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ORIGINAL ARTICLE

Epidemiology of aplasia cutis congenita: A population-based study in Europe

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Abstract

Background: Aplasia cutis congenita (ACC) is a rare congenital anomaly characterized by localized or widespread absence of skin at birth, mainly affecting the scalp. Most information about ACC exists as individual case reports and medium-sized studies.

Objectives: This study aimed to investigate the epidemiology of ACC, using data from a large European network of population-based registries for congenital anomalies (EUROCAT).

Methods: Twenty-eight EUROCAT population-based registries in 16 European countries were involved. Poisson regression models were exploited to estimate the overall and live birth prevalence, to test time trends in prevalence between four 5-year periods and to evaluate the impact of the change of coding for ACC from the unspecific ICD9-BPA code to the specific ICD10 code. Proportions of ACC cases associated with other anomalies were reported.

Results: Five hundred cases were identified in the period 1998–2017 (prevalence: 5.10 per 100,000 births). Prevalence across 5-year periods did not differ significantly and no significant differences were evident due to the change from ICD9 to ICD10 in ACC coding. Heterogeneity in prevalence was observed across registries. The scalp was the most common site for ACC (96.4%) and associated congenital anomalies were present in 33.8% of cases. Patau and Adams–Oliver syndromes were the most frequent among the associated chromosomal anomalies (88.3%) and the associated genetic syndromes (57.7%), respectively. 16% of cases were associated with limb anomalies and 15.4% with congenital heart defects. A family history of ACC was found in 2% of cases.

Conclusion: To our knowledge, this is the only population-based study on ACC. The EUROCAT methodologies provide reliable prevalence estimates and proportions of associated anomalies.

INTRODUCTION

Aplasia cutis congenita (ACC, non-syndromic [or isolated] ORPHA: 1114, OMIM: 107600) is a rare anomaly characterized by a localized or widespread absence of skin at birth. ACC mainly affects the scalp involving the midline over the skull vertex, less commonly, the underlying periosteum and bone.[1] It usually presents as a solitary lesion, but multiple lesions can occur on the scalp or elsewhere. The individual lesion can vary from a superficial, circular or oval, well-demarcated defect or atrophic scar with alopecia to a weeping or granulating ulcer extending to the bone (non-membranous ACC). The lesions can range from a few millimetres to more than 10 cm in diameter. Some defects can have a membranous covering that can be filled with fluid, giving it a bullous appearance (membranous ACC).[2] Although most frequently seen on the scalp, ACC can affect any part of the body, including the trunk and limbs.[3–5] ACC can be isolated or part of a heterogeneous group of chromosomal or monogenic syndromes. Diagnosis is usually based on the findings of the clinical examination at birth. Prenatal diagnosis is limited to ACC types of genetic origin.

The aetiology of ACC remains unclear and heterogeneous. Due to the great variability of ACC expression and the associated congenital anomalies, it can be assumed that ACC results from different pathophysiological mechanisms. Numerous factors have been considered as possible causes of ACC. They include genetic factors (e.g. pathogenic variants in the *BMS1* gene associated with non-syndromic ACC, in *DLL4* gene associated with Adams–Oliver syndrome type6, and in genes causing ectodermal dysplasia),[6–9] teratogenic agents, intrauterine infections and trauma, vascular anomalies, adhesions of the amniotic membrane to the foetal skin, amniotic rupture sequence, imperfect neural tube closure.[10] Moreover, maternal cigarette smoking has been found to be a risk factor for ACC.[11] The association between exposure to methimazole, diclofenac sodium, benzodiazepines, heparin and valproic acid during pregnancy and ACC has also been reported.[12–17]

Given the rarity of the condition, most information about ACC exists as individual case reports and in some medium-sized studies.[3–5,18–25]

This study aimed to investigate the epidemiology of ACC, including the prevalence of the associated anomalies, based on a large European network of population-based registries for congenital anomalies (EUROCAT).

