Epidemiology of Multiple Congenital Anomalies in Europe: A EUROCAT Population-Based Registry Study

Elisa Calzolari[1], Ingeborg Barisic[2], Maria Loane[3], Joan Morris[4], Diana Wellesley[5], Helen Dolk[3], Marie-Claude Addor[6], Larraitz Arriola[7], Fabrizio Bianchi[8], Amanda J. Neville[1], Judith L.S. Budd[9], Kari Klungsoyr[10], Babak Khoshnood[11], Bob McDonnell[12], Vera Nelen[13], Annette Queisser-Luft[14], Judith Rankin[15], Anke Rissmann[16], Catherine Rounding[17], David Tucker[18], Christine Verellen-Dumoulin[19], Hermien de Walle[20], and Ester Garne*[21]

Background: This study describes the prevalence, associated anomalies, and demographic characteristics of cases of multiple congenital anomalies (MCA) in 19 population-based European registries (EUROCAT) covering 959,446 births in 2004 and 2010. **Methods:** EUROCAT implemented a computer algorithm for classification of congenital anomaly cases followed by manual review of potential MCA cases by geneticists. MCA cases are defined as cases with two or more major anomalies of different organ systems, excluding sequences, chromosomal and monogenic syndromes. **Results:** The combination of an epidemiological and clinical approach for classification of cases has improved the quality and accuracy of the MCA data. Total prevalence of MCA cases was 15.8 per 10,000 births. Fetal deaths and termination of pregnancy were significantly more frequent in MCA cases compared with isolated cases ($p < 0.001$) and MCA cases were more frequently prenatally diagnosed ($p < 0.001$). Live born infants with MCA were more often born preterm ($p < 0.01$) and with birth weight < 2500 grams ($p < 0.01$). Respiratory and ear, face, and neck anomalies were the most likely to occur with other anomalies (34% and 32%) and congenital heart defects and limb anomalies were the least likely to occur with other anomalies (13%) ($p < 0.01$). However, due to their high prevalence, congenital heart defects were present in half of all MCA cases. Among males with MCA, the frequency of genital anomalies was significantly greater than the frequency of genital anomalies among females with MCA ($p < 0.001$). **Conclusion:** Although rare, MCA cases are an important public health issue, because of their severity. The EUROCAT database of MCA cases will allow future investigation on the epidemiology of these conditions and related clinical and diagnostic problems.

Birth Defects Research (Part A) 00:000–000, 2014.

Key words: epidemiology; multiple congenital anomalies; classification; prevalence; prenatal diagnosis

[1]IMER Registry- Azienda Ospedaliero-Universitaria di Ferrara, Italy
[2]Children's Hospital Zagreb, Medical School University of Zagreb, Croatia
[3]EUROCAT Central Registry, Centre for Maternal, Fetal and Infant Research, University of Ulster, Newtownabbey, United Kingdom
[4]Wolfson Institute of Preventive Medicine, Queen Mary University of London, United Kingdom
[5]University Hospitals Southampton Faculty of Medicine and Wessex Clinical Genetics Service, Princess Anne Hospital, Southampton, United Kingdom
[6]Division of Medical Genetics, Lausanne, Switzerland
[7]Public Health Division of Gipuzkoa, Instituto BIO-Donostia, Basque Government, CIBER Epidemiología y Salud Pública - CIBERESP, Spain
[8]CNR Institute of Clinical Physiology and G. Monasterio Tuscany Foundation, Pisa, Italy
[9]Department of Health Sciences, University of Leicester, United Kingdom
[10]Medical Birth Registry of Norway, Norwegian Institute of Public Health and Department of Global Public Health and Primary Care, University of Bergen, Norway
[11]INSERM U953, Paris, France
[12]Health Service Executive, Dublin, Ireland
[13]Provincial Institute for Hygiene, Antwerp, Belgium
[14]University Medical Center of the Johannes Gutenberg University, Mainz, Germany
[15]Institute of Health & Society Newcastle University, Newcastle upon Tyne, United Kingdom
[16]Malformation Monitoring Centre Saxony-Anhalt, Medical Faculty Otto-von-Guericke University, Magdeburg, Germany
[17]National Perinatal Epidemiology Unit, University of Oxford, United Kingdom
[18]Public Health, Wales, United Kingdom
[19]Institut de Pathologie et de Génétique, Charleroi, Belgium
[20]University of Groningen, University Medical Center Groningen, The Netherlands
[21]Pediatric Department, Hospital Lillebaelt, Kolding, Denmark

