Published in final edited form as:

Am J Med Genet A. 2008 October 1; 146A(19): 2495–2500. doi:10.1002/ajmg.a.32418.

Agenesis of the Corpus Callosum in California 1983–2003: A Population-Based Study

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Abstract

The objective of this study was to characterize the prevalence, demographic risk factors, and malformations associated with agenesis and hypoplasia of the corpus callosum diagnosed in infancy. Using a large population-based registry of birth defects, we ascertained 630 cases of agenesis (ACC) and hypoplasia (HCC) of the corpus callosum diagnosed in the first year of life among 3.4 million live births from 1983–2003. Infants with destructive lesions or specific complex central nervous system malformations (neural tube defects, lissencephaly, and holoprosencephaly) were excluded. Multivariable Poisson regression analysis was used to examine demographic risk factors. The combined prevalence of ACC and HCC was 1.8 per 10,000 live births. Fifty-two percent of cases were male. Infants with ACC had an almost four-fold higher prevalence among infants born prematurely when compared with children born ≥ 37 weeks gestation (RR 3.7, 95% CI 2.5–5.3). After adjusting for paternal age, advanced maternal age ≥ 40 years was associated with ACC in infants with a chromosomal disorder (ACC RR 5.9; 95% CI 1.8–19.3, HCC RR 3.5; 95% CI 0.9–14.1). Paternal age was not significantly associated with ACC after adjusting for maternal age. Callosal anomalies were often seen in the context of a chromosomal abnormality (17.3%) and with accompanying somatic (musculoskeletal 33.5% and cardiac 27.6%) and central nervous system malformations (49.5%). Callosal anomalies form a clinically significant and relatively frequent group of malformations of the central nervous system that are associated with increased risk of premature birth, are more common with advanced maternal age and are frequently part of a complex, multisystem disorder.

Keywords

Nervous system malformations; Risk factors; Epidemiology; Infant; Genetics; Agenesis of the corpus callosum

INTRODUCTION

Malformations of the corpus callosum are observed in a variety of conditions that disrupt early cerebral development, including chromosomal and metabolic disorders, as well as intrauterine exposure to teratogens and infection (reviewed in [Paul et al., 2007]). Callosal malformations are frequently associated with other central nervous malformations and/or somatic anomalies [Barkovich, 2005; Barkovich and Norman, 1988; Hetts et al., 2006; Marszal et al., 2000]. In a number of individuals, however, agenesis of the corpus callosum may be entirely asymptomatic, without apparent associated clinical deficits and with only

mild intellectual difficulties, such as problems with visual processing, higher order language functions and social deficits apparent only on detailed psychometric testing [Bayard et al., 2004; Huber-Okraïneć et al., 2005; Paul et al., 2007]. Many individuals with callosal agenesis also carry a diagnosis of attention deficit or autistic spectrum disorder [Badaruddin et al., 2007; Doherty et al., 2006].

Past studies of callosal malformations have been small and limited to single-center case series of symptomatic subjects presenting to specialized clinics. The prevalence of callosal anomalies based on these studies, therefore, varies widely, as do the associated clinical features. A single study from an unselected population estimated that the prevalence of callosal agenesis is 1:1000 [Wang et al., 2004].

The purpose of this study was to further describe the epidemiology, risk factors and accompanying malformations seen in subjects with callosal anomalies using a large, population-based database of all malformations diagnosed in the first year of life in California from 1983 to 2003.

MATERIALS AND METHODS

The California Birth Defect Monitoring Program (CBDMP) is a population-based registry that actively collects information on infants with congenital malformations from medical records of non-military hospitals in California. Cases included live born infants delivered between January 1, 1983 and December 31, 2003 [Croen et al., 1991]. For birth years 2001 and 2002, agenesis of the corpus callosum was not fully ascertained by the CBDMP owing to budget restrictions and, therefore, no population data were extracted from these years. Data collection specialists reviewed medical records at hospitals and genetic centers in selected California counties to identify all structural malformations diagnosed within one year of age. The CBDMP captures an estimated 97% of all malformations that are diagnosed [Schulman and Hahn, 1993].

