selected from hospital records or birth certificates in the same time period and geographic area as the cases. The NBDPS included cases and controls with estimated delivery dates from October 1, 1997 through December 31, 2011. Mothers of all eligible cases and controls were invited to participate in a computer-assisted telephone interview between 6 weeks and 24 months after the estimated date of delivery. Trained interviewers conducted the interviews in English and Spanish. The interview collected information on demographics, pregnancy history, various health conditions, and other exposures from three months before pregnancy through the end of pregnancy. Mothers were asked about all medications taken and information was collected on timing, frequency, and duration of medication use. The Slone Epidemiology Center Drug Dictionary was used to code all reported medications. During the study period, 66.7% of eligible case mothers and 63.7% of eligible control mothers participated in the interview. In total, 44,029 mothers (32,200 case and 11,829 control mothers) completed the NBDPS interview. Each study site obtained Institutional Review Board approval for the NBDPS and case and control mothers provided informed consent.

Classification of cerebellar hypoplasia cases was performed by a clinical geneticist to confirm diagnosis and assign each case as having either isolated (presence of this major birth defect within only one organ system, specifically in the central nervous system [CNS]) or multiple birth defects (presence of other unassociated major birth defects within other organ systems). The cerebellar hypoplasia case definition included cases described as isolated cerebellar vermis hypoplasia, cerebellar hypoplasia, cerebellar hemispheric aplasia, total agenesis, or vermis aplasia. Cerebellar hypoplasia must have been diagnosed on a postnatal

examination (brain imaging, surgical repair/correction, or autopsy) to be included in the NBDPS. Cases with cerebellar hypoplasia that was a component of Dandy-Walker malformation were counted in the NBDPS as cases of Dandy-Walker malformation and not as cerebellar hypoplasia cases. Thus, this analysis did not include cases diagnosed with Dandy-Walker malformation. Cases of cerebellar hypoplasia with other central nervous system defects were included as cerebellar hypoplasia cases. The same case classification definition was applied to all identified cerebellar hypoplasia cases, regardless of whether they completed the NBDPS interview. Prior to the current analysis, two clinicians (KKN, CMC) re-reviewed all cerebellar hypoplasia cases and assigned each case a more detailed classification: isolated cases were further classified as either (1) cerebellar hypoplasia only and (2) cerebellar hypoplasia plus other major CNS birth defects; and multiple cases were further classified as either (1) cerebellar hypoplasia plus other major non-CNS birth defects or (2) cerebellar hypoplasia plus other non-CNS and major CNS birth defects.

A small amount of demographic and clinical information was available for cerebellar hypoplasia cases regardless of whether the mother participated in the interview. We compared these demographic and clinical variables by interview status (interviewed/non-interviewed) and by the more detailed case classification using chi-square tests or Fisher's exact tests (when cell sizes were less than five). We analyzed demographic and clinical variables including sex at birth, birth outcome (live birth/stillbirth/fetal death<20 weeks/induced abortion), plurality (singleton/multiple), maternal age at delivery (<20 years/20–34 years/or 35+ years), and maternal race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other). For live-born cases, we analyzed gestational age at delivery (<37 weeks/37+ weeks) and birth weight (<2,500 grams/≥2,500 grams). Additionally, we used NBDPS data to estimate the prevalence of non-syndromic cerebellar hypoplasia. To do this, we estimated birth prevalence from the number of eligible cerebellar hypoplasia cases per 100,000 live births among the source population from which the cases were ascertained. We calculated the birth prevalence overall (1997–2011) and within two periods of NBDPS (1997–2004 and 2005–2011).

We used data from the NBDPS telephone interview to compare characteristics of cerebellar hypoplasia cases and controls. We explored potential risk factors in the following categories: (1) *maternal demographics*, including age at delivery (<20 years/20–34 years/or 35+ years), race/ethnicity (non-Hispanic white/non-Hispanic black, Hispanic/other), years of education (<12 years/12 years/>12 years), pre-pregnancy body mass index [(BMI) weight in kilograms/height in meters^2, ≤ 24.9/>24.9], nativity (United States/other), family history of cerebellar hypoplasia (yes/no), and state of residence at the time of birth (study site); (2) *pregnancy characteristics*, including birth year (1997–2004/2005–2011), plurality (singleton/multiple), number of previous pregnancies (none/1 or more), pregnancy intention (wanted to be pregnant/wanted to wait until later/did not want to be pregnant/did not care), previous miscarriage (yes/no), use of fertility treatment or procedures for the current pregnancy (yes/no), previous pregnancy resulting in cerebellar hypoplasia (yes/no), and season of conception (spring/summer/fall/winter); (3) *maternal health conditions*, including pre-existing diabetes (yes/no), gestational diabetes during pregnancy (yes/no), history of chronic or gestational hypertension (yes/no), history of seizures (yes/no), periconceptional maternal fever (yes/no; periconceptional is defined as the month before through the third month of

pregnancy), second trimester maternal fever (yes/no), third trimester maternal fever (yes/no), periconceptional respiratory infection (yes/no), second trimester respiratory infection (yes/no), third trimester respiratory infection (yes/no), periconceptional genitourinary infection (yes/no), second trimester genitourinary infection (yes/no), third trimester genitourinary infection (yes/no), and other infections during pregnancy (yes/no); (4) *maternal medication use*, including folic acid-containing supplement use during the month before through the first month of pregnancy (yes/no), periconceptional vasoactive medication use (yes/no), and periconceptional folate-antagonist medication use (yes/no); (5) *maternal behavioral exposures*, including periconceptional cigarette smoking (yes/no), periconceptional alcohol use (yes/no), and recreational drug use during pregnancy (yes/no); and (6) *infant characteristics*, including sex at birth, gestational age at delivery (<37 weeks/37+ weeks) and birth weight (<2,500 grams/≥2,500 grams). While we did not consider gestational age at delivery and birth weight as potential risk factors for cerebellar hypoplasia, we included them in the analysis to assess whether these factors were associated with live-born cerebellar hypoplasia cases when compared to control infants.