This study was co-funded by the European Commission under the framework of the European Union Health Programme, Grant Agreement 2006103 (Executive Agency for Health and Consumers). The UK registers are funded by Public Health England.

*Correspondence to: Ester Garne, Paediatric Department, Hospital Lillebaelt – Kolding, Denmark. E-mail: ester.garne@rsyd.dk

Published online 00 Month 2014 in Wiley Online Library (wileyonlinelibrary.com). Doi: 10.1002/bdra.23240

Introduction

Congenital anomaly (CA) registries have been established primarily to identify unexpected occurrence of CA which may be due to possible teratogenic agents. After 30 years of monitoring and surveillance only a few new teratogenic agents have been identified. Population surveillance programs show that classifying CA according to presumed etiology focuses further investigation of cases. Surveillance of multiple congenital anomaly (MCA) cases is considered to be more sensitive for detecting new teratogens than surveillance of all or isolated CA cases because many known human teratogens are associated with a spectrum of birth defects rather than single defects (Khoury et al., 1987, 1993, 1994; Kalter, 1998; Källen et al., 1999). Furthermore, the goal of case classification is to use knowledge of embryologic and pathogenetic mechanisms to make case groups used for analysis more comparable. However the etiology of many CAs remain unknown and there are still concerns about environmental causes (Khoury et al., 1994; Opitz, 1994; Martinez-Frias et al., 1997, 2001; Zhu et al., 2009). New areas of developmental biology have been derived due to findings that external environmental agents can alter normal gene expression patterns through DNA methylation and other epigenetic mechanisms (Gilbert, 2004; Kubota, 2008; Martinez-Frias, 2010; Hales et al., 2011). As imprinted genes have an important role in growth and development, aberrant expression of imprinted genes due to genetic or epigenetic abnormalities is involved in the pathogenesis of human disorders, or imprinting disorders. Beckwith-Wiedemann syndrome is a representative imprinting disorder characterized by macrosomia, macroglossia, and abdominal wall defects, and exhibits a predisposition to tumorigenesis.

Many other unrecognized multiple anomalies may have the same etiology. As MCA are quite rare, they also represent a diagnostic and management problem, especially when counseling affected families (de Jong and Kirby, 2000).

The ability of congenital anomaly registries to identify cases in a consistent and standardized manner is required to allow epidemiological and etiological studies. Finally, the completeness and accuracy of reporting of MCA cases is relevant for monitoring defect combinations and specific malformation patterns occurring among different categories of malformed cases.

For the present study, MCA cases are defined as cases with two or more structural malformations that cannot be explained by an underlying syndrome or sequence. Cases were classified according to the computer algorithm developed by EUROCAT (Garne et al., 2011) which was based on the International Classification of Disease version 10 (ICD-10) codes. The algorithm gives explicit coding rules for classification and picks out a subset of potential MCA cases to be manually checked by three geneticists. The aim of this study is to show the application of the algorithm to EUROCAT data (2004–2010) for surveillance of MCA in Europe.

