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Prevalence and associated factors for agenesis of corpus callosum in Emilia Romagna (1981–2015)

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ABSTRACT

Agenesis and hypoplasia of the corpus callosum (ACC and HCC) are heterogeneous group with a large variation in published prevalence based on few population based studies. The aim of this work is to describe prevalence, associated factors and other malformations present in cases with either agenesis or hypoplasia of the corpus callosum, using a population-based database of all malformations diagnosed in Emilia-Romagna, Italy, (the Emilia-Romagna Registry on Congenital Malformations, IMER).

This registry links and integrates hospital discharge records, birth certificates with cases reported by referral clinicians to identify all structural malformations diagnosed within one year of life regarding live birth, fetal death or termination of pregnancy due to fetal malformations (TOPFA). During the study period (1981–2015) the number of cases with ACC or HCC was 255, in a reference population of 1,023,784 live births, giving an overall prevalence of 2.49 per 10,000 (1.47 per 10,000 only live birth). After 1996, with the inclusion of TOPFA in IMER registry, the overall prevalence rate increase significantly from 1.42 to 3.03 cases per 10,000 birth (p-value < 0.001). Prenatal diagnosis was made in 192 cases (75.3%), at a median gestational age of 20.7 [IQR: 19.71–22.71]. Termination of pregnancy occurred in 105 of the 255 cases (41,2%). Where a prenatal diagnosis was available, 55% of cases ended in TOPFA (105/192), with higher prevalence of cases associated to central nervous system malformations and multiple birth defects, and median gestational age at diagnosis significantly less than in live birth cases (20.3 vs 29 weeks). Agenesis/hypoplasia ratio was 5.7 (217/38). The most frequently associated malformations were musculoskeletal. Trisomies were the most frequent chromosomal anomalies, in particularly trisomy18 and 13 (respectively 9/32 and 4/32 cases). Our study showed an increased risk for male infants (RR of 1.68, RR 95% CI 1.19–2.37). No differences were detected analyzing maternal age and ethnicity, and the increased risk associated to preterm birth disappeared when compared with other malformed infants.

This is one of the few population based studies dealing with prevalence of agenesis and hypoplasia of corpus callosum. Prevalence is still debated, but this study adds comprehensive data, in particular inclusion of TOPFA cases. Early prenatal diagnosis, not always possible, could be crucial for decision making regarding continuation of pregnancy.

1. Introduction

The corpus callosum is the major interhemispheric connective structure of the brain (Barkovich and Norman, 1988). Congenital structural abnormalities include total or partial agenesis of the corpus callosum (ACC), and hypoplasia of the corpus callosum (HCC). The reported prevalence of these anomalies ranges 1.8 per 10,000 in the general population to 230–600 per 10,000 in children with neurodevelopmental disability (Glass et al., 2008; Palmer and Mowat, 2014). Difficulty in determining prevalence is due to the heterogeneity of clinical condi-

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tions associated with agenesis and hypoplasia of the corpus callosum. These range from asymptomatic cases to children with devastating effects on neurological function. Agenesis or hypoplasia of corpus callosum can be isolated or part of complex association of cerebral or other malformations, and neurodevelopmental outcome could differs even when the neuroanatomy appears relatively similar (Palmer and Mowat, 2014). This variability reflects the underlying complexity of corpus callosum development and is due to different etiopathogenetic processes or a different spectrum of the same process. Congenital structural abnormalities of the corpus callosum are probably the result of disruption at an early stage due to genetic, infectious, vascular or toxic causes (Paul et al., 2007). An increasing number of genetic causes of ACC are being identified linked to genetic syndromes (Edwards et al., 2014). ACC is also associated with cerebral dysgenesis (e.g., lissencephaly and Dandy-Walker), various metabolic disorders, and first trimester exposure to teratogens including alcohol and cytomegalovirus infection (Paul et al., 2007; Shevell, 2002). The cognitive and neurological outcomes for patients with ACC is usually normal or with mild behavioral problems in isolated cases while prognosis is poorer in cases with associated cerebral malformations (Margari et al., 2016; Sotiriadis and Makrydimas, 2012). Recent long term follow up studies and a systematic review show normal neurodevelopmental outcome or mild disabilities in 65–88% of isolated ACC or HCC cases (D'antonio et al., 2016; Des Portes et al., 2018; Folliot-Le Doussal et al., 2018).