To assess “other infections” reported during pregnancy, we scanned responses to a question asking mothers about “any other diseases” and comment fields to determine if any other infections were reported by mothers of cerebellar hypoplasia cases. The only “other infection” reported during pregnancy among mothers of cerebellar hypoplasia cases was herpes simplex virus. Vasoactive medications included antihypertensive medication, aspirin, bronchodilators, decongestants, antimigraine medications, and nonsteroidal anti-inflammatory drugs (NSAIDS). Folate-antagonist medications included trimethoprim, triamterene, sulfasalazine, phenytoin, phenobarbital, primidone, carbamazepine, cholestyramine resin, methotrexate, aminopterin sodium, pyrimethamine, valproate sodium, valproic acid, and divalproex sodium.

We used bivariate logistic regression to calculate crude odds ratios (ORs) and 95% confidence intervals (CIs) for the association between these potential risk factors and the occurrence of cerebellar hypoplasia. If less than 5 cases were in a level of a given covariate, exact confidence intervals were calculated using the Fisher’s exact test. We did not calculate crude odds ratios and confidence intervals for variables with cell sizes of 1. The Cochran-Armitage trend test was used to explore the trend in cerebellar hypoplasia across the study period. Analyses were performed using SAS software, version 9.4 (SAS Corporation, Cary, NC) and R (3.1.1; Vienna, Austria).

Results

From 1997–2011, 87 eligible cases with non-syndromic cerebellar hypoplasia were identified as part of the NBDPS, resulting in an overall birth prevalence of 1.30 per 100,000 births. The birth prevalence differed by time period; the prevalence of cerebellar hypoplasia from 1997–2004 was 0.68 per 100,000, whereas the prevalence of cerebellar hypoplasia for 2005–2011 was 2.00 per 100,000.

These 87 cases included 55 (63.2%) cases whose mothers participated in the NBDPS interview and 32 (36.8%) whose mothers did not (Table 1). We did not find any statistically

significant differences in clinical characteristics between the cerebellar hypoplasia cases whose mothers completed the NBDPS interview and the cerebellar hypoplasia cases whose mothers did not.

Of the 87 cerebellar hypoplasia cases, 23 (26.4%) had cerebellar hypoplasia only, which included cases with findings of enlarged cisterna magna (Table 2). Twenty-six (29.9%) cases were considered isolated, but had other major CNS birth defects, with absent/hypoplastic corpus callosum and hydrocephalus being the most common other CNS birth defects.

Of the 38 cerebellar hypoplasia cases with non-CNS birth defects, 16 (18.4%) had one or more non-CNS birth defect(s) and 22 (25.3%) had both CNS and non-CNS birth defects. Cardiovascular defects were the most common non-CNS birth defects, observed in 21 cerebellar hypoplasia cases. The congenital heart defects were heterogeneous, including 15 cases with either ventricle septal defects or atrial septal defects. Seven cases had complex congenital heart defects, which included 2 occurrences of single ventricle complex, 2 occurrences of d-transposition of the great arteries, and single occurrences of Ebstein anomaly, heterotaxy, and complete AV canal. Nine cases had eye defects, although the specific eye defects varied and included colobomas, retinal dystrophy, micro/anophthalmia, cataracts, and congenital glaucoma. Of the 22 cases with cerebellar hypoplasia plus CNS and non-CNS birth defects, the most frequently observed CNS birth defects included corpus callosum defects, hydrocephalus, and neuronal migration defects (lissencephaly, schizencephaly, pachygyria, hemimegalencephaly).

Table 3 compares clinical characteristics by the detailed cerebellar hypoplasia classification. Cerebellar hypoplasia cases did not significantly differ by any of the clinical characteristics across the four classification categories. Yet, when we compared live-born isolated cases to live-born multiple cerebellar hypoplasia cases, multiple cerebellar hypoplasia cases were more likely to be preterm, although this difference did not reach statistical significance (P=0.0656).

Our analysis of potential risk factors for cerebellar hypoplasia included 55 interviewed cases and 11,829 non-malformed control infants (Table 4). The average time between the estimated delivery date and interview was 12.8 months among cases and 9.2 months among controls; this difference was statistically significant ($P<0.0001$). Cases were more likely to be from a multiple pregnancy than control infants (OR=3.3, 95% CI=1.3–8.2; Table 4). Cerebellar hypoplasia was significantly associated with birth year (OR=3.3, 95% CI=1.8–6.1), with more cases seen in the later years of the NBDPS (Figure 1). Most of the remaining risk factors examined, however, were not associated with cerebellar hypoplasia. We did not find any statistically significant differences between cases and controls in terms of maternal demographics, maternal health conditions, or maternal medication use. We found crude ORs that were elevated but not statistically significant for non-Hispanic black race (OR=1.8, 95% CI=0.9–3.6), history of hypertension (OR=1.8, 95% CI=0.9–3.3), and periconceptional use of vasoactive medications (OR=1.7, 95% CI=1.0–2.9). Additionally, cerebellar hypoplasia live-born cases were more likely than control infants to be born preterm (OR=4.6, 95% CI=2.5–8.3) and have a low birthweight (OR=7.3, 95% CI=4.0–13.3).