Materials and Methods

The study is based on routinely collected data for the years 2004 and 2010 from 19 European registries of congenital anomalies, extracted from the EUROCAT central database in November 2012. Data from 2004 were used for developing the computer algorithm for classification of cases (Garne et al., 2011). The year 2010 was the first dataset to be reviewed as part of the routine surveillance of MCA. Data for the years 2005 to 2009 have not yet been reviewed in relation to MCA. The EUROCAT registries are population based using multiple sources of information including hospital records, birth and death certificates, and postmortem examinations, and include information about live births, fetal deaths with gestational age (GA) $\geq$20 weeks and termination of pregnancy after prenatal diagnosis of fetal anomaly (TOPFA). All structural malformations, syndromes and chromosomal anomalies are included in the database except minor and poorly specified anomalies as detailed on the exclusion list. Registries may or may not report minor anomalies to EUROCAT central database. Cases with a false-positive prenatal diagnosis are not included in the database. Two registries included cases diagnosed up to 1 week after birth and 17 registries included cases diagnosed up to at least 1 year of age. A detailed description of registries, methods of case ascertainment, data collection and processing is available elsewhere (www.eurocat-network.eu/content/EUROCAT-Guide-1.3.pdf), (Boyd et al., 2011; Greenlees et al., 2011).

The EUROCAT classification of congenital anomaly cases is as follows (a case can belong to only one of these groups): (a) Chromosomal syndromes: All cases where an unbalanced chromosomal anomaly has been diagnosed, irrespective of types of anatomically defined anomalies. (b) Genetic and environmental syndromes: All cases due to a single gene defect or a known environmental teratogen, irrespective of types of anatomically defined anomalies. (c) Isolated anomalies: All cases with one congenital anomaly/anomalies occurring in only one organ subgroup or with a known sequence where multiple congenital anomalies cascade as a consequence of a single primary anomaly. (d) MCA: 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 syndrome or sequence.

The computer algorithm for classification of major congenital anomaly cases in the EUROCAT database was used for case classification. The group classified as potential MCA cases were manually reviewed by three geneticists to reach the final agreement on classification. The computer algorithm includes those sequences that can be coded by specific ICD10 codes for the anomalies involved in the sequence (step 21 in Appendix to Garne et al., 2011).

TABLE 1. *Prevalence of Congenital Anomalies and Multiple Congenital Anomalies Reported to 19 EUROCAT Registries in 2004 and 2010*

Year	Total births	Total congenital anomaly cases	Prevalence %	Prevalence 2004 vs 2010	Total multiple congenital anomaly cases	Prevalence per 10,000 births	Prevalence 2004 vs 2010
2004	445 838	12 410	2.78	$p < 0.001$	673	15.1	$p = 0.10$
2010	513 608	11 845	2.31		844	16.5	
Total	959 446	24 255	2.53		1517	15.8	

Remaining sequences will be found during the manual review and agreed by the geneticists.

All cases corresponding to the definition of MCA and born in the year 2004 or 2010 with data available for both years were included in the study. Nineteen EUROCAT registries met the study inclusion criteria. Epidemiological data for cases classified as isolated congenital anomaly from the same 19 registries in 2004 and 2010 was used for comparison.

The variables included in the analysis were: birth outcome, gender, maternal age at delivery, birth weight, GA at birth or termination, time of diagnosis (pre- or postnatal) and type of the congenital anomalies (ICD10 code and written text). All variables included in this study were EUROCAT core variables. The variables are defined in the EUROCAT Guide 1.3 available at the EUROCAT Web site. Prenatal diagnosis is defined as the first suspicion of a major congenital anomaly in a live fetus at any GA.

Statistics: Descriptive statistics and chi square tests were performed using STATA version 12.1 (StataCorp LP, College Station, TX).