Given the doubtful neurological prognosis, termination of pregnancy for fetal anomaly (TOPFA) may occur especially when ACC is associated with other malformations. Early prenatal diagnosis however can be difficult as the final shape of the corpus callosum is complete only at 20 weeks of gestation (Edwards et al., 2014; Santo et al., 2012). ACC is usually suspected when there is the absence of the cavum septum pellucidum and a teardrop configuration of the lateral ventricles. These findings, however, are not always encountered in fetuses with partial agenesis, and become more evident after 24 weeks of gestation (Paladini et al., 2013). The course of the pericallosal artery, detected from 11 weeks of gestation has been considered an early sonographic marker of abnormal development of the corpus callosum (De Keersmaecker et al., 2018). In cases where fetal MRI was performed, 23% of cases presented additional intracranial anomalies, changing substantially the prognosis (Bell et al., 2015; Sotiriadis and Makrydimas, 2012).

Few population-based epidemiological studies of agenesis and hypoplasia of corpus callosum have been published and many consider only live birth (Glass et al., 2008; Szabó et al., 2011) or symptomatic patients (Bodensteiner et al., 1994).

The objective of this study was to describe overall prevalence of agenesis and hypoplasia of corpus callosum, associated anomalies and factors using a population-based congenital anomaly registry in Emilia-Romagna, Italy, from 1981 to 2015.

2. Materials and methods

The Emilia-Romagna Registry on Congenital Malformations (IMER) is a population-based registry of congenital malformations of the Emilia-Romagna Region and since 1981 a full member of EUROCAT, a European network of population-based registries for the epidemiologic surveillance of congenital anomalies. A description of the Registry can be found at the EUROCAT website (http://www.eurocat-network.eu/membersandregistrydescriptions) (Greenlees et al., 2011). The registry has systematically recorded TOPFA (termination of pregnancy for fetal anomalies) from 1996. Since 2003, the Registry uses multi source ascertainment. A validated algorithm (Astolfi et al., 2016, 2013) links and integrates hospital discharge record (SDO), birth certificate (CeDAP) with cases reported to the Registry by clinicians in order to identify all cases of congenital anomalies diagnosed up to one year of life.

The definition of each case was made from radiologic (head ultrasound, computed tomography or magnetic resonance imaging) or autopsy reports and completed with genetic testing performed at the discretion of the treating physician.

Each IMER report of live birth (LB), fetal death (FD) or TOPFA identified with the ICD 9 BPA code 74221 (agenesis of the corpus callosum) was reviewed by a pediatrician specialized in the field (EB) and classified as either agenesis of the corpus callosum (complete or partial: ACC) or hypoplasia of the corpus callosum (HCC: the corpus callosum is fully formed, but thinner) according to the description by the local reporting radiologist or pathologist.

Of the 259 identified cases, 4 were eliminated due to presence of isolated septal agenesis or thickening of corpus callosum.

The 255 remaining cases were classified into five groups:

Group 1 Isolated agenesis/hypoplasia of the corpus callosum. No other malformations identified. Colpocephaly, Probst bundles and temporal horn abnormalities with malrotated hippocampus, if present, were regarded as part of the isolated corpus callosum abnormality complex, and not as an additional malformation.

Group 2 Agenesis/hypoplasia of the corpus callosum associated with other central nervous system (CNS) abnormalities but without other major anomalies.

Group 3 Agenesis/hypoplasia of the corpus callosum with anomalies of the CNS and/or other organ systems.

Group 4 Agenesis/hypoplasia of the corpus callosum in patient with chromosomal anomalies.

