ARTICLE

Acardia: Epidemiologic Findings and Literature Review From the International Clearinghouse for Birth Defects Surveillance and Research

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Acardia is a severe, complex malformation of monozygotic twinning, but beyond clinical case series, very few epidemiologic data are available. The goals of this study were to assess the epidemiologic characteristics of acardia from birth defect registries in the International Clearinghouse for Birth Defects Surveillance and Research (Clearinghouse), and compare these findings to current literature. The study included 17 surveillance programs of the Clearinghouse representing 23 countries from North and South America, Europe, China, and Australia. Anonymized individual records with clinical and demographic data were reviewed centrally by clinical geneticists. A literature search was performed. A total of 164 cases of acardia were reported from an underlying cohort of 21.2 million births. Of these, 23% were elective pregnancy terminations. Rates did not vary significantly by maternal age. For many cases, information on pregnancy exposures and genetic testing was missing. However, these limited data did not suggest high rates of chronic illnesses (diabetes, seizure disorders) or lifestyle factors such as smoking. One case had trisomy 13. Major malformations were reported in 2.4% of co-twins. With some basic assumptions, the total prevalence of acardia was estimated at 1 in 50,000–70,000 births, and 1 in 200–280 monozygotic twins. In summary, acardia is a dramatic, probably underreported, and incompletely understood malformation. Studies on its epidemiology and etiology are challenging and still rare. An international collaboration of epidemiologists, clinicians, and geneticists is necessary to understand the etiology, pathogenesis, and occurrence of this severe malformation complex.

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INTRODUCTION

Acardia is a rare and complex malformation seen in multiple births, usually in monozygotic twins but also in triplets and quadruplets [Phelan and Hall, 2006; Benirschke, 2009]. Very rarely, it has been reported in dizygotic twins, typically with fused placentas [Lattanzi et al., 2006; Phelan and Hall, 2006]. Sometimes the terms "acardius" or "acardiac twin" are also used, to underscore the two main findings, the rudimentary or absent heart (α- not [alpha privative] and καρδία, heart) and the twinning. A different term, based on presumed pathogenesis rather than clinical description and used commonly in the obstetric literature, refers to this condition as twin reversed arterial perfusion (TRAP) sequence.

Regardless of nomenclature, the phenotype in acardia is complex and variable. In addition to the heart, many other structures, most frequently head and upper limbs, are typically missing or are significantly malformed. The variability of the phenotype is reflected in the clinical classifications of acardia, which are based in particular on the appearance of cephalic structures.

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The striking phenotype of acardia has been noted repeatedly in history, well before the increasing interest with novel obstetric approaches to management. A recent historical review documents precise descriptions and illustrations from the 1500s, as well as remarkable anatomic studies in the last two centuries [Obladen, 2010]. In more recent years, several case series have been reported, mainly in the obstetric literature: obstetricians and perinatologists are invariably involved in cases of acardia as the outcomes are either a spontaneous abortion, an elective termination of pregnancy for fetal anomaly (ETOPFA), or a stillbirth. Yet, even with increasing reports of this rare malformation, the basic epidemiology of occurrence—the birth prevalence and distribution in the population—and of risk—genetic or environmental risk factors—remains unclear. For example, a prevalence of 1 in 35,000 births is commonly cited [James, 1977; Phelan and Hall, 2006] but appears to be based on very little data.

This report summarizes the findings of an international study of acardia conducted by birth defect surveillance programs from the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR). The main goal of the study was to evaluate the basic epidemiology of acardia in an international setting. In addition, we examined the current literature for comparative epidemiologic findings and summarized the clinical presentation and presumed pathogenesis.

METHODS

Programs and Study Population

For this study (Table I), 17 surveillance programs of the ICBDSR provided data on acardia from 23 countries in North and South America, Europe, Asia (China), and Australia. Some programs covered different parts of the same country (e.g., Italy), whereas one program, ECLAMC, included data from 10 South American countries. Cases included live births, stillbirths, and, for some programs, ETOPFAs (Table I). Cases from Spain ECEMC include those reported in a previous epidemiologic study [Martinez-Frias, 2009].

Inclusions and Case Review

The study included cases of acardia identified by the participating programs. Case selection and data submission followed a systematic protocol common to the very rare defects (VRD) study of the Clearinghouse, as detailed in the Introduction by Castilla and Mastroiacovo in this issue [Castilla and Mastroiacovo, 2011]. Briefly, programs were asked to provide anonymized individual records with information on clinical findings, selected demographics, genetic testing, and selected prenatal information, including pregnancy exposures. All records were reviewed by clinical geneticists (PM and LB) and coded and classified uniformly. When information was unclear, missing, or doubtful (e.g., acardia in a liveborn infant) the submitting program was contacted for clarification and further information.

Statistical Methods

As a measure of occurrence we used "total prevalence," defined as the number of cases divided by the sum of

TABLE I. Total Prevalence of Acardia in 17 Surveillance Programs, International Clearinghouse for Birth Defects Surveillance and Research