Discussion

In this population-based, case-control study we describe the clinical features of non-syndromic cerebellar hypoplasia, estimate prevalence, and examine potential non-genetic risk factors. Using NBDPS data, we found 87 cases with non-syndromic cerebellar hypoplasia. Our analysis excluded cases of cerebellar hypoplasia that were a component of Dandy-Walker malformation, instead focusing on cerebellar hypoplasia but not the other Dandy-Walker malformation components. We found a birth prevalence for cerebellar hypoplasia of 1.30 per 100,000 persons. The prevalence of cerebellar hypoplasia at birth is unknown and few have attempted to estimate the prevalence of cerebellar hypoplasia (Wassmer et al., 2003). Some studies have described the prevalence in specific populations, but previous prevalence estimates have not been population-based, instead existing estimates use hospital- or clinic-based reports. For example, one study documented cerebellar hypoplasia in 11 of 2,500 (0.4%) children seen by a pediatric neurologist (Shevell & Majnemer, 1996), while another identified that among 70 children with cerebellar malformations seen in the authors' clinical practice, 6 infants had cerebellar hypoplasia (Patel & Barkovich, 2002). Wassmer et al. (2003) documented that nine children (4.5%) had cerebellar hypoplasia out of 188 children presenting with developmental delays at a large regional secondary and tertiary children's hospital. Another report by Pinar et al. (1998) found cerebellar malformations to be 3% of all CNS malformations in a perinatal and neonatal autopsy series.

We observed that the cerebellar hypoplasia cases whose mothers participated in the NBPDS were more likely than controls to be from a multiple pregnancy, be born preterm, and have a low birthweight. Additionally, cases with cerebellar hypoplasia were more likely to be born in or after 2005, as opposed to the earlier part of NBDPS. We found elevated OR that did not reach statistical significance for maternal use of vasoactive medications. Of the 25 mothers of cerebellar hypoplasia cases who reported using at least one vasoactive medication in the periconceptional period, 21 reported using an NSAID; thus, the increased risk of cerebellar hypoplasia associated with vasoactive medication use [cOR 1.7 (1.0, 2.9)] was largely driven by those using NSAIDs [cOR 1.8 (1.1, 3.2)]. In addition to NSAID use, 2 mothers reported using a bronchodilator, 5 reported using aspirin, 1 reported using a calcium channel blocker, and 1 reported using a beta-blocker. Five mothers used two medications classified as vasoactive. We also observed elevated ORs that did not reach statistical significance for non-Hispanic black mothers, and mothers with a history of hypertension. We found that there were not statistically significant differences between interviewed and non-interviewed cases of cerebellar hypoplasia.

Several of these findings are consistent with existing literature. Several studies have identified that cerebellar hypoplasia cases are often preterm and have low birth weight, which we observed. Our findings also suggest that cerebellar hypoplasia cases classified as multiple (meaning they had non-CNS birth defects) were more likely to be preterm than isolated cerebellar hypoplasia cases. Abnormal development of the cerebellum has recently been determined to play a significant role in outcome after preterm birth (Araujo Junior et al., 2007; Tam, 2013). In addition to the increased risk for preterm birth among cerebellar hypoplasia pregnancies, studies have explored potential postnatal exposures among preterm

babies that are associated with poor cerebellar maturation and development, including glucocorticoid use and injury (Aden et al., 2008; Bohn & Lauder, 1980; Brossard-Racine et al., 2017; Jacobs, Trinh, Rootwelt, Lomo, & Paulsen, 2006; Limperopoulos et al., 2014; Limperopoulos et al., 2005; Parikh et al., 2007; Tam, 2013; Tam et al., 2011). While the crude OR did not reach statistical significance, we found non-Hispanic black maternal race/ethnicity was associated with cerebellar hypoplasia. We also found that among cerebellar hypoplasia cases, those with multiple defects were more likely to be Hispanic. Two other studies have identified differences in cerebellar size by race/ethnicity, although these studies examined ethnicity based on country of origin, which is different than how race/ethnicity is approached within the NBDPS (Araujo Junior et al., 2007; Jacquemyn, Sys, & Verdonk, 2000; Koning et al., 2016). Additionally, a recent analysis of Dandy-Walker malformation cases within NBDPS found an association with non-Hispanic black race (Reeder et al., 2015).

Our finding that the number of cerebellar hypoplasia cases increased in later years of NBDPS (Figure 1) is potentially consistent with the literature. We also found that the birth prevalence in earlier years of NBDPS (0.68) was much smaller than the birth prevalence in later years of NBDPS (2.00). Cranial magnetic resonance imaging (MRI) and cranial computer tomography (CT) have enhanced the ability to identify abnormalities of the cerebellum (Wassmer et al., 2003). Advances in MRI and CT are changing our understanding of normal development of the cerebellum, as well as our understanding of deviations in development (Limperopoulos, 2016; Patel & Barkovich, 2002). The significant finding that there were more cerebellar hypoplasia cases within NBDPS in the latter study period is consistent with the idea that cerebellar malformations are more likely to be recognized because of improvements in MRI/CT technology. Improvements in technology have impacted diagnosis of other birth defects. For example, the prevalence of ventricular septal defects has increased dramatically with advances in imaging and screening techniques (Minette & Sahn, 2007). Some changes to NBDPS may also account for an increase in cerebellar hypoplasia over time, including the addition of two sites (North Carolina and Utah) in 2003 and modifications to the cerebellar hypoplasia classification guidelines. Because of clarifications to the case classification guidelines, it may be possible that cerebellar hypoplasia cases with mega cisterna magna could have been included in NBDPS as a Dandy-Walker malformation case earlier in NBDPS, but as a cerebellar hypoplasia case later in NBDPS. Yet, we do not see evidence of this, as the number of Dandy-Walker malformation cases does not differ across time periods of NBDPS, so it is unlikely that this accounts for the increase of cerebellar hypoplasia cases over time. Our estimates of cerebellar hypoplasia birth prevalence may be underestimates of the truth if we missed cases during the earlier periods of the NBDPS. Additionally, a strength of NBDPS is that one clinical geneticist (KKN) reviewed and classified all cerebellar hypoplasia and Dandy-Walker malformation cases, so we do not expect there to be variations in the classification of these birth defects over time.