METHODS

The EUROCAT population-based congenital anomaly registries report cases diagnosed mostly up to 1 year of age with major structural congenital anomalies, chromosomal abnormalities and genetic syndromes. Live births (LB), foetal deaths (FD) with gestational age ≥ 20 weeks and terminations of pregnancy for foetal anomalies (TOPFA) following prenatal diagnosis at any gestation are registered using standardized definitions and coding.[26] Major congenital anomalies are defined in EUROCAT as structural changes that have significant medical, surgical, social or cosmetic consequences for the affected individual and typically require medical intervention.

The defined populations, the methods of case ascertainment, and the definitions and coding instructions of EUROCAT have been described in previous publications and on the EUROCAT website.[26–30]

Twenty-eight EUROCAT full member registries of 16 European countries participated in the study. All cases of ACC born between 1 January 1998 and 31 December 2017, coded with the International Classification of Diseases, ninth (ICD-9) or tenth revision (ICD-10) with British Paediatric Association (BPA) one-digit extensions for ACC (ICD9-BPA, 75739; ICD10-BPA, Q8480) were extracted from the EUROCAT Central Database which is operated by the JRC-EUROCAT Central Registry, European Commission Joint Research Centre in Ispra (Italy). Registries submit individual anonymized records of cases of congenital anomalies; thus, no ethical approval for the study was required.

Text descriptions reported in the database were evaluated to ensure that all the relevant clinical information was included in the study. Local registries were contacted for any additional information required. A medical geneticist (IB) and a paediatrician (EG) reviewed all anomaly codes and written text descriptions of the anomalies in this study.

The overall and live birth prevalence were estimated using Poisson regression with random effects models allowing the prevalence in different registries to vary. 95% confidence intervals (95%CIs), based on the Poisson distribution, were calculated for prevalence estimates. The χ^2 test for homogeneity was performed to assess whether differences in prevalence estimates across registries reflected actual differences or were due to random fluctuation.

A Poisson regression model was also used to test time trends in prevalence between the four 5-year periods 1998–2002, 2003–2007, 2008–2012 and 2013–2017 (reference baseline period: 1998–2002). An analogous model was used to evaluate the impact of the change of coding for ACC from the unspecific ICD9-BPA code 75739 (other specified anomalies of skin) and the specific ICD10 code Q8480.

Survival up to 1 week of age was estimated only for registries with a percentage of unknown/missing information less than 10%.

Proportions of ACC cases associated with EUROCAT congenital anomaly subgroups were reported. Following the EUROCAT Multiple Congenital Anomaly Algorithm, non-isolated ACC cases were further classified into: (i) ACC cases associated with non-genetic and non-chromosomal multiple congenital anomalies (i.e. cases with two or more major congenital anomalies in different organ systems, where the pattern of anomalies has not been recognized as part of a genetic [single-gene] or chromosomal syndrome or sequence); (ii) ACC cases associated with chromosomal anomalies; (iii) ACC cases associated with genetic syndromes.

The Student's *t*-test was used to determine eventual significant differences in birth weight, gestational age and maternal age between isolated and non-isolated live birth cases of ACC.

A *p*-value less than 0.05 was considered statistically significant when performing the statistical analyses.

Statistical analysis was conducted using Stata version 16.[31]

RESULTS

The total number of births covered by the 28 EUROCAT registries over the 20-year study period, 1998–2017, was 10,984,537. Five hundred cases with ACC were identified during the same period, giving an overall prevalence of 5.10 per 100,000 births (95%CI: 3.83–6.80) and a live birth prevalence of 4.81 per 100,000 births (95%CI: 3.58–6.47). Out of the 500 cases collected, there were 473 live births (LB; 94.6%), nine foetal deaths (FD; 1.8%) and 18 pregnancies resulted in a termination of pregnancy for foetal anomalies (TOPFA; 3.6%). The male to female ratio was 1.27:1.