Nine hundred and two live births with British Pediatric Association (BPA) code 742.21 (agenesis of the corpus callosum) were identified from amongst a population of 3,440,576 live births for an initial birth prevalence estimate of 2.6/10,000. These determinations were made from radiologic (head ultrasound, computed tomography or magnetic resonance imaging) or autopsy reports. Of these, we then excluded infants with complex central nervous system (CNS) malformations for which the callosal malformation is thought to be secondary to the embryonic change that generated the principal malformation (neural tube defect, lissencephaly and holoprosencephaly, 238 cases), as well as cases where the callosal defect was considered secondary to a destructive lesion (porencephaly or calcification, 34 cases). Six hundred and thirty cases were analyzed. Two child neurologists (HCG and ES) reviewed individual reports and classified each case as either agenesis of the corpus callosum (ACC) or hypoplasia of the corpus callosum (HCC) according to the description by the local reporting radiologist or pathologist. We classified the anomaly as ACC for any complete or partial callosal agenesis and as HCC when the corpus callosum was described as thin. Accompanying CNS anomalies were classified only in the subset of 317 cases where a magnetic resonance imaging (MRI) report was available. The remaining cases were diagnosed based on computed tomography (CT, 112 cases), head ultrasound (86 cases), surgery or autopsy findings (48 cases) or some combination of these methods. Diagnostic testing for accompanying chromosomal and somatic abnormalities was performed at the discretion of the treating physician.

Maternal and infant characteristics were acquired by linking cases to California live birth certificates. Relative risks for the ratio of prevalence comparing an at-risk group to its

reference, and corresponding 95% confidence intervals (CIs) were calculated using Poisson regression (Statistical Analysis Software, version 9.1, SAS institute, Cary, NC) for the following variables: infant sex, gestational age (≤ 27 , 28–31, 32–36 or ≥ 37 weeks), maternal and paternal age (< 20 , 20–24, 25–29, 30–34, 35–39 or ≥ 40 years), multiple versus single gestation and maternal race/ethnicity (Non-Hispanic White, U.S.-born Hispanic White, Foreign-born Hispanic White, Black, Asian or Other). Dichotomous variables were evaluated using chi-square test.

RESULTS

There were 630 infants with callosal anomalies over the study period (ACC 472 cases, HCC 158 cases) for an overall birth prevalence of 1.8 per 10,000 live births. Approximately, two-thirds (63%) of cases were diagnosed within 10 days of delivery. The other one-third of cases was diagnosed throughout the remaining months in the first year post delivery. This diagnostic timing pattern was similar across the 20 years of data ascertainment.

As shown in Table I, we did not observe substantial risks in either case group for infant sex or plurality. There was a significant association between maternal race/ethnicity and agenesis of the corpus callosum. The risk of callosal anomaly was lower in Asian infants (RR 0.5; 95% CI 0.3–0.9) and higher in black infants (RR 1.4; 95% CI 1.0–2.0) when compared to non-Hispanic white infants, and persisted with similar point estimates and confidence intervals after adjusting for maternal age.

Advanced Parental Age

In unadjusted analyses, both advanced maternal and paternal age were associated with increased risks of callosal anomalies. These risks remained elevated for advanced maternal age when adjusted for paternal age. Paternal age, when adjusted for maternal age, was only modestly associated with increased risk (Table II). In infants for whom a chromosomal anomaly was detected, advanced maternal age (≥ 40) was associated with an almost six-fold increased risk for ACC (RR 5.9; 95% CI 1.8–19.3) when compared to a reference age of 25–29 years. There was also a trend toward increased risk of HCC in this age group (RR 3.5; 95% CI 0.9–14.1). For cases without chromosomal anomalies, the effect of advanced maternal age, when adjusted for paternal age, was substantially lower (ACC RR 1.3; 95% CI 0.7–2.5, HCC RR 2.1; 95% CI 0.7–6.5).

Premature Birth

In unadjusted analyses, infants born prematurely (< 37 weeks) were more likely to have callosal anomalies, compared to term births, with a relative risk for ACC of 3.7 (95% CI 3.0–4.6) and for HCC of 3.6 (95% CI 2.5–5.3). Adjusting for maternal age did not substantially alter these estimated effects (ACC adjusted RR 3.7, 95% CI 3.0–4.6; HCC adjusted RR 3.5, 95% CI 2.4–5.2).