The existing literature has identified some potential risk factors, mainly through animal studies and case reports, that we did not find among NBDPS cerebellar hypoplasia cases. Several studies, reviews, and case reports have found associations between prenatal infections, particularly viral infections, and cerebellar hypoplasia (Ceballos et al., 1976; de

Fatima Vasco Aragao et al., 2016; Hazin et al., 2016; Koning et al., 2016; Melo et al., 2016; Meneses et al., 2017; Patel & Barkovich, 2002; Poretti, Wolf, & Boltshauser, 2008; M. I. Steinlin et al., 1996). Yet, the possible role of an infectious etiology remains unclear from our NBDPS results. There were very few reports of infection among mothers of cerebellar hypoplasia cases. While mothers of cerebellar hypoplasia cases did report cold/flu, genitourinary infections, and fever during pregnancy, these were not associated with cerebellar hypoplasia regardless of time period of the reported exposure. No mother of a cerebellar hypoplasia case reported CMV infection. The only “other infection” reported during pregnancy among mothers of cerebellar hypoplasia cases was herpes simplex virus, which was reported by 2 of the 55 interviewed mothers of cerebellar hypoplasia cases. The OR for the association between herpes simplex virus infection and cerebellar hypoplasia was elevated (cOR=3.2); however, the confidence interval was wide and not significant. Of the two mothers of cerebellar hypoplasia cases who reported a herpes infection during pregnancy, one reported herpes infection beginning in the third month of pregnancy and reported starting medication for the herpes infection at that time and continuing throughout pregnancy. The other mother with herpes infection reported herpes for the entire pregnancy but did not report taking any medication during pregnancy for the herpes infection.

Other studies have associated valproic acid use with cerebellar hypoplasia (Main & Kulesza, 2017; Squier et al., 1990). In our study, we found that only 1 mother used an anti-folate medication, but the mother did not report using valproic acid. Instead she reported using carbamazepine, a different anticonvulsant. Carbamazepine monotherapy has been associated with an increased risk for spina bifida (Jentink et al., 2010). Additionally, a meta-analysis of prospective studies (including 1,255 carbamazepine exposure pregnancies) found an increased rate of neural tube defects, cardiovascular birth defects, urinary tract anomalies and cleft palate, in addition to a pattern of minor congenital anomalies and developmental delays (Matalon, Schechtman, Goldzweig, & Ornoy, 2002). We also explored maternal behavioral risk factors, including cocaine use, alcohol use, and smoking, all of which have been associated with cerebellar hypoplasia previously (Bellini et al., 2000; Ekblad et al., 2010; Koning et al., 2016; Norman et al., 2009). No mother of a cerebellar hypoplasia case in the NBDPS reported cocaine use. While 36% of mothers of cerebellar hypoplasia cases reported alcohol use during the periconceptional period, we saw no suggestion of an increased risk of cerebellar hypoplasia. Thirteen of the 55 interviewed mothers of cerebellar hypoplasia cases reported periconceptional smoking. The OR for smoking was elevated (cOR=1.4) but the confidence interval did not reach statistical significance.

Some of the maternal exposures we identified as associated with cerebellar hypoplasia in the crude analysis, including hypertension, vasoactive medications, and multiple gestations, have been postulated to impact blood flow to the fetus or affect the development of blood vessels, resulting in vascular disruptions that could lead to the development of birth defects (Dawson et al., 2016; Schinzel, Smith, & Miller, 1979; van Gelder, de Jong-van den Berg, & Roeleveld, 2014; van Gelder et al., 2010). While cerebellar hypoplasia has not been examined specifically as a vascular disruption birth defect (van Gelder et al., 2010), other CNS defects, specifically hydranencephaly and porencephaly, have been (Hoyme, Higginbottom, & Jones, 1981; Mittelbronn et al., 2006).

Several methodological limitations in this study should be considered when interpreting the results. Despite the large size of the NBDPS, the small number of cerebellar hypoplasia cases raised problems in the analysis. Coupled with low power given the small number of cases, we were unable to examine the effect of numerous risk factors simultaneously and to adjust for potential confounding, so only have presented crude ORs. The NBDPS relies on retrospective reporting of maternal exposures in NBDPS, which could lead to recall bias, if there is differential recall among NBDPS case and control mothers. Our findings include associations with infant characteristics (including multiple births, preterm birth, low birth weight and birth year) which are not subject to recall difficulties or differences by case/control status. Additionally, the NBDPS standardized interview was conducted by trained interviewers and included standardized prompts, medication lists, and pregnancy calendars, which aided mothers in identifying and recalling such exposures. Our analysis examined a variety of potential exposures, so multiple associations were tested and some associations may have occurred by chance alone. Yet we do not believe this is a concern because we did not find many associations overall and several of our findings had been previously identified as being associated with cerebellar hypoplasia in the literature. Our classification of cerebellar hypoplasia was based on reports of radiologic procedures. The authors did not independently review images, instead relied on interpretations of the diagnosing physician(s).