The prevalence rates for four 5-year periods are reported in Table 1. Prevalence across the 5-year periods did not differ significantly ($p = 0.798$).

Data on the number of cases and prevalence by registry are presented in Table 2. Prevalence between registries differed significantly ($p < 0.001$), with the highest prevalence estimates of ACC observed for Vaud (Switzerland) and Malta registries (17.36 and 11.95 per 100,000, respectively).

The impact of the change of ACC coding from ICD9-BPA to ICD10-BPA on prevalence estimates has been investigated including only registries ($n = 12$) where a switch between the two systems has occurred. The Poisson regression model did not identify evidence of significant differences ($p = 0.169$) between the prevalence estimate based on cases coded with ICD9 (4.47 per 100,000 births) and the prevalence calculated on cases coded with ICD10 (5.89 per 100,000 births).

The scalp was the most common site for ACC in our sample, affecting 96.4% (482/500) of cases. Among the 18 cases of ACC with no involvement of the scalp, extremities were

the most involved (10 cases), followed by trunk (3 cases) and face and neck (2 cases). For three cases, ACC in multiple unspecified areas was reported.

We observed 331 (66.2%) isolated cases of ACC (all live births); major associated congenital anomalies were present in 169 cases (33.8% of total), 60 of which (12.0%) were ACC cases associated with chromosomal anomalies and 26 (5.2%) associated with genetic syndromes and monogenic disorders.

The proportions of ACC associated with major congenital anomalies in other organ systems are listed in Table 3. According to the EUROCAT Multiple Congenital Anomaly

TABLE 1 Five-year prevalence (per 100,000 births) of aplasia cutis congenita in 28 EUROCAT registries

Surveillance period	Total births	Total no. of cases	Prevalence (per 100,000)	95%CI
1998–2002	2,004,919	102	5.09	4.15–6.18
2003–2007	2,662,190	102	3.83	3.12–4.65
2008–2012	3,403,372	155	4.55	3.87–5.33
2013–2017	2,914,056	141	4.84	4.07–5.71
1998–2017	10,984,537	500	5.10[a]	3.83–6.80

[a]Prevalence does not correspond to the simple ratio between cases and births, as it is estimated using Poisson regression with random effects models to adjust for Registry (see Methods).

TABLE 2 Number of cases and prevalence (per 100,000 births) of aplasia cutis congenita in 28 EUROCAT registries

Registry	Years included	Total births	Number of cases	Prevalence (95%CI)
Vaud (Switzerland)	1998–2017	155,522	27	17.36 (11.44–25.26)
Malta	1998–2017	83,668	10	11.95 (5.73–21.98)
Tuscany (Italy)	1998–2017	566,324	56	9.89 (7.47–12.84)
Odense (Denmark)	2000–2015	81,392	8	9.83 (4.24–19.37)
Brittany (France)	2011–2017	244,690	24	9.81 (6.28–14.59)
Basque Country (Spain)	1998–2016	367,440	32	8.71 (5.96–12.29)
Auvergne (France)	1998–2017	268,338	23	8.57 (5.43–12.86)
Wielkopolska (Poland)	1998–2017	741,725	55	7.42 (5.59–9.65)
Saxony Anhalt (Germany)	1998–2017	336,187	23	6.84 (4.34–10.27)
Cork & Kerry (Ireland)	1998–2017	181,756	11	6.05 (3.02–10.83)
Isle de Reunion (France)	2002–2017	232,043	13	5.60 (2.98–9.58)
Wales (UK)	1998–2017	668,205	37	5.54 (3.90–7.63)
Antwerp (Belgium)	1998–2016	370,959	20	5.39 (3.29–8.33)
Emilia Romagna (Italy)	1998–2017	690,381	35	5.07 (3.53–7.05)
Styria (Austria)	1998–2016	199,998	7	3.50 (1.41–7.21)
Paris (France)	1998–2017	561,416	18	3.21 (1.90–5.07)
North Netherland	1998–2017	360,762	10	2.77 (1.33–5.10)
OMNI-Net (Ukraine)	2005–2016	360,948	10	2.77 (1.33–5.10)
East Midlands & South Yorkshire (UK)	1998–2012 & 2016–2017	1,143,462	30	2.62 (1.77–3.75)
South East Ireland	1998–2017	137,175	3	2.19 (0.45–6.39)
South Portugal	1998–2017	366,939	8	2.18 (0.94–4.30)
Northern England (UK)	2000–2017	575,155	12	2.09 (1.08–3.64)
South West England (UK)	2005–2017	641,971	12	1.87 (0.97–3.27)
Valencian Region (Spain)	2007–2016	489,361	8	1.63 (0.70–3.22)
French West Indies (France)	2009–2017	85,250	1	1.17 (0.03–6.54)
Thames Valley (UK)	2005–2017	387,555	4	1.03 (0.28–2.64)
Wessex (UK)	1998–2017	570,130	3	0.53 (0.11–1.54)
Zagreb (Croatia)	1998–2015	115,785	0	0.00
Total		10,984,537	500	5.10 (3.83–6.80)