Results

A total of 24,255 cases with congenital anomalies among 959,446 births were reported for the years 2004 and 2010 giving an overall prevalence of congenital anomalies of 253 per 10,000 births in the 19 registries. Over the same period 1,517 MCA cases were identified with a prevalence of 15.8 per 10,000 (Table 1). The prevalence of all anomalies decreased from 2004 to 2010 ($p < 0.001$); however, the prevalence of multiple anomalies remained fairly constant ($p = 0.10$). Of the 1,517 MCA cases 1,096 (72.3%) were live births, 49 (3.2%) were fetal deaths and 372 (24.5%) were TOPFA. Fetal death and TOPFA were significantly more frequent in MCA compared with isolated congenital anomalies ($p < 0.001$; Table 2).

MCA cases were more likely to be diagnosed prenatally than isolated cases (54.8% compared with 31.0%, $p < 0.001$) (Table 3). Few MCA cases were diagnosed after 1 month of age. The proportion of MCA cases diagnosed prenatally increased significantly between the years 2004 and 2010 ($p < 0.05$).There were large differences in prenatal detection rate by registry (range, 31–79%), but there was no association between the prenatal detection rate and the prevalence of MCA by registry.

Among the MCA cases there were 826 males (54.4%) and 601 females (39.6%; Table 4). The gender distribution was the same as for isolated CA ($p > 0.05$). A total of 345 of 1096 live births (31.5%) were born with a GA < 37 weeks compared with 2290 of 15,025 (15.2%) isolated cases ($p < 0.01$) and 321 (29.3%) were born with a birth weight less than 2500 grams compared with 12.92% of isolated cases ($p < 0.01$). Of the 19 registries that participated in the study, 16 provided data on chromosomal analysis. A karyotype analysis was carried out in 59.0% of the MCA cases in these 16 registries (418/709). A postmortem examination was performed in 83.9% of MCA cases resulting in TOPFA.

The 1517 MCA cases presented with approximately 5000 anomalies and the number of anomalies per case showed a tendency to increase depending on the outcome:

TABLE 2. *Comparison between Outcomes of Pregnancies with Multiple Congenital Anomalies and Isolated Congenital Anomalies, 19 EUROCAT Registries in 2004 and 2010*

	Multiple congenital anomalies[a]			Isolated congenital anomalies[a]		
Year	Live births (%)	Fetal deaths (%)	TOPFA[b] (%)	Live births (%)	Fetal deaths (%)	TOPFA[b] (%)
2004	491 (73.0)	23 (3.4)	159 (23.6)	7510 (89.4)	115 (1.4)	772 (9.2)
2010	605 (71.7)	26 (3.1)	213 (25.2)	7515 (89.5)	114 (1.4)	765 (9.1)
Total	1096 (72.2)	49 (3.2)	372 (24.5)	15025 (89.5)	229 (1.4)	1537 (9.2)

[a]The outcomes for multiple congenital anomalies were significantly different from those for isolated congenital anomalies ($p < 0.001$). The outcomes were similar for 2004 and 2010 ($p > 0.8$).

[b]TOPFA, termination of pregnancy for fetal anomaly.

TABLE 3. *Time of Diagnosis of Multiple Congenital Anomaly Cases and Isolated Congenital Anomaly Cases in 19 EUROCAT Registries in 2004 and 2010*

	Multiple congenital anomalies					Isolated congenital anomalies
	Year 2004		Year 2010			
When diagnosed	*N*	%	*N*	%	Total (%)	Total (%)
Prenatal diagnosis	341	50.7%[a]	491	58.2%[a]	832 (54.8%)[b]	5,197 (31.0%)[b]
At birth	231	34.3%	258	30.6%	489 (32.2%)	7,331 (43.7%)
Less 1 week after birth	27	4.0%	22	2.6%	49 (3.2%)	1,209 (7.2%)
1–4 weeks after births	7	1.0%	12	1.4%	19 (1.3%)	281 (1.7%)
1 month – 1 year after birth	10	1.5%	9	1.1%	19 (1.3%)	911 (5.4%)
After 1 year	2	0.3%	1	0.1%	3 (0.2%)	111 (0.7%)
At spontaneous abortion	1	0.1%	1	0.1%	2 (0.1%)	8 (0.1%)
At post mortem	4	0.6%	0	0.0%	4 (0.3%)	13 (0.1%)
Postnatal, time not known	-		12	1.4%	12 (0.8%)	341 (2.0%)
Not known	50	7.4%	38	4.5%	88 (5.8%)	1,389 (8.3%)
Total cases	673		844		1517	16,791