Despite these limitations, there were several strengths of our analysis. First, we used data from a population-based, case-control study of major birth defects to explore potential risk factors for cerebellar hypoplasia. Most evidence for associations with cerebellar hypoplasia come from animal studies and case reports, and a recent review stated that the “amount and quality of evidence regarding potential risk factors for cerebellar hypoplasia is relatively low” (Koning et al., 2016). The NBDPS obtained information on a wide-range of potential risk factors through a standardized and comprehensive maternal interview, which allowed us to investigate a large number of variables. Second, NBDPS used a clear and consistent cerebellar hypoplasia definition and the NBDPS case classification was standardized. All cases of cerebellar hypoplasia (both interviewed and non-interviewed) were reviewed by a clinical geneticist. Subsequently, all cerebellar hypoplasia cases were re-reviewed prior to this analysis by two study investigators (KKM and CMC) to confirm the case classification, and further group cerebellar hypoplasia cases by the co-occurring birth defects. Third, we used NBDPS data to estimate the prevalence of cerebellar hypoplasia in the general population.

This population-based study examined potential cerebellar hypoplasia risk factors. While we identified several infant characteristics that were associated with cerebellar hypoplasia, no other exposure variables reached statistical significance. We did find elevated ORs that did not reach statistical significance for maternal use of vasoactive medications, non-Hispanic black mothers, and mothers with a history of hypertension, suggesting some new epidemiologic risk factors. Given that our results are unadjusted, further investigations of the role of non-genetic, as well as genetic, risk factors are needed to further understand the underlying cause(s) of cerebellar hypoplasia. Our findings can contribute to new hypotheses regarding the etiology of cerebellar hypoplasia.

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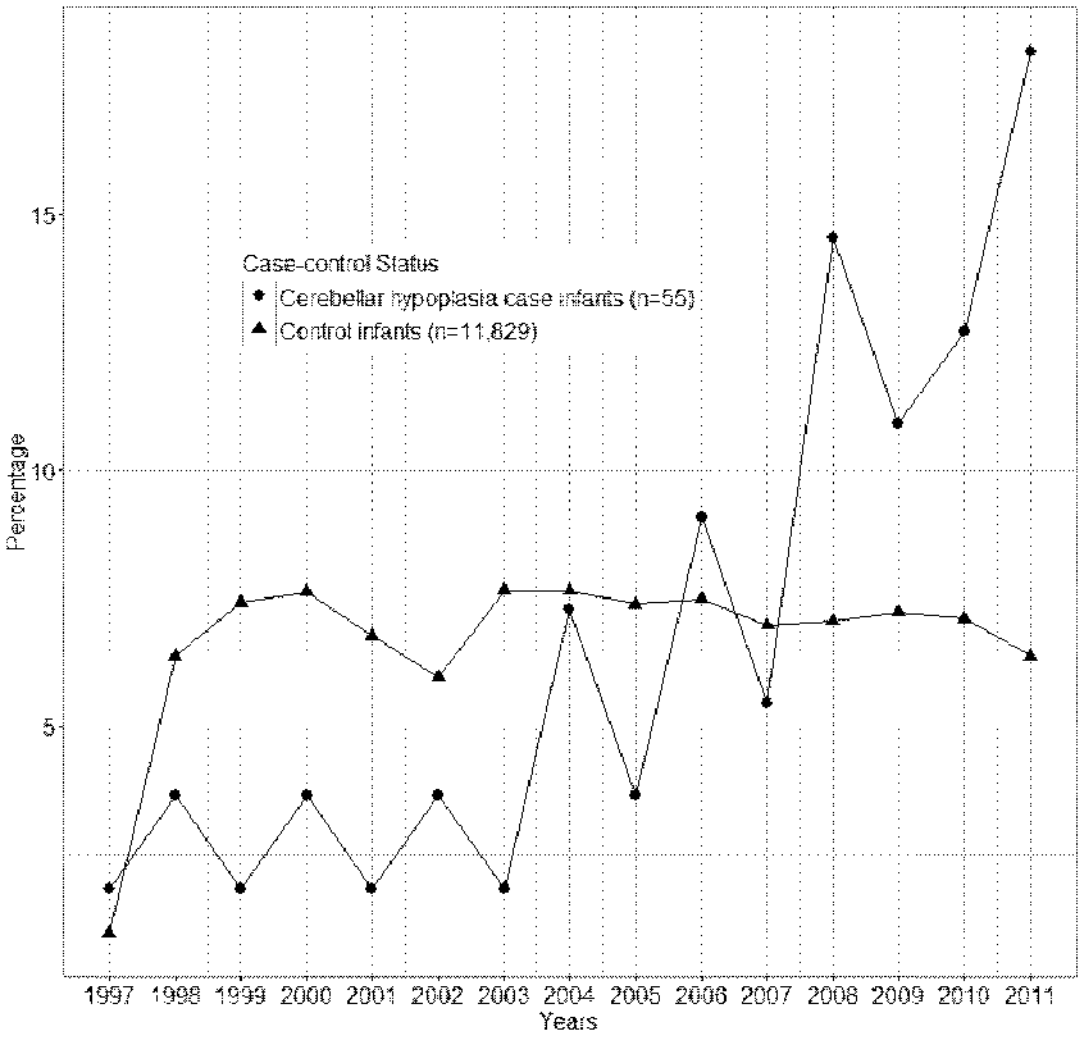

Figure 1.