Surveillance program	Period	Births	Total cases	% of ETOPFA[a]	Total prevalence[b]	95%CI
Canada Alberta	1980–2005	1,062,483	8	12.5	0.75	0.38–1.49
USA Utah	1997–2004	380,706	8	12.5	2.10	1.06–4.15
USA Texas	1996–2002	2,054,788	14	28.6	0.68	0.41–1.14
Mexico RYVEMCE	1978–2005	1,058,885	7	NP	0.66	0.32–1.36
South America ECLAMC	1982–2006	4,556,173	27	NP	0.59	0.41–0.86
Finland	1993–2004	713,494	9	25.0	1.26	0.66–2.40
Wales	1998–2004	222,309	2	0	0.90	0.25–3.28
Northern Netherlands	1981–2003	369,658	4	0	1.08	0.42–2.78
Germany Saxony-Anhalt	1980–2004	355,184	5	20.0	1.41	0.60–3.30
France Central East	1979–2004	2,500,214	29	37.9	1.16	0.81–1.67
Italy North East	1981–2004	1,186,497	1	100	0.08	0.01–0.48
Italy Emilia Romagna	1982–2004	558,176	2	50.0	0.36	0.10–1.31
Italy Campania	1992–2004	643,962	2	100	0.31	0.09–1.13
Spain ECEMC	1980–2004	2,045,751	11	NR	0.54	0.30–0.96
Israel	1975–2005	151,562	1	0	0.66	0.12–3.74
China Beijing	1992–2005	1,927,622	7	NR	0.36	0.18–0.75
Australia Victoria	1983–2004	1,390,179	27	7.4	1.94	1.33–2.83
Total		21,177,643	164	15.8[a]	0.77	0.66–0.90

Programs are listed by continent, and within continent by country (approximately from north to south).
CI, confidence interval; NP, not permitted; NR, not reported; RYVEMCE, Registro y Vigilancia Epidemiológica de Malformaciones Congénitas; ECLAMC, Estudio Colaborativo Latino-Americano de Malformaciones Congénitas; ECEMC, Estudio Colaborativo Español de Malformaciones Congénitas.
[a]ETOPFA = elective termination of pregnancy for fetal anomaly. The proportion of ETOPFAs among only the programs that include pregnancy terminations is 23.2% (26/112).
[b]Per 100,000 births. Total prevalence: total cases (live births and stillbirths, plus elective terminations for fetal anomaly where these are legal and ascertained by program) divided by the sum of live births and stillbirths.

live births and stillbirths. This rate (more properly, ratio) is presented per 100,000 births. Confidence intervals of total prevalence use Wilson's confidence limits [Wilson, 1927; Rothman, 2002]. Pearson correlation was used as a measure of correlation between the total prevalence of different VRD. Statistical calculations were done using Microsoft Excel and SAS (Cary, NC) version 10. As a proxy for prenatal ascertainment in a given registry we used data from a previous study that estimated the proportion of cases of Down syndrome that are potentially missed by a program. This proportion, expressed as an OE (observed/expected) ratio, compares a program's observed rate of Down syndrome (O, Observed) with the rate expected based on the maternal age distribution in the underlying population (E, expected). Details of this approach are available [Leoncini et al., 2010].

Literature Review

Relevant papers were sought through online databases, mainly PubMed (National Library of Medicine, http://www.ncbi.nlm.nih.gov/pubmed/) and selected books on clinical genetics, malformations, embryology, and obstetrics and gynecology. Search terms included "acardiac" (286 results), "acardiac twin" (256 results), "acephalus" (68 results), "twin reversed arterial perfusion" (135 results), as well as combinations of these terms, with and without the additional search term "epidemiology." Further references were identified from these primary sources and book chapters. A total of 325 references were abstracted from PubMed; of these, 235 were published between 1990 and June 2011, and 137 on or after the year 2000.

RESULTS

The 17 participating programs provided data on 164 individual cases of acardia, identified among an underlying birth population of 21.2 million. The birth years included in the study varied by program (Table II) from as early as 1978 through 2005. Half of the cases (51%) were contributed by three programs: France Central East, South America ECLAMC (with hospitals from 10 South American countries), and Victoria-Australia.

Twin, Triplets, and Co-Twins

Of the 164 cases, 155 (94.5%) were twins and 9 (5.5% or 1 in 18) were triplets. All

TABLE II. Selected Family and Pregnancy Findings Among 164 Cases of Acardia in 17 Surveillance Programs, Members of the International Clearinghouse for Birth Defects Surveillance and Research

Finding	Number (total = 164)	%
Sex		
Male	57	34.8
Female	53	32.3
Indeterminate	42	25.6
Missing data	12	7.3
Maternal age (years)		
<20	15	9.1
20–24	34	21
25–29	51	31
30–34	38	23
≥35	16	9.8
Missing data	10	6.1
Maternal education		
Less than High School	15	9.1
High School	11	6.7
More than High School	44	26.8
Missing data	94	57.3
Paternal age (years)		
<20	0	0.0
20–24	9	5.5
25–29	17	10.4
30–34	17	10.4
≥35	10	6.1
Missing data	111	67.7
Parity		
0	19	11.6
1	38	23.2
≥2	57	34.8
Missing data	50	30.5
Gravidity		
0	11	6.7
1	41	25.0
≥2	69	42.1
Missing data	43	26.2
Previous spontaneous abortions		
0	41	25.0
≥1	12	7.3
Missing data	111	67.7