TABLE 3 Proportions of aplasia cutis congenita associated with EUROCAT congenital anomaly subgroups. Associated cases are also reported according to the EUROCAT Multiple Congenital Anomaly Algorithm (multiple anomalies, genetic syndromes and chromosomal anomalies)

Associated anomaly subgroups	Total[a], *n* (%)	Multiple anomalies[b], *n* (%)	Genetic syndromes, *n* (%)	Chromosomal anomalies, *n* (%)
Limb	80 (16.0)	29 (36.2)	14 (17.5)	37 (46.3)
CHD	77 (15.4)	29 (37.7)	9 (11.7)	39 (50.6)
Nervous system	36 (7.2)	10 (27.8)	4 (11.1)	22 (61.1)
Eye	26 (5.2)	3 (11.5)	0 (0.0)	23 (88.5)
Genital system	26 (5.2)	12 (46.2)	3 (11.5)	11 (42.3)
Urinary system	25 (5.0)	11 (44.0)	4 (16.0)	10 (40.0)
Digestive system	23 (4.6)	9 (39.1)	6 (26.1)	8 (34.8)
Oro-facial cleft	11 (2.2)	2 (18.2)	2 (18.2)	7 (63.6)
Ear, face and neck	15 (3.0)	3 (20.0)	2 (13.3)	10 (66.7)
Respiratory system	6 (1.2)	2 (33.3)	3 (50.0)	1 (16.7)

Abbreviation: CHD, Congenital heart defects.

[a]The sum of the percentages does not equal to 100% because each aplasia cutis congenita case can be associated with more than one anomaly across different subgroups. Proportions are calculated on 500 total aplasia cutis congenita cases.

[b]Cases with two or more major congenital anomalies in different organ systems, where the pattern of anomalies has not been recognized as part of a monogenic or chromosomal syndrome or sequence.

Algorithm,[26] associated anomalies with ACC were also categorized as multiple anomalies, genetic syndromes and chromosomal anomalies, as defined in the Methods.

Among the associated chromosomal anomalies, Patau syndrome (trisomy 13) was the most frequent (53/60 cases, 88.3%; corresponding to 10.6% of total ACC cases; Table 4). Four partial trisomies/monsomies of the autosomes refer to two 4q31 interstitial microdeletions, a duplication in 20q13.33 region and a 1q21.1 microdeletion syndrome.

Among the associated genetic syndromes, Adams–Oliver was the most frequent (15/26 cases, 57.7%; corresponding to 3% of total ACC cases), followed by Johanson–Blizzard syndrome. Goltz–Gorlin syndrome, epidermolysis bullosa, Opitz G syndrome, nevus sebaceous syndrome, and Pena-Shokeir syndrome were also observed (Table 4).