Group 5 Agenesis/hypoplasia of the corpus callosum in patient with recognized conditions ie. syndromes, sequences or associations

The overall prevalence rate (LB + FD + TOPFA) and proportion of TOPFA were calculated and evaluated across different time periods using denominator data from the Regional health authority birth database (CeDAP). Comparison between proportions was made using chi-squared test.

Median gestational age at diagnosis was calculated for TOPFA and LB + FD separately and compared with the Wilcoxon-Mann-Whitney test.

Characteristics of ACC and HCC cases were compared to all neonates born in the same period using data from CeDAP, available from 2003. Prevalence rates per 10,000 birth, Rate ratio (RR) to compare an at-risk group to its reference group, and the corresponding 95% confidence interval (95% CI) were calculated for the following variables: infant sex, gestational age (<37or ≥ 37 weeks), maternal age (<25, 25–29, 30–34, 35–39 or ≥ 40 years), and maternal citizenship (Italian, other European, Asiatic, African, Other). Analysis for preterm birth was performed for all births.

Analysis was done using Stata 13 for Windows (StataCorp, College Station, TX) and Excel, significance level was set at 0.05.

3. Results

3.1. Prevalence

Two hundred and fifty-five cases of ACC or HCC were identified in the study period in a reference population of 1,023,784 live births, giving an overall prevalence of 2.49 per 10,000. Live birth and fetal death (LB + FD) prevalence was 1.47 per 10,000.

Fig. 1 shows prevalence during the study period, in a 5-years analysis. The time periods before and after 1996 are compared as in 1996 the IMER registry started collecting TOPFA data (indicated with red

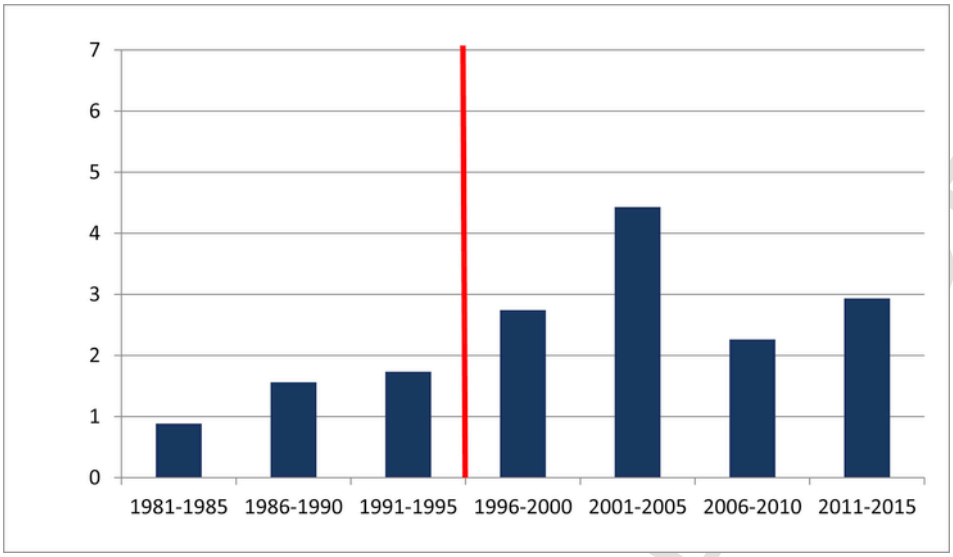

Fig. 1. Overall prevalence in a 5-years period analysis. Red vertical line define starting of inclusion of termination of pregnancy in the database. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

line in the figure) and the overall prevalence rate increased significantly from 1.42 to 3.03 cases per 10,000 birth (p-value < 0.001). The LB + FD prevalence rate remain stable (from 1.42 to 1.49 cases per 10,000 birth).