Chromosomal Abnormalities

A chromosomal abnormality was identified in 109 cases (17.3%), with a similar percentage in both ACC and HCC groups. Aneuploidy was common, with 17 cases of Patau syndrome (trisomy 13), 15 cases of Edward syndrome (trisomy 18), six cases of Down syndrome (trisomy 21), two cases of Klinefelter (XXY) and a single case of 45,X Turner syndrome. Additional chromosomal abnormalities detected in more than one individual in the cohort included: duplication 8p23 (four cases), as well as alterations of 1p36, 1q42–43, and 6qter. These regions have been previously reported in association with ACC [Boland et al., 2007; Guo et al., 1995; Sherr et al., 2005].

Accompanying Somatic and Central Nervous System Malformations

Both infants with and without chromosomal anomalies had accompanying somatic and CNS malformations. Infants with a callosal anomaly and concurrent chromosomal abnormality were more likely to have a cardiac (61.5% vs. 20.5%), musculoskeletal (49.5% vs. 30.1%), genitourinary (29.4% vs. 11.5%) and gastrointestinal (18.3% vs 7.5%) defect (Table III). Of the 317 infants who were evaluated with magnetic resonance imaging (MRI), 49.5% had additional CNS malformations (Table IV). Eighty-six (27.1%) had cortical malformations, 45 (14.2%) had posterior fossa abnormalities, sixteen (5.0%) a cyst, and four (1.3%) an encephalocele. The most common posterior fossa abnormality was a cerebellar vermis or hemisphere anomaly (34 infants, 10.7%), followed by brainstem abnormality (10 infants, 3.2%) and Chiari malformation (5 infants, 1.6%). There was no significant difference in the rate of associated CNS malformations in infants with and without identified chromosomal abnormality.

DISCUSSION

Based on this population-based study, callosal anomalies (agenesis of the corpus callosum, ACC, and hypoplasia of the corpus callosum, HCC) detected in the first year of life have an estimated birth prevalence of 1.8 per 10,000. Advanced maternal age was an important risk factor for ACC, especially for infants with an identified chromosomal abnormality, where women age 40 and older had a risk that was more than five times higher than that of women aged 25–29. Premature birth was more common among affected children: infants with callosal agenesis were 3–4 times more likely to be born prior to 37 weeks gestation. Infant ethnicity was also significantly associated with agenesis of the corpus callosum. Infants of Asian mothers were at lower risk and infants of black mothers were at higher risk of ACC when compared with infants of non-Hispanic white mothers.

Past prevalence estimates of ACC vary widely owing to vagaries of non-population-based ascertainment and range from 0.5 per 10,000 based on an unselected autopsy series [Grogono, 1968] to as high as 230–600 per 10,000 in children with neurodevelopmental disability or a suspected neurogenetic condition [Jeret et al., 1985; Schaefer and Bodensteiner, 1992]. Case series using unselected MRI review have yielded estimates that are closer to those for symptomatic populations, ranging from 25–300 per 10,000 patients, likely owing to the fact that patients are imaged at referral centers [Bodensteiner et al., 1994; Hetts et al., 2006]. At our institution, after unselected review of approximately 66,000 imaging studies, 230 were ACC cases, however only three of these were detected incidentally.

In unadjusted analyses, advanced maternal and paternal age were risk factors for callosal anomalies. When adjusted for paternal age, the risk of advanced maternal age remained elevated, especially in cases where a chromosomal anomaly was identified. In cases without chromosomal anomaly, there was an estimated increase in the adjusted relative risk for women age 40 years or older. Although advanced paternal age when adjusted for maternal age suggested an increased risk, the magnitude of the effect was lower and the risk estimate was imprecise. The effect of advanced maternal age on chromosomal anomalies, and especially aneuploidy, is well known, making this an expected risk factor for callosal anomalies [Tsuji and Nakano 1978]. In the group without chromosomal anomalies, the estimated relative risk suggested an increased risk in women 40–45, however, the confidence intervals were wide indicating a lack of precision in risk estimation likely because of the relatively small number of women in this advanced age group (ACC RR 1.3; 95% CI 0.7–2.5 and HCC RR 2.1; 95% CI 0.7–6.5). De novo copy number changes (mutations) identified by comparative genomic hybridization are responsible for a number of non-chromosomal cases of agenesis of the corpus callosum [Sherr et al., 2005]. Recent work

suggests that higher rates of spontaneous paternal point mutations may explain the increased incidence of certain congenital disorders with advanced paternal age [Croen et al., 2007; Moloney et al., 1996]. Advanced maternal and paternal age, while a theoretically plausible cause for non-chromosomal cases of ACC/HCC, could not be verified in this study.