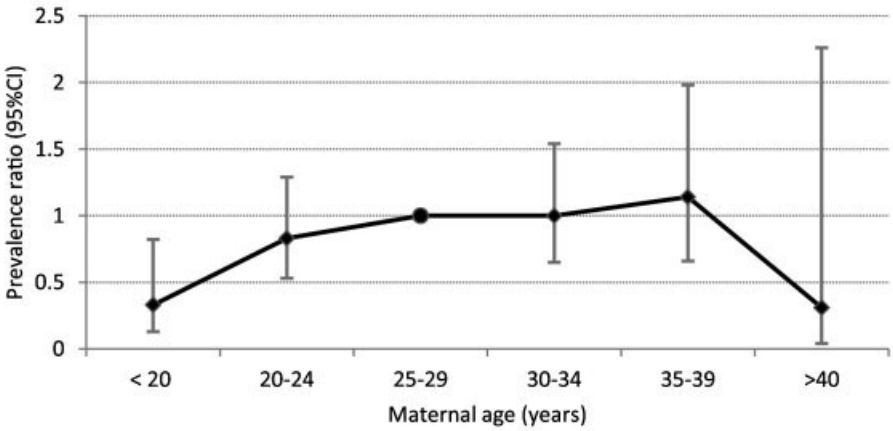
164 cases came from distinct twin sets. In the general population, the rate of monozygotic twins is estimated to be stable at approximately 4 per 1,000 births (1 in 250), whereas the rate of spontaneous triplets is estimated at approximately 0.12 per 1,000 birth (1 in 8,000). About half of all triplets have a monozygotic twin pair, according to recent estimates [Guilherme et al., 2009]. If these reference data are valid, the expected ratio of triplets to twins would be approximately 1–3%. Thus, the frequency of triplets in acardia in this data set appears to be two to five times higher than expected. Some information on structural malformations was provided on co-twins, that is, the other twin(s) from the same twin sets of the acardiac fetus. In total, structural malformations were reported in the co-twins of seven cases of acardia (4.3%). In four co-twins (2.4%), the following isolated major malformations were described: prune belly, kidney agenesis, large intestinal atresia, and limb deficiency. One additional co-twin had spina bifida occulta. The remaining two co-twins had the following multiple findings: (a) craniosynostosis and hypertelorism and (b) cerebral cyst and minor anomalies of the toes.

Stillbirths and Pregnancy Terminations

Of the 164 cases, 26 (23%) were ETOPFAs and the remainder were stillbirths. There were no live births with acardia. The proportion of ETOPFAs varied by program (Table I). In two programs, Mexico RYVEMCE and South America ECLAMC (with data on 10 Latin American countries), ETOPFAs are not recorded because these are not allowed legally in those countries. In two other programs, Spain ECEMC and China Beijing, ETOPFAs are not recorded by design. Among the 13 programs that register ETOPFAs, 23% of cases (26/112) were ETOPFAs.

Pregnancy and Parental Demographics

The sex of the baby (pregnancy) was indeterminate in 26% of cases, and male or female in approximately equal proportions (32–35%) (Table II). For several of the other demographic findings, the proportion of missing data was 30% or higher. For this reason they are presented in Table II but not discussed. Approximately 10% of mothers were 35 years of age or older. Maternal age information was available for the underlying birth cohort in the programs that contributed 151 of the 164 cases, and allowed an evaluation of maternal-age specific rates of acardia. As shown in Figure 1, maternal age specific rates were similar across age groups (prevalence rate ratios close to one), with perhaps slightly lower total prevalence in pregnancies of women under 20 years or age.



Maternal age (years)	Births	Cases	Total Prevalence (per 100,000)	95% CI		Prevalence ratio	95% CI	
< 20	1,807,069	5	0.28	0.09	0.65	0.33	0.13	0.82
20-24	4,574,377	32	0.70	0.48	0.99	0.83	0.53	1.29
25-29	5,804,883	49	0.84	0.62	1.12	1.00	(Reference)	
30-34	4,271,537	36	0.84	0.59	1.17	1.00	0.65	1.54
35-39	1,769,640	17	0.96	0.56	1.54	1.14	0.66	1.98
≥40	379,010	1	0.26	0.01	1.47	0.31	0.04	2.26

Figure 1. Total prevalence of acardia by maternal age, International Clearinghouse for Birth Defects Surveillance and Research. Figure (**top panel**) shows the prevalence rate ratios comparing total prevalence in each maternal age group to a fixed reference group (age 25–29 years). The table (**bottom**) also includes the number of cases, births, and total prevalence by maternal age group. Cases (n = 24) and births were excluded for the following programs and years, because of unavailable maternal age distribution in the birth population: China <1997 and >2003, Germany Saxony-Anhalt <1991, Italy Emilia Romagna <1985, Italy North East.

Genetic and Environmental Factors

Exposure information was incomplete, and unavailable in over 50% of cases for most exposures. For those in which these were known, rates of fever, smoking, diabetes, consanguinity, and fertility problems were low and similar to samples of malformed and non-malformed controls within the programs (data not shown). Genetic analysis, including karyotype, was available in a small fraction (18/164 or 11%) of the case group; among this group, one case was diagnosed with trisomy 13 (47,XX, +13).

Correlations With Other Very Rare Defects

Using the data collected for the other malformations in the VRD study, we evaluated the degree of correlation between reported rates of acardia and reported rates of the other VRD, one of which, conjoined twins, is also a complication of monozygotic twinning (Fig. 2). The other VRDs included conjoined twins, cyclopia, phocomelia, amelia, exstrophy of the cloaca, exstrophy of the bladder, and sirenomelia. Each point in the figure represents one program. The Pearson correlation between acardia and conjoined twins was 0.50, whereas there was no correlation (Pearson $r = -0.01$) with the combined group of all other VRD unrelated to twinning.