The 5-years analysis of TOPFA and LB + FD prevalence in the time period 1996–2015 (Fig. 2) shows no significant trend. The move to multi source ascertainment in 2003 did not increase significantly the notification of cases to the registry as 254 of the 255 selected cases were reported to the registry by IMER reference clinicians. Only 1 case was identified through the birth certificate database (CeDAP).

3.2. ACC and HCC cases

Of the 255 identified cases, 217 (85%) were ACC and 38 (15%) HCC, with an agenesis/hypoplasia ratio of 5.7. A similar ratio is seen when considering only LB + FD cases (127/23, agenesis/hypoplasia ratio 5.5).

The presence of associated malformations, in TOPFA or LB + FD cases, is shown in Table 1.

Group 1 -Isolated anomalies of corpus callosum - included 108 of the 255 cases (42%) were the most common. In Group 2 there were 28 cases with one or more other CNS malformation, such as severe hydrocephalus (7), anomalies or reduction of gyration (6) and cerebellar hypoplasia (3).

The most frequent malformations associated with ACC or HCC cases (Group 3, 67/255, 26% of our cases) regarded the musculoskeletal system (35 malformations registered), followed by genitourinary (30), cardiovascular (24) and gastrointestinal (18) systems.

In Group 4 (32/255; 13%), trisomies were the most common, in particularly trisomy18 and 13 (respectively 9/32 and 4/32 cases).

In Group 5, (20/255, 8%), Rubinstein-Taybi syndrome (3/20), Holoprosencephaly (3/20), Septo-optic dysplasia (2/20) and Mowat-Wilson syndrome (2/20) were the most frequent.

3.3. Prenatal diagnosis and TOPFA cases

Prenatal diagnosis was made in 192 (75.3%) of the 255 cases. Data from 1996 onwards, shows prenatal diagnosis was made in 85% of cases, with an increase from 60% in the period 1996–2000 to 90% in

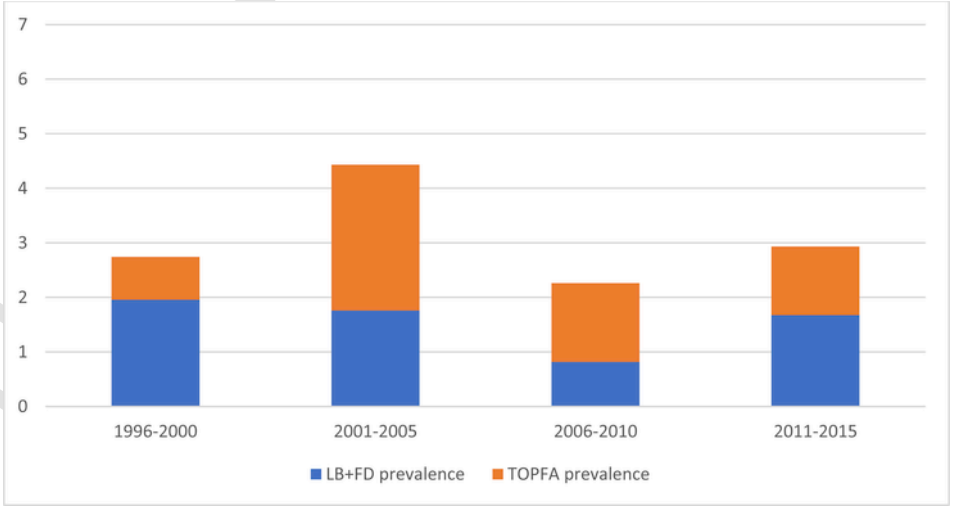

Fig. 2. Prevalence from 1996 to 2015, with distinction between prevalence of live birth and termination of pregnancy.

Table 1
Distribution of cases considering associated anomalies, presence of agenesis or hypoplasia of corpus callosum and termination of pregnancy.