Proportion of CH case and control infants, by birth year, in the National Birth Defects Prevention Study (NBDPS), 1997–2011. The proportion of CH case infants whose mother completed the NBDPS interview each year is denoted with a black dot. The proportion of control infants whose mother completed the NBDPS interview each year is denoted with a black triangle. The increase in the proportion of CH cases over the study period was statistically significant.

Table 1.

Clinical characteristics for all cerebellar hypoplasia cases, by interview status, National Birth Defects Prevention Study, 1997–2011 (n=87)

	Total cerebellar hypoplasia cases n (%)	Interviewed Cerebellar hypoplasia cases n (%)	Non-interviewed cerebellar hypoplasia cases n (%)
	87 (100%)	55 (63.2%)	32 (36.8%)
Classification Isolated With other CNS defects With other non-CNS defects With other CNS and non-CNS defects	23 (26.4) 26 (29.9) 16 (18.4) 22 (25.3)	16 (29.1) 18 (32.7) 9 (16.4) 12 (21.8)	7 (21.9) 8 (25.0) 7 (21.9) 10 (31.3)
Sex Male Female	45 (51.7) 42 (48.3)	32 (58.2) 23 (41.8)	13 (40.6) 19 (59.4)
Birth outcome Live birth Fetal death ≥ 20 weeks Induced abortion	79 (90.8) 1 (1.2) 7 (8.0)	50 (90.9) 1 (1.8) 4 (7.3)	29 (90.6) 0 3 (9.4)
Gestational age at delivery†‡ < 37 weeks ≥ 37 weeks	30 (38.5) 48 (61.5)	16 (32.0) 34 (68.0)	14 (50.0) 14 (50.0)
Birth weight‡ < 2,500 grams ≥2,500 grams	30 (38.0) 49 (62.0)	16 (32.0) 35 (68.0)	14 (48.3) 15 (51.7)
Plurality Single Multiple	80 (92.0) 7 (8.0)	50 (90.9) 5 (9.1)	30 (93.8) 2 (6.3)
Maternal age at delivery <20 years 20–34 years 35+ years	6 (6.9) 70 (80.5) 11 (12.6)	2 (3.6) 46 (83.6) 7 (12.7)	4 (12.5) 24 (75.0) 4 (12.5)
Maternal race/ethnicity Non-Hispanic white Non-Hispanic black Hispanic Other	52 (59.8) 14 (16.1) 15 (17.2) 6 (6.9)	32 (58.2) 11 (20.0) 8 (14.6) 4 (7.3)	20 (62.5) 3 (9.4) 7 (21.9) 2 (6.3)

CNS=central nervous system

†One non-interviewed case is missing gestational age.

‡Only live born cerebellar hypoplasia cases were included in this analysis.

Table 2.

Other major structural NBDPS birth defects seen among infants with cerebellar hypoplasia and other major birth defects (n=64), National Birth Defect Prevention Study, 1997–2011[†]

Cerebellar hypoplasia plus CNS birth defect(s) (n=26)		Cerebellar hypoplasia plus non-CNS birth defect(s) (n=16)		Cerebellar hypoplasia plus CNS and non-CNS birth defects (n=22)	
Defect	**n (%)**	**Defect**	**n (%)**	**Defect**	**n (%)**
Corpus callosum agenesis/hypoplasia[‡]	12 (46)	Cardiovascular	10 (62)	CNS	22 (100)
Hydrocephalus	9 (35)	Musculoskeletal	5 (31)	Cardiovascular	11 (50)
Midbrain (brainstem) hypoplasia	4 (15)	Cleft palate	3 (19)	Eye	8 (36)
Optic nerve hypoplasia	4 (15)	Renal	3 (19)	Musculoskeletal	7 (32)
Lissencephaly	3 (12)	Diaphragmatic hernia	1 (6)	Orofacial	6 (27)
Hemimegalencephaly	2 (8)	Ear/hearing loss	1 (6)	Renal	5 (23)
Schizencephaly	2 (8)	Eye	1 (6)	Gastrointestinal	3 (14)
		Gastrointestinal	1 (6)	Ear/hearing loss	1 (4)
		Genital	1 (6)	Genital	1 (4)
		Omphalocele	1 (6)	Pulmonary	1 (4)

CNS=central nervous system

[†]A case may have more than one defect or defect group listed.

[‡]Includes partial agenesis.

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Table 3.

Clinical characteristics for all cases (n=87), by classification status, National Birth Defects Prevention study, 1997–2011