[a]The proportion of multiple congenital anomaly cases diagnosed prenatally was significantly higher in 2010 compared with 2004 ($p < 0.05$).
[b]The proportion of multiple congenital anomaly cases diagnosed prenatal was significantly higher than for isolated anomalies ($p < 0.001$).

live birth, fetal death or TOPFA. The most common anomalies among the 1517 MCA cases were congenital heart defects (CHD) (767) followed by congenital limb anomalies (443), congenital renal anomalies (438), and congenital anomalies of the digestive system (428). Of the 767 cases with a CHD, 216 (28%) had ventricular septal defect as the only cardiac anomaly and 141 (18%) had atrial septal defect as the only cardiac defect. Important differences in organ type are seen between isolated congenital anomalies and MCA cases (Table 5; $p < 0.001$). Respiratory and ear, face, and neck anomalies are the most likely to occur with other anomalies (34% and 32% occurred with other anomalies) and CHD, limb, and genital were the least likely to occur with other anomalies (12–13%). However, due to the high frequency of CHD, they were present in half of all MCA. There was a highly significant difference in the proportion of genital anomalies involved in MCA for male and females (Fig. 1; $p < 0.001$). For limb defects, the gender difference

TABLE 4. *Characteristics of Multiple Congenital Anomaly Cases and Isolated Congenital Anomaly Cases in 19 EUROCAT Registries in 2004 and 2010*

Characteristics	Number of multiple congenital anomaly cases (*n*=1,517)	Number of Isolated congenital anomaly cases (*n*=16,791)	
Gender			
Male	826 (54%)	9484 (56%)	Non significant
Female	601 (40%)	6716 (40%)	
Indeterminate sex	6 (< 1%)	15 (<1%)	
Unknown	84 (6%)	576 (3%)	
Gestational age at live birth – gender known	1095 live births	14993 live births	
< 37	345 (32%)	2290 (15%)	$p < 0.01$
37–41	707 (65%)	11634 (78%)	
≥ 42	15 (1%)	440 (3%)	
Unknown	28 (3%)	629 (4%)	
Gestational age at prenatal diagnosis (mean, SD) (range)	20.7 (6.0) (10–41)	21.9 (6.4) (5–42)	$p < 0.01$
Gestational age at TOPFA (mean, range)	19.5 (4.2) (11–35)	18.9 (4.6) (10–38)	$p < 0.05$
Mean maternal age at birth	29.6	29.5	Non significant

TABLE 5. *Number and Frequency of Anomalies by Organ System in Multiple Congenital Anomalies and Isolated Congenital Anomalies in 19 EUROCAT Registries in 2004 and 2010*

EUROCAT organ system Subgroups	Multiple congenital anomalies	Isolated congenital anomalies	Multiple congenital anomalies as a proportion of Isolated & multiple congenital anomalies (95% CI)
Cases	1,517 (100%)	16,791 (100%)	
Organ system			
Respiratory	172 (11.3%)	333 (2.0%)	34% (30%–38%)
Ear, face, and neck	62 (4%)	132 (0.8%)	32% (25%–39%)
Eye	101 (6.6%)	238 (1.4%)	30% (25%–35%)
Digestive system	428 (28.2%)	1038 (6.2%)	29% (27%–32%)
Nervous system	428 (28%)	1,553 (9.3%)	22% (20%–23%)
Abdominal wall defects	99 (6.5%)	451 (2.7%)	18% (15%–21%)
Renal	438 (28.9%)	2,233 (13.3%)	16% (15%–18%)
Oro-facial clefts	203 (13.4%)	1068 (6.4%)	16% (14%–18%)
Congenital heart defects	767 (50.6%)	5,091 (30.3%)	13% (12%–14%)
Limb	443 (29.2%)	3,071 (18.3%)	13% (12%–14%)
Genital	226 (14.9%)	1,630 (9.7%)	12% (11%–14%)

was also significant ($p < 0.001$), but there was no significant gender difference for the other organ systems.