	Agenesis of corpus callosum		Tot ACC n 217	Hypoplasia of corpus callosum		Tot HCC n 38	ACC + HCC		TOT n 255 (%)
	TOPFA	LB + FD		TOPFA	LB		TOPFA	LB + FD	
Group 1 isolated	34 (36%)	50[a] (64%)	94	5 (36%)	9 (64%)	**14**	**39 (36%)**	**69[a] (64%)**	**108[a] (42%)**
Group 2 Associated CNS	14 (64%)	8 (36%)	22	5 (83%)	1 (17%)	**6**	**19 (68%)**	**9 (32%)**	**28 (11%)**
Group 3 Multiple malf	27 (50%)	27 (50%)	54	2 (15%)	11 (85%)	**13**	**29 (43%)**	**38 (57%)**	**67 (26%)**
Group 4 Chromosomal	11 (39%)	17 (61%)	28	3 (75%)	1 (25%)	**4**	**14 (44%)**	**18 (56%)**	**32 (13%)**
Group 5 Recognized conditions	4 (21%)	15 (79%)	19	0	1 (100%)	**1**	**4 (20%)**	**16 (80%)**	**20 (8%)**
TOT	**90 (42%)**	**127 (59%)**	**217**	**15 (40%)**	**23 (60%)**	**38**	**105 (41%)**	**150 (59%)**	**255**

The percentages are calculated considering the totals per row, while in the last column the percentages are calculated on the column total.
ACC: agenesis of corpus callosum.
HCC: hypoplasia of corpus callosum.
TOPFA: termination of pregnancy for fetal anomalies.
LB + FD: live birth and fetal death.
CNS: central nervous system.
[a] Two fetal death.

the remaining 5-years periods. Terminations of pregnancy were 105/255 (41.2%), all after 1996.

TOPFA due to ACC or HCC, ranges between 2 and 4% of the total TOPFA cases recorded by the IMER registry, and resulted not statistically different in a four time periods comparison.

Prenatal diagnosis was made in 58% of LB + FD (87/150) and 100% of TOPFA (105/105).

Among cases with prenatal diagnosis (192), type of malformation distribution was nearly the same as in the whole cases studied, while it became significantly different comparing LB + FD (45%, 87/192) and TOPFA cases (55%, 105/192). Table 2 shoes there was a higher prevalence of associated cases (Group 2) and multiple malformations (Group 3), while isolated (Group 1) and recognized conditions (Group 5) were less frequent in TOPFA group (Pearson's Chi-squared test, p-value = 0.02).

The gestational age at diagnosis is available in 114 of the 192 cases, all from 2003 (Table 2). The median gestational age was 20.7 weeks [IQR: 19.7–22.7]. Apart from an isolated peak in 2003, due to 4 cases with prenatal diagnosis at or after 30 weeks of gestation, there were not relevant differences across time in the median gestational age.

TOPFA median gestational age at diagnosis is significantly less than in LB + FD cases: 20.3 [IQR:19–21] in TOPFA cases and 29 [IQR: 21–32.6] in LB + FD, p-value = < 0.001. The same trend is recognizable in all groups, even if not statistically analyzable because of paucity of cases in some groups.

3.4. Associated factors

From 2003 it was possible to examine data on associated factors. One hundred and fifty-four cases (131 ACC and 23 HCC) were found

Table 2
Distribution of cases with prenatal diagnosis (numbers, in grey column, and median gestational age). Comparison between cases undergoing termination of pregnancy and live birth or fetal death.

	TOPFA N° (%)	TOPFA Median GA[a] (IQR)	LB + FD N° (%)	LB + FD Median GA[a] (IQR)	TOPFA + LB + FD N° (%)	TOPFA + LB + FD Median GA (IQR)
Group 1 isolated	39 (37%)	20.6 (19.7-21)	46 (53%)	27 (21–32)	85 (44.3%)	20.8 (20.1-23.1)
Group 2 Associated CNS	19 (18%)	20.3 (19.1-21.4)	6 (7%)	30.4 (30-30.7)	25 (13%)	21.1 (20 -21.4)
Group 3 Multiple malf	29 (28%)	19.7 (17.7-21)	15 (17%)	22.7 (19.7-32.1)	44 (22.9%)	20 (17.9-21.1)
Group 4 Chromosomal	14 (13%)	19 (16.6-20.4)	12 (14%)	30 (20-34.3)	26 (13.5%)	20.2 (17.9-28.1)
Group 5 Recognized conditions	4 (4%)	21.6 (16.7-21.6)	8 (9%)	31.3 (21.3-33.3)	12 (6.3%)	21.6 (21.1-32.3)
TOTAL	**105 (100%)**	**20.3 (19–21)**	**87 (100%)**	**29 (21-32.6)**	**192 (100%)**	**20.7 (19.7-22.7)**