Estimates of Total Prevalence

The total prevalence by country, grouped by geography, is shown in Table I. Among all programs combined, the total prevalence of acardia was 0.77 per 100,000 births (1 in 129,000). However, total prevalence varied considerably by program, and sometimes between programs within a country. To explore the relation between reported prevalence and program methodology, programs were grouped in one of five classes (Fig. 3), depending on reporting of ETOPFAs (done, not done because procedure not legal in country, not done because data not recorded) and adjusted odds ratio (aOR) for the reporting of Down syndrome (>0.90, between 0.75 and 0.90, less than 0.75). The latter metric is valid for Down syndrome, and here it was used here as a rough proxy for the ability to report fetal anomalies in pregnancy terminations. Among the programs that ascertain pregnancy terminations and have high aOR values for Down syndrome reporting (0.90 or above), the average total prevalence of acardia was 1.43 per 100,000 (95% confidence interval, 1.10–1.87), or 1 in 69,800 births (95% confidence interval, 1 in 91,000 to 1 in 53,500), significantly higher than the overall average of 0.77 per 100,000 (Table I). The group average total prevalence decreased in the group with lower aOR values (prevalence, 0.98 per 100,000), in programs reporting from

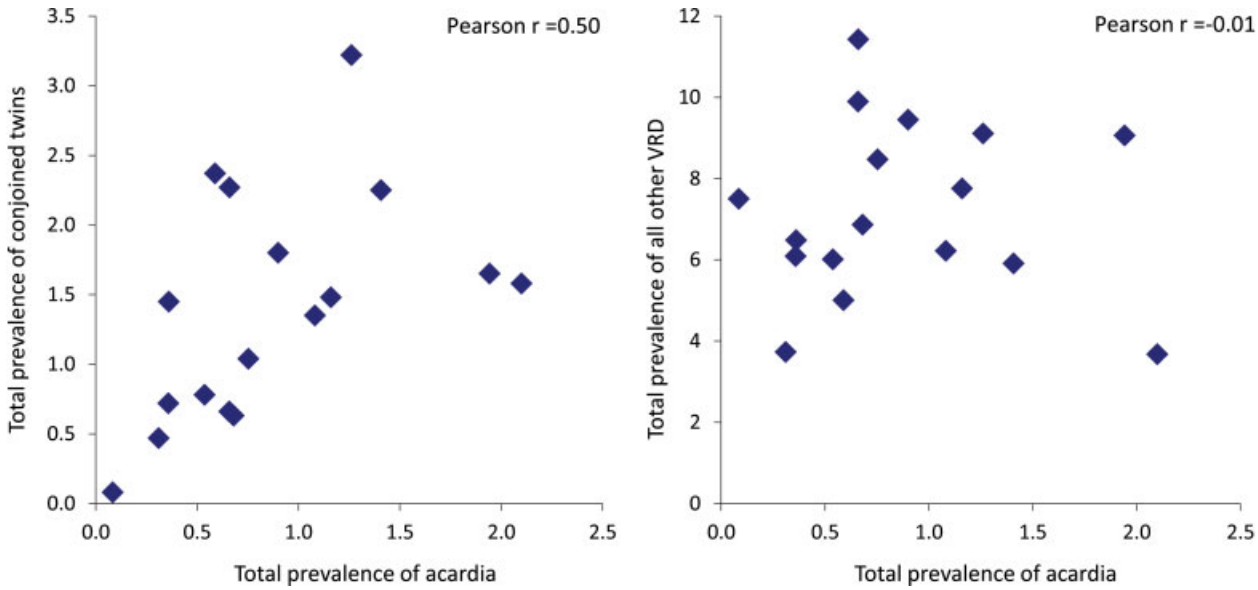


Figure 2. Correlation between a program's total prevalence of acardia and total prevalence of conjoined twins (left panel) and all other very rare defects, non-twinning related (see text), combined (right panel). Diamonds represent surveillance program, International Clearinghouse for Birth Defects Surveillance and Research. Total prevalence is per 100,000 births.

countries where pregnancy terminations are legally not allowed (prevalence, 0.61), in programs in which pregnancy terminations, while legal, are unreported (prevalence, 0.45), and in those with low aOR for Down syndrome reporting (prevalence, 0.21).

DISCUSSION

Acardia (Fig. 4) is a complex, variably ascertained, and incompletely understood malformation seen in twins and triplets. In this report, we describe a large cohort of 164 cases of acardia recorded from 21 million births by 17 surveillance programs from 23 countries across four continents. To put the findings in context, some basic aspects of acardia will be briefly summarized from the current literature, including definitions, clinical presentations, history, and pathogenesis. Clinical management is outside of the scope of this report. Additional information on acardia is available from a comprehensive review [Phelan and Hall, 2006], a beautifully illustrated historical review [Obladen, 2010] and a recent epidemiologic study [Martinez-Frias, 2009].

Definitions, Clinical Classification, and Additional Malformations

In the acardiac twin, the heart is absent or rudimentary, whereas the vascular system is fairly well preserved. The cardiac findings are always accompanied by severe structural malformations, most frequently involving the cephalic structures and limbs. A common classification [Phelan and Hall, 2006] uses these elements to classify acardia in four major groups (Table III). More commonly [Chi, 1989; Phelan and Hall, 2006; Rohilla et al., 2008; Martinez-Frias, 2009; Guimaraes et al., 2011], the head and parts of the upper torso are missing (acephalus) with relative preservation of the lower body, which however can still be significantly malformed (Fig. 4). Less commonly, some cephalic structures remain (anceps). Acephalus and anceps are sometimes grouped together and appear to account for most (>70–80%) reported cases of acardia. Very rarely, the reverse situation is observed: cephalic structures are present with little or no truncal development (acormus) [Morizane et al., 2002; Abi-Nader et al., 2009; Cruz-Hernández et al., 2009; Obladen, 2010; Guimaraes et al., 2011; Huss et al., 2011]. Finally, all cephalic and truncal differentiation may be lacking (amorphous), to the extent that the fetal parts may be misclassified as a teratoma [Dahiya et al., 2004; Lattanzi et al., 2006; Phelan and Hall, 2006; Hanley et al., 2007; Kariappa et al., 2007]. However, unlike a teratoma, the amorphous fetus has an umbilical cord, sometimes attenuated [Hanley et al., 2007], and maintains some skeletal organization.