	Isolated birth defects†		Multiple birth defects	
	Cerebellar hypoplasia only n (%)	Cerebellar hypoplasia plus CNS birth defect(s) n (%)	Cerebellar hypoplasia plus non-CNS birth defect(s) n (%)	Cerebellar hypoplasia plus CNS and non-CNS birth defects n (%)
	23 (26.4%)	26 (29.9%)	16 (18.4%)	22 (25.3 %)
Sex Male Female	11 (47.8) 12 (52.2)	15 (57.7) 11 (42.3)	9 (56.3) 7 (43.8)	10 (45.5) 12 (54.6)
Birth outcome Live birth Fetal death ≥ 20 weeks Induced abortion	21 (91.3) 0 2 (8.7)	24 (92.3) 0 2 (7.7)	15 (93.8) 1 (6.3) 0	19 (86.4) 0 3 (13.6)
Gestational age at delivery‡§ < 37 weeks ≥ 37 weeks	4 (20.0) 16 (80.0)	9 (37.5) 15 (62.5)	8 (53.3) 7 (46.7)	9 (47.4) 10 (52.6)
Birth weight§ < 2,500 grams ≥2,500 grams	6 (28.6) 15 (71.4)	8 (33.3) 16 (66.7)	9 (60.0) 6 (40.0)	7 (36.8) 12 (63.2)
Plurality Single Multiple	22 (95.7) 1 (4.4)	24 (92.3) 2 (7.7)	15 (93.8) 1 (6.3)	19 (86.4) 3 (13.6)
Maternal age at delivery <20 years 20–34 years 35+ years	1 (4.4) 20 (87.0) 2 (8.7)	1 (3.9) 19 (73.1) 6 (23.1)	3 (18.8) 11 (68.8) 2 (12.5)	1 (4.6) 20 (90.9) 1 (4.6)
Maternal race/ethnicity Non-Hispanic white Non-Hispanic black Hispanic Other	14 (60.9) 6 (26.1) 2 (8.7) 1 (4.4)	17 (65.4) 4 (15.4) 5 (19.2) 0	9 (56.25) 2 (12.5) 4 (25.0) 1 (6.25)	12 (54.6) 2 (9.1) 4 (18.2) 4 (18.2)

CNS=central nervous system

† Isolated birth defects are defined as major birth defect(s) within only one organ system, which in this analysis would be the central nervous system.

‡ One non-interviewed case is missing gestational age.

§ Only live born cerebellar hypoplasia cases were included in this analysis.

Table 4.

Selected characteristics of interviewed cerebellar hypoplasia case and control infants and their birth mothers, National Birth Defects Prevention Study, 1997–2011

	Control infants	Cerebellar hypoplasia cases	Crude Odds Ratio
	n = 11,829 n (%)	n = 55 n (%)	OR (95% CI)
Maternal demographics			
Maternal age at delivery <20 years 20–34 years 35+ years	1,177 (10.0) 8,988 (76.0) 1,644 (14.1)	2 (3.6) 46 (83.6) 7 (12.7)	0.3 (0.0, 1.3)† – 0.8 (0.4, 1.8)
Race/ethnicity Non-Hispanic white Non-Hispanic black Hispanic Other	6,836 (57.8) 1,308 (11.1) 2,908 (24.6) 771 (6.5)	32 (58.2) 11 (20.0) 8 (14.6) 4 (7.3)	– 1.8 (0.9, 3.6) 0.6 (0.3, 1.3) 1.1 (0.3, 3.1)†
Education < 12 years 12 years > 12 years	1,905 (16.6) 2,725 (23.7) 6,854 (59.7)	6 (10.9) 16 (29.1) 33 (60.0)	0.5 (0.2, 1.4) – 0.8 (0.5, 1.5)
Pre-pregnancy body mass index (kg/m^2) Underweight/normal (≤ 24.9) Overweight/obese (> 24.9)	6,644 (58.9) 4,631 (41.1)	30 (56.6) 23 (43.4)	– 1.1 (0.6, 1.9)
Nativity United States Other	9,102 (79.2) 2,392 (20.8)	45 (81.8) 10 (18.2)	1.2 (0.6, 2.4) –
Family history of cerebellar hypoplasia Yes No	1 (0.01) 11,828 (99.99)	1 (1.6) 54 (98.4)	NC
Study site Arkansas California Iowa Massachusetts New Jersey New York Texas Atlanta North Carolina Utah	1,471 (12.4) 1,263 (10.7) 1,300 (11.0) 1,402 (11.9) 578 (4.9) 989 (8.4) 1,416 (12.0) 1,267 (10.7) 1,016 (8.6) 1,127 (9.5)	10 (18.2) 2 (3.6) 8 (14.6) 2 (3.6) 0 (0.0) 4 (7.3) 5 (9.1) 10 (18.2) 8 (14.6) 6 (10.9)	– 0.2 (0.00, 1.1)† 0.9 (0.4, 2.3) 0.2 (0.00, 1.0)† NC 0.6 (0.1, 2.1)† 0.5 (0.2, 1.5) 1.2 (0.5, 2.8) 1.2 (0.5, 3.0) 0.8 (0.3, 2.2)
Pregnancy-related variables			
Birth year 1997–2004 2005–2011	5,952 (50.3) 5,877 (49.7)	13 (23.6) 42 (76.4)	– 3.3 (1.8, 6.1)
Plurality Singleton Multiples	11,452 (97.0) 351 (3.0)	50 (90.9) 5 (9.1)	– 3.3 (1.3, 8.2)
Number of previous pregnancies 0 1 or more	3,471 (29.5) 8,307 (70.5)	16 (29.1) 39 (70.9)	– 1.0 (0.6, 1.8)
Pregnancy intention Wanted to be pregnant then Wanted to wait Did not want to be pregnant Did not care	5,677 (59.1) 1,963 (20.5) 1,115 (11.6) 846 (8.8)	33 (68.8) 6 (12.5) 5 (10.4) 4 (8.3)	– 0.5 (0.2, 1.3) 0.8 (0.3, 2.0) 0.8 (0.2, 2.3)†