TOPFA: termination of pregnancy for fetal anomalies.
LB + FD: live birth and fetal death (in this table, FD is 1 cases, in group 1).
GA: gestational age.
IQR: inter quartile range.
CNS: central nervous system.
[a] Gestational age at diagnosis is known in 114 cases, 70 TOPFA and 43 LB + FD.

from 2003 to 2015. There appears an increased risk for male gender and preterm birth, while no differences were detected analyzing maternal age and citizenship (Table 3).

Since preterm birth is associated to malformations in general, data from this study were compared with the whole IMER registry, excluding chromosomal and syndromic cases. Of the resulting 50 cases with ACC or HCC, 11 were preterm (22%, 11/50), while in IMER registry cases 1293 of 8221 (15.7%) were preterm, with no significant difference (p-value = 0.308).

4. Discussion

The overall prevalence of agenesis and hypoplasia of the corpus callosum in live births, fetal death and termination of pregnancy in Emilia Romagna is 2.49 per 10,000 during the study period. Considering the period after 1996, with systematic inclusion of TOPFA cases, overall prevalence reach 3.03 per 10,000. There are only two population based comparable studies, to our knowledge (Glass et al., 2008; Szabó et al., 2011), presented in Table 4. Only live birth prevalence is comparable and at 1.47 per 10,000 is lower than previous studies. This maybe due to the longer follow period in these studies.

Other studies citing ACC or HCC prevalence (Table 4) are heterogeneous and hampered by evident selection bias or low numbers of cases reported. Data range from hospital based ultrasound screening of term babies at birth to MRI performed in adulthood and childhood in level III referral centers, or MRI studying fetal encephalon for a brain abnormality suspected at ultrasonography and autopsies series (Ballardini et al., 2017; Craven et al., 2015; Hetts et al., 2006; Kitova et al., 2014; Ruland et al., 2016; Wang et al., 2004).

Prevalence in the IMER Registry varies before and after 1996 due to changes in case ascertainment (inclusion of TOPFA).

The agenesis/hypoplasia ratio in our study is 5.7 (5.5 considering only LB + FD). In the literature there is great variability from 1 to 3 (Glass et al., 2008; Schell-Apacik et al., 2008; Szabó et al., 2011) to 6–10 (Alby et al., 2016; Ruland et al., 2016; Serhat et al., 2013).

The cases analyzed were 42% of isolated cases, 11% associated with other CNS malformations, 26% with multiple malformations, 13% with chromosomal anomalies identified and 8% with recognized conditions, figures comparable to the literature (Glass et al., 2008; Szabó et al., 2011).

The group with chromosomal anomalies was slightly less represented, maybe due to the subtle differentiation with group 5 (recognized conditions): 13% vs 17–20% (Glass et al., 2008; Ruland et al., 2016; Santo et al., 2012). As in other reports, trisomy 18 and 13 were the most common form, with a number of variable chromosomal rearrangements (Palmer and Mowat, 2014; Ruland et al., 2016; Santo et al., 2012).

As in the California study (Glass et al., 2008), the musculoskeletal system was most frequently involved in cases of multiple malformation.