Discussion

Surveillance of MCA cases is considered to be more sensitive for the detection of new teratogens than surveillance of all or isolated congenital anomalies. The current literature proposes the manual review of all cases for classification but this can lack uniformity. By implementing a computer algorithm for the classification of cases and the manual review only of potential MCA cases by an expert panel of geneticists, EUROCAT has established a feasible, efficient, and transparent way to monitor MCA cases for surveillance and research. The combination of this epidemiological and clinical approach to the classification of cases has improved the quality and accuracy of data that can be used for further investigation of a large series of MCA patients.

The use of different methodologies and different case classification systems impacts on the estimated prevalence of MCA cases. The available prevalence data on MCA cases in the literature range from 10.9 per 10,000 births (ICBD – EUROCAT 1998) to 16.3 per 10,000 births (Martinez-Frias et al., 1990), and 26 per 10,000 births (Czeizel et al., 1988). The EUROCAT study found a prevalence of 15.8 per 10,000 births. This prevalence remained stable (15.1 per 10,000 in 2004 and 16.5 in 2010), and is in agreement with other large population studies (Khoury et al., 1991) making it a possible reference point for future epidemiological studies.

Changes over time in prenatal and postnatal diagnostic methods may also impact on the prevalence of MCA cases. The increasing use of first trimester ultrasound scan may diagnose severe MCA cases as anencephaly or large abdominal wall defects resulting in an early TOPFA without recognition of additional anomalies. Most MCA cases were diagnosed prenatally, but still 40% of them remained undiagnosed until birth. The TOPFA rate of MCA cases remained constant from 2004 to 2010, despite a significant increase in the prenatal detection rate. This may be explained by an increased detection of less severe anomalies as cleft lip, club foot and hydronephrosis. For these anomalies the TOPFA rate will continue to be low unless associated with other more severe anomalies. The

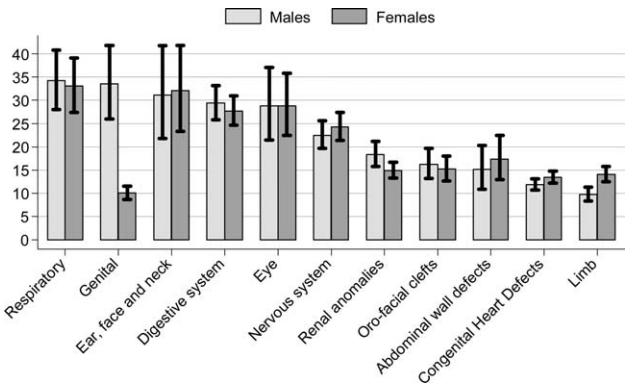

FIGURE 1. *Multiple congenital anomalies by organ system as a proportion of multiple and isolated congenital anomalies for males and females in 19 EUROCAT registries in 2004 and 2010. Black bars are 95% confidence intervals.*

differences in prenatal detection rates between countries are well known and have been reported to be related to different prenatal screening policies (Boyd et al., 2008; Garne et al., 2010). This represents a challenge for the future surveillance of MCA cases, and monitoring of prenatal diagnosis of MCA cases may be used as a public health indicator of the effectiveness of prenatal diagnostic services. Increasing use of second trimester ultrasound screening and postnatal ultrasound examinations may diagnose congenital anomalies that may have been undiagnosed in earlier time periods (for example, hydronephrosis, atrial septal defect, or ventricular septal defect) and thereby increase the prevalence of MCA cases.