	Control infants	Cerebellar hypoplasia cases	Crude Odds Ratio
Previous miscarriage Yes No	2,673 (22.7) 9,105 (77.3)	16 (29.1) 39 (70.9)	1.4 (0.8, 2.5) –
Any fertility treatment or procedures Yes No	547 (4.6) 11,282 (95.4)	4 (7.3) 51 (92.7)	1.6 (0.4, 4.4)† –
Previous pregnancy with cerebellar hypoplasia Yes No	0 (0) 11,829 (100.0)	1 (1.8) 54 (98.2)	NC
Season of Conception‡ Winter Spring Summer Fall	2,931 (24.8) 2,897 (24.5) 2,944 (24.9) 3,057 (25.8)	16 (29.1) 11 (20.0) 13 (23.6) 15 (27.3)	-- 0.7 (0.3, 1.5) 0.8 (0.4, 1.7) 0.9 (0.4, 1.8)
Maternal health conditions			
Pre-existing Type 1 or 2 diabetes Yes No	71 (0.6) 11,679 (99.4)	1 (1.8) 54 (98.2)	NC
Gestational diabetes during pregnancy Yes No	536 (4.6) 11,214 (95.4)	2 (3.9) 50 (96.1)	0.8 (0.1, 3.1)† –
History of hypertension Yes No	1,596 (13.7) 10,016 (86.3)	12 (21.8) 43 (78.2)	1.8 (0.9, 3.3) –
History of seizures Yes No	319 (2.7) 11,429 (97.3)	2 (3.6) 53 (96.4)	1.4 (0.2, 5.2)† –
Periconceptional maternal fever Yes No	1,853 (17.2) 8,902 (82.8)	6 (11.5) 46 (88.5)	0.6 (0.3, 1.5) –
Second Trimester maternal fever Yes No	1,747 (16.2) 9,034 (83.8)	8 (15.4) 44 (84.6)	0.9 (0.4, 2.0) –
Third trimester maternal fever Yes No	1,455 (13.5) 9,330 (86.5)	4 (7.8) 47 (92.2)	0.6 (0.1. 1.5)† –
Periconceptional respiratory infection Yes No	2,850 (26.3) 7,977 (73.7)	11 (21.2) 41 (78.9)	0.8 (0.4, 1.5) –
Second Trimester respiratory infection Yes No	2,706 (25.0) 8,121 (75.0)	6 (11.5) 46 (88.5)	0.4 (0.2, 0.9) –
Third trimester respiratory infection Yes No	1,980 (18.3) 8,847 (81.7)	5 (9.6) 47 (90.4)	0.5 (0.2, 1.2) –
Periconceptional genitourinary infection Yes No	879 (7.6) 10,734 (92.4)	5 (9.1) 50 (90.9)	1.2 (0.5, 3.1) –
Second Trimester genitourinary infection Yes No	941 (8.1) 10,680 (91.9)	4 (7.3) 51 (92.7)	0.9 (0.2, 2.4)† –
Third trimester genitourinary infection Yes No	841 (7.2) 10,781 (92.8)	3 (5.6) 51 (94.4)	0.8 (0.2, 2.3) –
Herpes infection during pregnancy Yes	139 (1.2) 11690 (98.8)	2 (3.6) 53 (96.4)	3.2 (0.4, 12.3)† –

	Control infants	Cerebellar hypoplasia cases	Crude Odds Ratio
No			
Maternal medication use			
Folic Acid supplement use[§] Yes No	6,165 (52.8) 5,507 (47.2)	34 (61.8) 21 (38.2)	– 0.7 (0.4, 1.2)
Periconceptional vasoactive medication use Yes No	3,778 (33.0) 7,680 (67.0)	25 (45.5) 30 (54.6)	1.7 (1.0, 2.9) –
Periconceptional anti-folate medication use Yes No	122 (1.0) 11,482 (99.0)	1 (1.8) 54 (98.2)	NC
Maternal behavioral exposures			
Periconceptional smoking Yes No	2,075 (18.0) 9,454 (82.0)	13 (23.6) 42 (76.4)	1.4 (0.8, 2.6) –
Periconceptional alcohol use Yes No	4,280 (37.3) 7,210 (62.8)	20 (36.4) 35 (63.6)	1.0 (0.6, 1.7) –
Marijuana use during pregnancy[¶] Yes No	557 (5.0) 10,940 (95.0)	3 (5.5) 52 (94.6)	0.9 (0.3, 4.6)[†] –
Infant characteristics			
Sex Female Male	5,793 (49.0) 6,024 (51.0)	23 (41.8) 32 (58.2)	1.3 (0.8, 2.3) –
Gestational age at delivery[¥] < 37 weeks ≥ 37 weeks	1,099 (9.3) 10,691 (90.7)	16 (32.0) 34 (68.0)	4.6 (2.5, 8.3) –
Birth weight[¥] < 2,500 grams ≥2,500 grams	709 (6.1) 10,973 (93.9)	16 (32.0) 34 (68.0)	7.3 (4.0, 13.3) –

OR=odds ratio; CI=confidence interval; NC=Not Calculated; Periconceptional is defined as the month before through the third month of pregnancy

[†]Exact P value and 95% confidence interval were calculated.

[‡]Spring, March–May; Summer, June–August; Autumn, September–November; Winter, December–February.

[§]From one month before pregnancy through the first month of pregnancy Mothers of cerebellar hypoplasia cases did not reporting using any other recreational drug during pregnancy.

[¶]Mothers of cerebellar hypoplasia cases did not reporting using any other recreational drug during pregnancy.

[¥]Only live born cerebellar hypoplasia cases were included in this analysis.