A fundamental aspect affecting agenesis and hypoplasia of corpus callosum prevalence and the number of TOPFA cases is early prenatal diagnosis. However, a prenatal sonographic evaluation, with correct prenatal counselling including MRI, can be performed only after 20 weeks' gestation and there is a general consensus that diagnosing abnormalities of corpus callosum is difficult (Santo et al., 2012;). In our population, prenatal diagnosis was made in 75.3% of cases (193/255), at a median gestational age of 20.7 [IQR: 19.71–22.71], earlier than the reported median age of 22-24-25 weeks (range 19–40) in other studies with different methodology (Ghi et al., 2010; Paladini et al., 2013; Ruland et al., 2016). Median gestational age at diagnosis did not change over time while percentage of prenatal diagnosis increased from 60% to 90%.

Ultrasound screening at 20 weeks of gestation has been actively offered to all pregnant women during the last 30 years of the study period without substantial changes in screening policies, while improvements have occurred in the availability of MRI.

Variation of the percentage of TOPFA during the study period reflects variation in the percentage of TOPFA overtime in the IMER Registry as a whole rather than change in percentage of ACC or HCC cases, with the percentage of the cases as a proportion of all TOPFA cases reported to the Registry remaining stable.

Where a prenatal diagnosis was available 55% of cases ended in TOPFA and this was more frequent in cases with associated CNS malformations or multiple system malformations. Median gestational age at diagnosis was less in TOPFA cases (20.3 weeks) than in live birth cases (29 weeks). Associated malformations may lead to an earlier di-

Table 3
Characteristics of infants with agenesis and hypoplasia of corpus callosum compared with general population. Analysis of the period 2003–2015.

	ACC +HCC (n = 154)	References population (n = 504,747)	Prevalence x 10,000	RR	RR 95% CI
Sex					
Male	89	259,949	3.4	1.68	1.19–2.37
Female	50	244,798	2.0	1.00	
Gestationa age (weeks)					
25–36	20	40,672	4.9	3.56	2.15–5.88
≥37	64	462,931	1.4	1.00	
Maternal age (years)					
<25	20	55,182	3.6	1.38	0.82–2.34
25–29	39	115,508	3.4	1.29	0.84–1.97
30–34	46	175,626	2.6	1.00	
35–39	38	125,781	3.0	1.15	0.75–1.77
> =40	9	32,135	2.8	1.07	0.52–2.18
Mothers citizenship					
Italian	116	372,720	3.2	1.60	0.81–3.16
European	13	51,423	2.5	1.29	0.55–3.02
Asiatic	11	24,425	4.5	2.30	0.95–5.55
African	9	45,979	2.0	1.00	

ACC: agenesis of corpus callosum.
HCC: hypoplasia of corpus callosum.

Table 4
Tab: 4. Comparison with studies reporting data on prevalence of agenesis and hypoplasia of corpus callosum.