In addition to the malformations of the heart, head, and limbs (more frequently, the upper limbs), many other malformations are observed in those fetuses that undergo an autopsy. These include absent or malformed larynx, lungs, spleen, liver, small and large intestine and genitalia, and clefts [Jones et al., 2008]. In some case reports, the fetus with acardia was described as also having sirenomelia [Zanforlin Filho et al., 2007] or VACTERL association [Athwal et al., 2010], although it is unclear whether these descriptions reflect the same primary, early embryonic origin seen in typical cases of these two multiple congenital anomaly complexes.

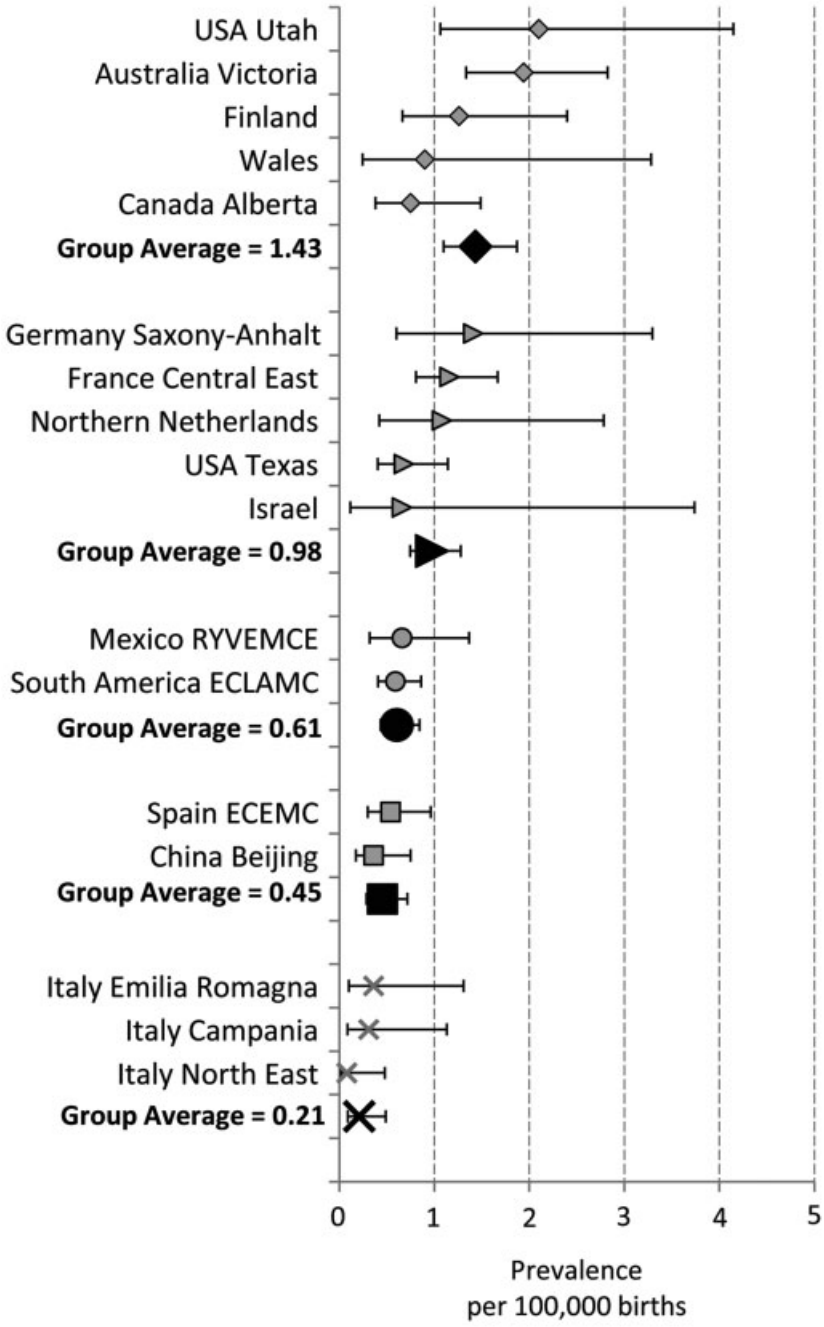


Figure 3. Total prevalence of acardia, with 95% confidence interval, in 17 surveillance programs of the International Clearinghouse for Birth Defects Surveillance and Research. Programs are grouped by ascertainment of ETOPFAs (elective termination of pregnancy for fetal anomaly) and adjusted odds ratio (aOR) for the reporting of Down syndrome (see text): (◆) program ascertains ETOPFAs, and aOR > 0.90; (▶) ascertains ETOPFAs, and aOR 0.75 to <0.90; (●) ETOPFAs not legal and therefore unreportable; (■) ETOPFAs legal but not reported to program; (×) pregnancy terminations legal and reportable, and aOR < 0.75 or unknown. RYVEMCE, Registro y Vigilancia Epidemiológica de Malformaciones Congénitas; ECEMC, Estudio Colaborativo Español de Malformaciones Congénitas; ECLAMC, Estudio Colaborativo Latino-Americano de Malformaciones Congénitas.