In a number of cases, callosal abnormalities co-occurred with somatic and central nervous system anomalies. This result likely reflects not only the known association between these malformations and callosal anomalies, but also the unavoidable bias toward detection of the most serious cases. Our results are in keeping with past studies that have identified several complex malformation syndromes in association with callosal anomalies. These include disorders in which cardiac, limb and other anomalies are common, such as chromosomal disorders (e.g. trisomies 13 and 18), inborn errors of metabolism (e.g. mitochondrial disorders) and teratogenic exposure (e.g. alcohol) [Barkovich, 2005; Marszal et al., 2000; Shevell, 2002; Sztriha, 2005]. Hetts et al. evaluated 142 cases of callosal agenesis identified on MRI to examine the association with other CNS malformations [Hetts et al., 2006]. Most cases were associated with complex brain anomalies including high rates of malformations of cortical development (especially heterotopias and abnormal sulcation), commissural and white matter abnormalities, as well as interhemispheric cysts and malformations of the posterior fossa.

The large sample size, high ascertainment rate and diverse cohort strengthen this population-based study. However, our estimate of the population prevalence and risk factors for callosal anomalies is limited by several factors. First, the CBDMP collects data for malformations identified only within the first year of life. Children who remain undiagnosed for more than one year due to mild clinical presentation or inadequate evaluation are, therefore, not captured within this database. However, a recent survey of more than 700 subjects with agenesis of the corpus callosum found that the majority of cases were recognized in the first year of life (P. Moes, personal communication). In this study, 73% of children with diagnosed “simple” ACC (without associated cognitive or neurological abnormalities) and 91% of children with ACC plus associated deficits presented by 12 months of age. The second limitation is that case ascertainment by the CBDMP relies on the completeness and accuracy of medical records. Cases where the treating physician failed to correctly document the malformation may not be captured. Third, stillbirths and voluntary terminations were not captured by the CBDMP. Fourth, during the period of case ascertainment for this study, thinning of the corpus callosum was not considered a reportable malformation. Based on our review of the radiological description, we determined that a number of the cases represent thinning of the corpus callosum and classified these accordingly as HCC. It is impossible to know how many cases of HCC were present but not reported. Finally, we recognize that HCC itself is a heterogeneous malformation, however, we chose to include these cases in our analysis given recent reports that ACC and HCC are frequently linked by a common genetic defect [Boland et al., 2007; Li et al., 2007; Lu et al., 2007; Mowat et al., 2003].

This is the first population-based study of callosal anomalies. Agenesis and hypoplasia of the corpus callosum represent a heterogeneous array of brain disorders that, as a group, have a population prevalence of 1.8 per 10,000 in children under age one and are among the most common brain malformations.

Acknowledgments

This study was supported by grants from the NIH and March of Dimes to EHS, the UCSF Strategic Opportunities Support Center of the Clinical and Translational Sciences Institute. This study was also made possible National Center for Research Resources (NCRR UL RR024131-01) and the National Institute of Neurological Disorders Neurological Sciences (R01 NS050249 and NS01692) components of the National Institutes of Health (NIH). Its

contents are solely the responsibility of the authors and do not necessarily represent the official view of the NCRR or the NIH.

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Clinical characteristics of infants with agenesis (ACC) and hypoplasia of the corpus callosum (HCC) diagnosed ≤ 1 year of age from a population of over 3 million live births in California from 1983 to 2003.