Reference	Study interval (yrs)	Location (source of data)	Population examined (denominator)	Case included	Prevalence of callosal anomalies per 10,000 Overall/ Live Birth	Prenatal cases	Postnatal diagnosis
This study	1981–2015 (34)	Emilia-Romagna, Italy (IMER registry)	Live birth, foetal death TOPFA (1,023,784 live births)	ACC + HCC	2.49/1.47	Fetal death and TOPFA since 1996	1 wk of life; from 2003 1 yr
Glass et al., 2008	1983–2000 and 2003 (18)	California (CBDMP registry)	Live birth (3,440,576 live births)	ACC + HCC	NA/1.8	NA	1 yr of life
Szabò et al., 2011	1992–2006 (14)	South-eastern Hungary (Data base of pediatric clinics)	Live birth (185,486 live births)	ACC + HCC	NA/2.05	NA	Pediatric age: not specified
Wang et al., 2004	1999–2001 (3)	Sin-Lau Christian Hospital, Taiwan (sonographic screening)	Term birth (2309 live term births)	ACC	NA/8.7	NA	3 days
Ballardini et al., 2017	2008–2013 (5)	Sant' Anna University Hospital of Ferrara, Italy (sonographic screening)	Term birth (6771 live term births)	ACC + HCC	NA/4.4	NA	Hospital stay
Ruland et al., 2016	1999–2012 (13)	Department of Obstetrics and Prenatal Medicine, University Hospital Bonn, Germany (level III referral center for fetal neurosonography)	second and third trimester fetuses at risk or not for CNS anomalies (48907 pregnant women)	ACC + HCC	29/15	Only prenatal diagnosis	NA
Craven et al., 2015	2004–2011. (7)	Academic Unit of Radiology, University of Sheffiel, UK (Referral center for fetal MRI)	second and third trimester fetuses at risk or not for CNS anomalies (1722 pregnant women)	ACC + HCC	615/NA	Only prenatal diagnosis	NA
Kitova et al., 2014	2006–2009 (3)	Clinic of Fetopathology in the Center for Maternity and Neonatology Tunis, Tunisia (Autopsies)	Autoptic series (all but 2 cases were TOPFA) (2238 fetuses)	ACC + HCC	89	Nearly all prenatal diagnosis	NA
Hetts at al., 2006	1985–2003 (18)	Department of Radiology, tertiary care center San Francisco, California (Brain MRI)	All the brain MRI performed (66,736 exams)	ACC + HCC	25	NA	Up to adulthood

NA not assessed.
ACC Agenesis of the corpus callosum.
HCC hypoplasia of the corpus callosum.
TOPFA: termination of pregnancy for fetal anomalies.
IMER: "Indagine sulle Malformazioni congenite in Emilia-Romagna".
CBDMP: "California Birth Defect Monitoring Program".

agnosis or earlier diagnosis may permit the choice of termination of pregnancy which in Italy is allowed up to 23 week of gestation. In addition to an early diagnosis, appropriate counselling and support is necessary to accompanying women in a complex decision, considering in particular ethical dilemma for cases with a possible favorable outcome (Folliot-Le Doussal et al., 2018). Termination of pregnancy in isolate group were 37% of the whole TOPFA and 36% of the isolated cases.

In this study males were more than half of the cases (58%, 89/154) in line with reported literature (Glass et al., 2008; Shevell, 2002; Szabó et al., 2011).

In a study in California, the authors found an association with preterm birth (Glass et al., 2008) which this study confirms with a risk ratio of 3.56. However, when compared to the IMER population, without chromosomal and syndromic cases, the proportion of preterm birth was no longer significantly higher. Preterm birth is associated with congenital anomaly cases in general rather than being a specific risk factor for ACC or HCC.

Data related to alcohol assumption, maternal disease, such as diabetes and assisted procreation were not detailed enough to be analyzed, though in the literature they are considered potentially related to anomalies of corpus callosum (Palmer and Mowat, 2014).

The strengths of this study are: 1) the large population-based sample and the inclusion of TOPFA cases in the prevalence; 2) the consistent use of EUROCAT methodology so these results are comparable to other EUROCAT registries; 3) the long study period; 4) the stable geographic coverage of the registry.

Limitations include: 1) changes in diagnostic accuracy and methods of ascertainment; 2) underestimation due to difficulties in prenatal diagnosis of ACC and even more of HCC.

Cases missed at prenatal diagnosis could be asymptomatic and obtain diagnosis only later in childhood. 3) Definition of hypoplasia and partial agenesis, in particular by ultrasound, could be doubtful. Even if normative charts are available, abnormal size of the corpus callosum is easy to recognize only in the presence of an evident alteration (Santo et al., 2012). 4) Retrospective analysis on data not collected specifically for ACC or HCC may mean some information is missed (e.g. genetic tests reported only if positive).

5. Conclusion

Agenesis or hypoplasia of corpus callosum constitutes a clinically significant and relatively frequent malformations of the nervous system. Prevalence is still debated, but this study adds comprehensive data, in particular inclusion of TOPFA cases. Early prenatal diagnosis, not always possible, could be crucial for decision making regarding continuation of pregnancy.

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