Historical Note

Probably because of its striking phenotype, the acardiac twin has been described in detail in past centuries. In one review, the first report was attributed to Benedetti, published in Venice in 1533 [Benedetti, 1533]. A beautifully illustrated historic overview, focused on the German cultural area [Obladen, 2010], shows a remarkable leaflet printed in Breslau in 1551 that includes a drawing of what is clearly an acephalus–acardiac twin. In the author's

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translation [Obladen, 2010], the leaflet describes how "on the fourth of December, 1551, [. . .] three children were born in the new hospital at Breslaw named All Saints' to a butcher's wife [. . .] The third [. . .] was of wondrously rare and frightening shape. For it had neither head nor hands and arms, only the trunk and the feet could be discerned. But it was imperfect (immature) and stillborn." These words and the drawing describe accurately the key findings in acardia: a stillbirth, a twin (actually a triplet) pregnancy, and the common phenotype of acephalus–acardius. The review also discusses the later pathology research of the 1700s and 1800s, and includes remarkable dissection drawings showing the placental vascular connections

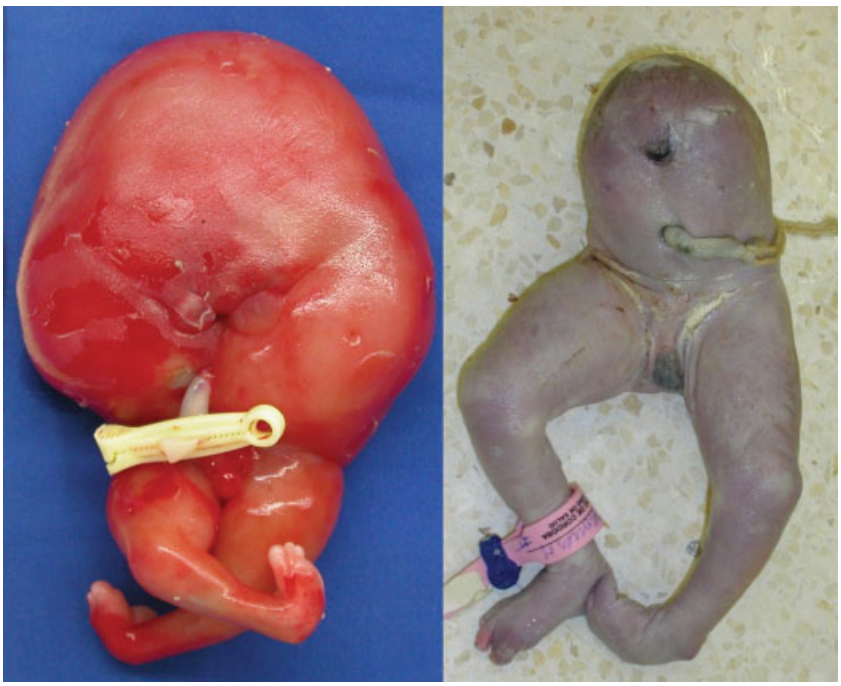

Figure 4. Two cases of acardiac twin, acephalus type, reported by ECLAMC—Estudio Colaborativo Latino-Americano de Malformaciones Congénitas (courtesy of Dr. Eduardo E. Castilla).

between the twins, which already then were recognized as a significant finding in this condition.

Pathogenesis

Historically, three main hypotheses have been put forth on the pathogenesis of acardia [Phelan and Hall, 2006]. These hypotheses (Table IV) have been developed over nearly two centuries, and have had alternating fortune among researchers and practitioners. All three allow for the key finding of artery–artery and vein–vein anastomoses, but in the first hypothesis they are exclusively a factor of survival, whereas in the other two they play a primary pathogenetic role.

Specifically, the first hypothesis (Table IV) posits that the primary event is a deficit in one of the embryos. Such deficit, perhaps in one of the germinal layers, could be secondary to factors such as an unequal distribution of cells between two embryos during the early twinning process, an underlying chromosomal anomaly, or perhaps epigenetic modifications [Phelan and Hall, 2006; Benirschke, 2009; Martinez-Frias, 2009]. The deficient embryo would die undetected in most cases; however, if artery–artery and vein–vein anastomoses develop in the common placenta, the twin reverse arterial perfusion (TRAP), sustained by the "pump" co-twin, would help the acardiac, malformed twin survive until detection. In short, the "malformation" comes first, whereas the anastomoses are primarily a survival rather than a causative factor.

The second and third hypotheses are similar in that these vascular anastomoses (artery–artery and vein–vein) are viewed as a primary pathogenetic event. They differ in that the second notion requires a second event such as a flow obstruction due an omphalocele [Phelan and Hall, 2006] to set in motion the reverse arterial perfusion. In the third hypothesis, the anastomoses are the primary determinant of the TRAP circulation and do not require a second event. Once the reverse circulation in the twin is in place, this hypothesis speculates that the recipient twin is injured by the inflow of poorly oxygenated blood with limited nutrient content. In short, the anastomoses come first, and are the cause of the malformations.

This third hypothesis (primary vascular pathogenesis) is widely held in the current literature. However, supporters of the primary malformation hypothesis highlight how there are frequent reports of chromosomal anomalies in the acardiac twin, as well as malformations in the co-twin, and suggest that these findings are more consistent with anastomoses being a secondary survival factor rather than a cause. A broader hypothesis

TABLE III. A Common Classification of Acardia [Phelan and Hall, 2006]

Group	Description
Acephalus	No cephalic structures, or very rudimentary. Limbs and trunk are more or less developed. Most frequent form (>70%)
Anceps	Some cranial structures and/or neural tissue are present. It is sometimes included in the acephalus type
Acormus	Head/cephalic structures are present but with limited/no truncal development. The head is usually attached directly to the placenta via a cord. Very uncommon
Amorphus	Little evidence of cephalic and truncal differentiation with very few recognizable structures such as limbs. Can resemble a teratoma, but unlike teratoma skeletal structures and an umbilical cord are present. May represent 20% of acardia