Limb anomalies were the most frequent structural anomalies associated with ACC and occurred in 80 out of 500 cases of ACC (16.0%). A similar proportion was observed for ACC associated with CHD (77 out of 500 ACC cases, 15.4%). Among the 77 cases of ACC associated with CHD, 25 were severe CHD as defined in EUROCAT.[26] Atrio-ventricular septal defects, tetralogy of Fallot, common arterial truncus and hypoplastic left heart were the most frequent (Table 4). In one case, ACC was associated with three severe CHD (double outlet right ventricle, hypoplastic left heart and coarctation of aorta).

Among the 36 cases of ACC associated with anomalies of the nervous system, 10 (27.8%; corresponding to 2% of total ACC cases) were associated with arhinencephaly/holoprosencephaly, followed by seven cases each of neural tube defects, agenesis of corpus callosum and severe microcephaly; ACC associated with other congenital anomalies were often part of a chromosomal syndrome. This was the case for 88.5% (23/26) of the congenital anomalies of the eye, 66.7% (10/15) of the ear, face and neck, 61.1% (22/36) of the nervous system, 63.6% (7/11) of the oro-facial clefts and 50.6% (39/77) of CHDs.

Concerning the association with possible known teratogens, five mothers took benzodiazepines in the first trimester of pregnancy (from the 1st day of the last menstrual period to the 12th week of gestation) and two mothers took methimazole or heparin. None of the mothers took diclofenac or valproic acid. Among live births, differences in birth weight, gestational age and maternal age between isolated ACC and associated with major congenital anomalies ACC are reported in Table 5.

Statistically significant differences ($p < 0.05$) were observed between isolated and non-isolated ACC in birth weight for term-born infants (gestational age ≥ 37 weeks), especially for ACC associated with genetic syndromes (2831 vs. 3697 g). On the contrary, no significant differences in gestational age and maternal age were found between isolated and non-isolated ACC.

Among the 452 cases (out of 500) with available information about survival beyond 1 week of age, 18 (4.0%) died within the first week. As expected, most deaths were observed for ACC associated with chromosomal anomalies (15/18, 83.3%). No deaths before 1 week of age were reported for liveborn infants with isolated ACC.

A family history of ACC was found in 10 patients (10/500, 2.0%): five with ACC from the father's family, four from the mother's family (one maternal relative with Adams–Oliver syndrome) and one from both mother's and father's families with ACC.

DISCUSSION

This study, using data from EUROCAT, a large European network of population-based registries for surveillance of

TABLE 4 Distribution of associated congenital anomalies among the groups of chromosomal anomalies, genetic syndromes, congenital heart defects (CHD) and anomalies of the nervous system

Group	*n*	%	% on total ACC cases (*n* = 500)
Chromosomal anomalies (*n* = 60)			
Patau syndrome (Trisomy 13)	53	88.3	10.6
Partial trisomies/monosomies of the autosomes	4	6.7	0.8
Klinefelter syndrome	1	1.7	0.2
Deletion of X chromosome	1	1.7	0.2
Karyotype 47, XYY	1	1.7	0.2
Genetic syndromes (*n* = 26)			
Adams–Oliver syndrome	15	57.7	3.0
Johanson–Blizzard syndrome	4	15.4	0.8
Goltz–Gorlin syndrome	2	7.7	0.4
Epidermolysis bullosa	2	7.7	0.4
Opitz G syndrome	1	3.8	0.2
Nevus sebaceous syndrome	1	3.8	0.2
Pena-Shokeir syndrome	1	3.8	0.2
Severe CHD (*n* = 25)			
Atrio-ventricular septal defects	5	6.5	1.0
Hypoplastic left heart	5	6.5	1.0
Tetralogy of Fallot	4	5.2	0.8
Common arterial truncus	4	5.2	0.8
Transposition of great arteries	2	2.6	0.4
Pulmonary valve atresia	2	2.6	0.4
Coarctation of the aorta	2	2.6	0.4
Hypoplastic right heart	1	1.3	0.2
Aortic valve atresia/stenosis	1	1.3	0.2
Double outlet right ventricle	1	1.3	0.2
Anomalies of the nervous system (*n* = 36)			
Arhinencephaly/holoprosencephaly	10	27.8	2.0
Neural tube defects	7	19.4	1.4
Agenesis of corpus callosum	7	19.4	1.4
Severe microcephaly	7	19.4	1.4
Hydrocephalus	2	5.6	0.4
Cerebral cysts	2	5.6	0.4
Malformation of brain	2	5.6	0.4
Arnold–Chiari syndrome	1	2.8	0.2