Table 1

	ACC N = 472			HCC N = 158		
	N	(%)	Crude RR (95% CI)	N	(%)	Crude RR (95% CI)
Male sex	244	(51.7)	1.02 (0.85–1.22)	86	(54.4)	1.14 (0.83–1.56)
Multiple gestation	12	(2.5)	1.13 (0.64–2.00)	5	(3.2)	1.40 (0.57–3.41)
Race/Ethnicity						
Non - Hispanic White	145	(30.1)	---	46	(29.1)	---
US born Hispanic White	69	(14.6)	1.00 (0.75–1.33)	72	(45.6)	1.32 (0.83–2.11)
Foreign - born Hispanic White	160	(33.9)	1.06 (0.84–1.32)			0.89 (0.59–1.36)
Black	46	(9.7)	1.41 (1.00–1.96)	16	(10.1)	1.54 (0.84–2.72)
Asian	20	(4.2)	0.53 (0.34–0.85)	10	(6.3)	0.84 (0.43–1.67)
Other	24	(5.1)	1.12 (0.73–1.73)	12	(7.6)	1.77 (0.94–3.34)

Adjusted effect of parental age on agenesis (ACC) and hypoplasia of the corpus callosum (HCC) diagnosed < 1 year of age from a population of over 3 million live births in California from 1983 to 2003.

Table II

		ACC N = 472			HCC N = 158		
	Births N = 3,440,576	N	Crude RR (95% CI)	Adjusted RR (95% CI)	N	Crude RR (95% CI)	Adjusted RR (95% CI)
<u>Maternal Age adjusted for paternal age</u>							
< 20	414,783	53	0.88 (0.65–1.21)	0.72 (0.46–1.13)	15	1.03 (0.56–1.89)	1.14 (0.48–2.70)
20–24	865,000	99	0.79 (0.61–1.03)	0.74 (0.55–1.01)	38	1.25 (0.78–1.99)	1.42 (0.84–2.39)
25–29 (ref)	969,439	140	---	---	34	---	---
30–34	761,934	103	0.94 (0.73–1.21)	0.91 (0.69–1.21)	35	1.31 (0.82–2.10)	1.23 (0.74–2.06)
35–39	351,811	48	0.94 (0.68–1.31)	0.83 (0.56–1.23)	23	1.86 (1.10–3.16)	1.35 (0.70–2.61)
40–55	76,637	21	1.90 (1.20–3.00)	1.67 (0.96–2.91)	12	4.46 (2.31–8.62)	2.79 (1.23–6.37)
<u>Paternal Age adjusted for maternal age</u>							
< 20	151,991	17	0.96 (0.58–1.61)	1.20 (0.65–2.22)	5	0.79 (0.31–2.01)	0.79 (0.26–2.38)
20–24	612,014	84	1.18 (0.89–1.58)	1.36 (0.99–1.89)	21	0.82 (0.48–1.41)	0.75 (0.42–1.35)
25–29 (ref)	862,464	100	---	---	36	---	---
30–34	807,134	105	1.12 (0.85–1.48)	1.08 (0.80–1.44)	33	0.98 (0.61–1.57)	0.97 (0.58–1.62)
35–39	478,201	66	1.19 (0.87–1.62)	1.15 (0.81–1.64)	25	1.25 (0.75–2.09)	1.14 (0.62–2.09)
40–55	269,763	42	1.34 (0.94–1.93)	1.22 (0.79–1.88)	23	2.04 (1.21–3.45)	1.63 (0.82–3.26)

Table III

Associated somatic malformations in infants with agenesis of the corpus callosum diagnosed < 1 year of age from a population of over 3 million live births in California from 1983 to 2003.

	Chromosomal N = 109		Non-Chromosomal N = 521	
<i>N (%)</i>				
Cardiac	67	(61.5)	107	(20.5)
Musculoskeletal	54	(49.5)	157	(30.1)
Renal/Genitourinary	32	(29.4)	60	(11.5)
Gastrointestinal	20	(18.3)	39	(7.5)
Vascular	1	(0.9)	8	(1.5)

Table IV

Associated central nervous system malformations in 317 infants with agenesis of the corpus callosum diagnosed by magnetic resonance imaging at < 1 year of age from a population of over 3 million live births in California from 1983 to 2003.

	Chromosomal N = 36		Non-Chromosomal N = 281	
<i>N (%)</i>				
None	22	(61.1)	138	(49.1)
Cortical Malformation	7	(19.4)	79	(28.1)
Posterior fossa abnormality				
Cerebellar vermis or hemisphere	3	(8.3)	31	(11.0)
Chiari malformation	0	(0)	5	(1.8)
Brainstem abnormality	1	(2.8)	9	(3.2)
Encephalocele	1	(2.8)	3	(1.1)
Spinal cord abnormality	0	(0)	5	(1.8)