TABLE IV. Three Main Hypotheses of Pathogenesis of Acardia

Theory	Comments
Primary deficiency in germinal areas	An intrinsic deficiency of the embryo is the primary event. The anastomoses in the common placenta allow the survival of the twin until detection
Placental anastomoses combined with obstruction of blood return	Placental anastomoses are necessary but not sufficient: a flow obstruction is a second event that leads to reversal of flow in what will be the acardiac twin's placental connection. Fetal crowding, in twins and triplets, can predispose to the anastomoses
Placental anastomoses	Artery–artery and vein–vein connections are necessary and can be sufficient to create reverse arterial perfusion in one twin (TRAP). This in turn generates the acardiac twin and the "pump" co-twin. Fetal crowding can be a predisposing factor. Currently, this hypothesis is the more widely held

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could also be entertained. For example, a primary deficit would predispose to early demise and malformations, probably before gastrulation; the development of a reverse arterial perfusion, perhaps promoted by fetal crowding, would be in part a determinant of survival until detection, but also constitute a secondary teratogen specifically for the perfused area. This could explain the broadly consistent clinical findings in acardiac twins with the acephalus phenotype. An effect of fetal crowding could be consistent with the possibly increased risk of acardia in triplets compared to twins [Phelan and Hall, 2006].

Etiology

To date, no specific environmental teratogen has been strongly associated with acardia. Monozygotic twinning in humans has not itself been associated convincingly with teratogens; it is thought to occur at a relatively stable rate of 4 in 1,000 natural pregnancies with little international and racial-ethnic variation. Some investigators speculate that clomiphene, a medication used to induce ovulation, could increase rates of monozygotic twinning [Aoki et al., 2006; Derom et al., 2006], and at least two single case reports have described the occurrence of acephalus–acardiac twins after ovulation induction with clomiphene [Haring et al., 1993; Martinez-Roman et al., 1995]. In our epidemiologic study, we did not find evidence for high rates of environmental factors or maternal conditions. Whereas for many cases this information was missing, the rates of exposure, including the use of clomiphene, were low even among the pregnancies with recorded exposures (among which one might expect a positive reporting bias).

Chromosomal anomalies have been reported in several case series and case reports [Bieber et al., 1981; Van Allen et al., 1983; Shapiro et al., 1986; Moore et al., 1987; Wolf et al., 1991; Chaliha et al., 1999; Blaicher et al., 2000; Mihci et al., 2009], and the literature prior to 2000 has been reviewed [Blaicher et al., 2000]. In some cases, chromosomal anomalies such as 47,XXY syndrome were reported in the co-twin without acardia [Moore et al., 1987]. Some of the specific chromosomal anomalies in the acardiac twins are listed in Table V. The report of at least three cases of trisomy 2 is noteworthy. The finding in our study of trisomy 13 is the first such report that we are aware of. In general, the frequency of chromosomal anomalies may be under-ascertained in acardia because most affected fetuses are unlikely to have basic genetic testing such as a karyotype. In our study, for example, only 18 of 164 cases of acardia (11%) had information on record in the registry on karyotype or other genetic testing.

The frequency and distribution of chromosomal anomalies is relevant also to theories of pathogenesis. For example, it has been suggested that a high frequency of chromosomal anomalies would support more strongly the theory of primary embryonic deficit (first theory in Table IV) compared to theories based exclusively on the presence of vascular anastomoses, whereas the opposite might be true if chromosomal anomalies were infrequent [Benirschke and des Roches Harper, 1977].

The Co-Twin

The co-twin has been reported to have an increased risk of structural malformations, as high as 10% according to a recent review [Phelan and Hall, 2006]. Several structural malformations have been reported, including anencephaly [Pavone et al., 1985], prune belly sequence with dysplastic kidney [Buntinx et al., 1991], gastroschisis [Habbal et al., 2005], small intestinal

TABLE V. Chromosomal Anomalies in Fetuses With Acardia Reported in the Literature

Type	Details	Source
45,XX t(4;21)del(4p)	Complex rearrangement	Van Allen et al. [1983]
Triploidy	69,XXX	Bieber et al. [1981]
Polyploidy	94,XXXXYY, in fibroblasts and lymphocytes	Moore et al. [1987]
Isochromosome X	46,X,i(Xp), mosaicism in fibroblasts	Wolf et al. [1991]
Trisomy 2	47,XX, +2. In natural and in in-vitro fertilization pregnancies. At least three cases reported.	Chaliha et al. [1999], Blaicher et al. [2000], Mihci et al. [2009]
Trisomy 11	47,XX, +11, in fibroblasts	Shapiro et al. [1986] (abstr.)
Trisomy 13	47,XX, +13	This report

atresia [Wong et al., 2007], skeletal malformations of limbs and ribs [Chen et al., 2007], and malformations consistent with the VATER association [Moore et al., 1987], among others. In one triplet, two acardiac twins were reported [Ventura et al., 2011].

In this international study, we observed some of these same malformations in 4 of 164 cases (2.3%) including prune belly, kidney agenesis, large intestinal atresia, and limb deficiency. One additional co-twin had what was described as spina bifida occulta. Although the prevalence of malformations is not strikingly high, the consistency of the malformation type with what has been described in the literature is noteworthy. Regardless of structural malformations, the co-twin has significantly increased prenatal and perinatal mortality, due mainly to heart failure and cardiomegaly secondary to the co-twin's function as the "pump." Mortality continues to be high to this day, 30–50% or more, particularly if the acardiac twin is comparatively large [Sullivan et al., 2003; Tanawattanacharoen et al., 2004; Guimaraes Filho et al., 2007; Gupta et al., 2008; Chandramouly and Namitha, 2009; He et al., 2010; Lewi et al., 2010]. When the acardiac twin is comparatively smaller, survival rates of the co-twin could be higher [Jelin et al., 2010; Lewi et al., 2010].