Note: The sum of the percentages of each group does not equal to 100% because some aplasia cutis congenita cases can be associated with more than one anomaly.

congenital anomalies, represents the most extensive series of cases with ACC in Europe ever published.

To our knowledge, this is the first population-based study on ACC. Most of the studies on ACC are case reports and single hospital-based series mainly reporting clinical features. Whereas, our study is not based on disease-specific registries; instead, it is based on European population-based registries that register a wide range of congenital anomalies. For this reason, the different design of our study must be considered when comparing our results to case series and hospital series.

In this population-based study, the prevalence of ACC from 1998 to 2017 was 5.10 per 100,000 births, that is in line with the Orphanet estimate.[32] The prevalence estimate remained stable across the four 5-year periods, but with significant heterogeneity across the European registries. Differences in case ascertainment methods, especially for mild forms of ACC, may contribute to the observed geographical differences, but true regional differences cannot be excluded. To limit the effect of such high variability, we used a meta-analytical approach to produce an overall prevalence estimate of ACC.

TABLE 5 Differences in birth weight, gestational age and maternal age between isolated and non-isolated live birth cases of aplasia cutis congenita

Maternal and foetal characteristics	Isolated Mean (95%CI)	Non-isolated			
		Total, mean (95%CI)	Multiple anomalies, mean (95%CI)	Genetic syndromes, mean (95%CI)	Chromosomal syndromes, mean (95%CI)
Birth weight[a] (g)	3697 (3504–3890)	3207 (2973–3441)*	3320 (3600–3636)	2831 (2564–3098)*	3175 (2600–3750)
Gestational age (weeks)	40.6 (39.4–41.7)	39.1 (37.5–40.6)	39.1 (37.4–40.7)	38.2 (37.1–39.2)	39.5 (35.4–43.7)
Maternal age (years)	30.3 (29.4–31.2)	30.0 (29.0–31.1)	29.5 (28.3–30.8)	28.9 (26.3–31.5)	31.5 (29.2–33.8)

Abbreviation: 95%CI, Confidence Interval 95%.

[a]For term-born infants (gestational age ≥ 37 weeks).

*Statistically significant differences ($p < 0.05$) with respect to the reference (isolated ACC).

The change from the unspecific ICD9-BPA code to the specific ICD10-BPA code did not significantly impact the prevalence (4.47 vs. 5.89 per 100,000, respectively). This suggests that both the EUROCAT method of registration of cases (using ICD9-BPA in combination with a written text description) and the standardized inclusion/exclusion criteria were well established even in the early years and before the introduction of a specific ICD10-BPA code for ACC.

The male-to-female ratio was greater than 1 in our study, in line with what is commonly reported in the literature.[5,25] We found that the scalp was the most common site for ACC and more frequent (96.4%) than reported by Frieden (86.0%),[3] Sathishkumar et al.[5] (82.1%), and Mesrati et al.[4] (72.7%).

We observed that 66% of cases presented isolated ACC, which can be treated differently depending on the defect's extent. Using conservative wound care, healing by secondary intention is preferred when possible.[33] Larger lesions (3–4 cm) may require bone or skin grafts. After healing, scar revision can be considered. However, from a clinical point of view, it is essential after a diagnosis of ACC to assess the eventual presence of other and more severe associated anomalies that may affect the prognosis. In this case, additional treatments may be required.

Concerning the associated anomalies observed in our cohort, a comparison could be made with the paper of Schierz et al.,[24] who conducted a retrospective hospital-based study on 37 newborns, comparing isolated and non-isolated forms of ACC. The authors declared 49% of the isolated form of ACC. We found a higher proportion of isolated ACC than Schierz et al.[24] (66.2%), which might depend on the difference in the sample size and study design (population-based vs. hospital-based). In fact, a hospital-based study probably includes more complex cases with associated congenital anomalies referred for treatment at a specialized centre, whereas in our population-based study more isolated milder cases are identified, representing the reality of a wider range of the true pathophysiology.

We observed 16% of cases associated with limb anomalies (Type 2 ACC, according to Frieden's classification[3]), that is almost in line with what was found by Sathishkumar et al.[5] (12.9%) but higher than in Yang et al.[25] and Mesrati et al.[4] (5.1% and 9.1%, respectively).

ACC is often included as part of the Adams–Oliver syndrome, a rare disorder characterized by the combination of congenital limb anomalies and scalp defects, often accompanied by skull ossification defects. We found that 3.2% of our ACC cases had Adams–Oliver syndrome, a lower proportion than Mesrati et al.,[4] reporting 9% of Adams–Oliver syndrome cases in their series of 22 cases of ACC.

We observed three cases (0.6%) associated with epidermolysis bullosa, corresponding to Frieden's Type 6. This association was also observed by Yang et al.[25] (1 out of 59, 1.7%) and Schierz et al.[24] (3 out of 37, 8.1%).

Comparing isolated and non-isolated ACC among live birth cases, we found a significantly lower birth weight in term-born infants with ACC associated with genetic syndromes than in term-born infants with isolated ACC. This is also well known for other anomalies and similar differences in birth weight were also observed by Schierz et al.[24]

This study has some limitations; in particular, potential variation due to coding practices, completeness of data sources, and case description accuracy must be considered when combining epidemiological data from many registries. Moreover, clinical data might not be as detailed as in a case report or in hospital-based case series; for example, no information was collected in EUROCAT regarding associated foetus papyraceus or placental infarct, thus Frieden's Type 5 ACC cases cannot be identified.

CONCLUSION

Epidemiology studies on rare congenital anomalies are usually challenging because sufficiently large, standardized cohorts are difficult to obtain. In this study, we presented the first epidemiological population-based study on ACC, since most of the published studies are case reports or medium-sized hospital-based retrospective studies. Our study is based on a large European population and a standardized data collection, thus providing great statistical power to the epidemiological study on such a rare congenital anomaly compared with hospital-based case series. In particular, the methodology of data collection exploited within the EUROCAT guarantees the production of reliable estimates

both in terms of prevalence for all birth outcomes and proportion of associated anomalies.

AUTHOR CONTRIBUTIONS

AC and MS contributed to conceptualization; AC and LM contributed to data curation and investigation; AC contributed to formal analysis and writing—original draft; AC, MS and LM contributed to methodology; EG, M-CA, AAA, EB, LB, PB, JB, CC-C, HEKdeW, ESD, MG, MH, AK-O, AM-K, JJK, NL, KL, LM, CM, VN, MTO, IP, HR, JR, AR, FR, BS, DT, DW and LY contributed to resources; MS, IB and EG contributed to supervision; AC, IB, EG, AP, M-CA, AAA, EB, LB, PB, JB, CC-C, HEKdeW, ESD, MG, MH, AK-O, AM-K, JJK, NL, KL, LM, CM, VN, MTO, IP, HR, JR, AR, FR, BS, DT, DW, LY and MS contributed to writing—review and editing.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Restrictions apply to the availability of the data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors for scientifically valid requests and with permission of the participating registries of congenital anomalies.

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