Correlation With Other Very Rare Defects

As illustrated in Figure 2, the total prevalence of acardia was correlated more strongly with rates of conjoined twins than with other VRD (Pearson correlation of 0.54 vs. 0.26). The weak correlation with VRD unrelated to twinning could be due to methodological factors such as reporting among ETOPFAs or stillbirths. Many of the VRD are identifiable, to different degrees, by prenatal ultrasonography, and their outcomes could be an ETOPFA or a stillbirth. The stronger correlation with conjoined twinning (Pearson $r = 0.54$) likely is driven by biology: both conditions are complications of monozygotic twinning. The correlation of rates between these two conditions suggest that rates of monozygotic twinning could vary, at least in small part, by geography, and, at least in principle, could explain a small part of the variation in rates of acardia by geography.

Prevalence

The occurrence of acardia is not well known. Most reports on acardia are single case report and small case-series, typically with ten cases or less, though in recent years larger series have been published [Jelin et al., 2010; Lewi et al., 2010; Guimaraes et al., 2011]. Nevertheless, because case reports and case series cannot be readily related to the underlying source population—in this case, the number of births or pregnancies from the area from which the affected pregnancies derive—it is not possible to determine estimates of occurrence such as birth prevalence. Epidemiologic studies of prevalence are rare. The largest published to date, to our knowledge, was recently produced through the ECEMC registry in Spain [Martinez-Frias, 2009]. It described 11 acardiac twins ascertained among a hospital-based cohort of nearly 2.3 million births cohort, and estimated a frequency (prevalence among births) of 0.49 per 100,000 births (1 in 200,000). As underscored by the authors [Martinez-Frias, 2009] this is likely a minimum estimate, because of the unknown fraction of missed cases, such as unreported ETOPFAs or stillbirths. By contrast, in many papers the statement is repeatedly made that acardia affects 1 in 35,000 births or 1% of monozygotic twins. These figures are quoted from early reviews [James, 1977], which in turn cite still earlier works. However, this particular estimate seem to be based on scarce data with uncertain, likely questionable epidemiologic value.

In this study, the total prevalence among all programs (Table I) was 0.77 per 100,000 births (1 in 130,000). However, the estimates varied several-fold across programs (Table I). Also, total prevalence seemed to depend in part on certain methodological or structural aspects of the program or the program's country (Fig. 3) related to reporting of ETOPFAs and perhaps stillbirths. Using these data and assuming that programs with ascertainment of ETOFAs and high values of Down syndrome aOR would provide a more accurate estimate (first group in Fig. 3), a total prevalence estimate can be derived in the range of 1.4 per 100,000 births (1 in 70,000).

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Two programs in this group reported a total prevalence close to 2 per 100,000 births (1 in 50,000). Thus, although the confidence intervals were fairly wide, estimates of total prevalence between 1 in 50,000 and 1 in 70,000 (1.4–2 per 100,000) seem to be reasonable based on this large epidemiologic data base. Assuming that the frequency of monozygotic twins is 4 per 1,000 births [Phelan and Hall, 2006] and fairly stable in time and by geography, then these overall total prevalence estimates translate into a risk for acardia of approximately 1 in 200 to 1 in 280 monozygotic twins.

CONCLUSIONS

Acardia is a complex and rare malformation found almost exclusively in monozygotic twins and triplets. The main risk factor appears to be the twinning process itself. Currently, there is little evidence that other maternal or environmental factors have a major impact on the occurrence of acardia; however, etiologic studies in acardia are exceedingly rare. Chromosomal anomalies are uncommon in acardia and when they occur they lack a consistent pattern, except perhaps for a relative overrepresentation of trisomy 2.

The pathogenesis of acardia remains unclear. Broadly, it is accepted that placental anastomoses play a key pathogenetic role, but whether they are the only important factor is still uncertain. An alternative or complementary explanation posits a role of primary deficits in one of the embryos, due to environmental, genetic, or perhaps epigenetic factors. In this setting, placental anastomoses could be a survival factor, or perhaps both a survival as well as a teratogenic factor leading to the common presentation of the acephalus–acardiac twin. This study also provides data-based estimates of the total prevalence of acardia. With some assumptions, the study findings suggest a total prevalence of acardia of approximately 1 in 50,000 births (2 per 100,000) and 1 in 200 monozygotic twins. These estimates are higher than previous epidemiologic studies but lower than earlier, widely quoted estimates based on case series.

Further studies would be helpful to refine these estimates. Such studies need to take into account the complex methodological challenges of acardia, some of which were discussed in this review. First, it is crucial to promote accurate ascertainment and reporting of ETOPFAs and stillbirths. In addition to reporting, coding and classification are as important as they are challenging. As discussed in the Introduction by Castilla and Mastroiacovo [2011], acardia is not well served by many common coding systems. For example, to identify acardia the programs in this study used many different ICD-9 codes (755.200, 755.300, 759.480, 759.450, 759.23, 759.70, 759.89, 762.301) and ICD-10 codes (Q897, Q897.11, Q898). A consistent approach to coding, with extensively annotated verbatim descriptions, would be extremely helpful, particularly in collaborative studies. Second, on a clinical level, it is crucial to gather and report complete and accurate information on phenotype, maternal exposures, and genetic testing. Only a small fraction of cases of acardia in this study was evaluated by autopsy or even with a simple karyotype. Increasing the diagnostic effort could help fill some major knowledge gaps, including the frequency of chromosomal anomalies, the frequency of monozygotic versus dizygotic twins, the frequency and type of malformations in the co-twin, the frequency and type of malformations (aside from limb, head and heart) in the acardiac twin. Systematically collecting these data on all cases of acardia could help in gaining a better understanding of the basic causes and mechanisms underlying this rare but devastating malformation complex.

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