As postmortem examination is difficult at early GA, associated congenital anomalies in the fetus may be undiagnosed. Also use of array technique and DNA diagnostics may lead to a future decrease in the prevalence of MCA, as more cases will be diagnosed as genetic syndromes.

The outcome of pregnancy was significantly different for MCA cases compared with the outcome for isolated CA cases in the same time period, with a significantly higher prevalence of TOPFA and fetal deaths, indicating the seriousness of the condition. No differences were found for the sex ratio between MCA and isolated cases, whilst gestational age and birth weight were significantly lower for live births with MCAs.

The comparison of organ systems involved in MCA cases found that the organ system with the highest prevalence in general (CHD) was less likely to be involved in MCA cases (13% of CHD cases were part of MCA). However, congenital heart defects were included in half of all MCA cases because of the high prevalence in general. Eye anomalies and anomalies of ear, face, and neck were associated with MCA cases for almost one-third of the cases. There may have been some bias in the reporting to EUROCAT for these anomalies as part of an MCA case and they may be less likely to be reported as isolated congenital anomalies. The knowledge of the risk of associated major anomalies is important after a prenatal or neonatal diagnosis of an anomaly in one organ system.

MCA are an important subgroup of rare diseases with implications for public health, including the burden of their management, and the psychological and emotional implications for families (Rosenthal et al., 2001).

Epigenetics was defined by Waddington (1940) as "... the interactions of genes with their environment which bring the phenotype into being", and refers to heritable modifications of gene expression and cell phenotype in absence of alterations to the DNA sequence. The epigenetic control mechanism is responsible for multiple cell signaling events and may be vulnerable to deregulation by environmental factors. Epigenetic processes are required throughout development and modification of an epigenetic state has the capacity to create a new phenotype. Beckwith-Wiedemann syndrome is a representative imprinting disorder characterized by macrosomia, macroglossia, and abdominal wall defects, and exhibits a predisposition to tumorigenesis. Many other unrecognized multiple anomalies may have the same etiology, as epigenetics can be modified by environmental factors through molecular mechanisms derived from the environment to alter genomic activity and developmental biology. Epigenetics studies may help to establish the molecular basis of gene-environment interactions.

The major strengths of this study are the large number of births that have been evaluated, that it is population-based and that participating registries use the same epidemiological methods. Cases were actively ascertained through multiple data sources from geographically defined residential populations. The same definitions and coding system for the CA were used by all participants. A standardized algorithm for the evaluation of multiples using software and manual evaluation by genetic experts was used to determine prevalence and other characteristics of MCA cases, and can be used for further studies. In interpreting these results, the limitations and strengths of the study should be taken into consideration. The main limitation of our data is that not all MCA cases had a known cytogenetic result. Consequently, it is possible that some MCA cases would ultimately be reclassified as chromosomal. With the advances in cytogenetics and molecular genetics, it is expected that this type of reclassification of MCA cases into chromosomal or syndrome category will continue. Other potential limitations are that local registries may not code congenital anomalies according to the EUROCAT coding instructions and data on the postmortem results may be inadequate.

CONCLUSIONS

MCA cases are an important subgroup of rare diseases with implications for public health, due to the severity and the burden related to their management. This study provides further epidemiologic data on MCA cases using the EUROCAT algorithm comparing cases from two time periods. The prevalence of MCA cases seems stable, but further monitoring is needed. By creating a standardized database of MCA cases across Europe, it may be possible to conduct statistical surveillance of MCA looking for new teratogens and to investigate the possible role of epigenetics in the occurrence of complex developmental disorders.

Acknowledgment

The authors declare no conflict of interest.

References

Boyd PA, de Vigan C, Khoshnood B, et al. 2008. Survey of prenatal screening policies in Europe for structural malformations and chromosome anomalies, and their impact on detection and termination rates for neural tube defects and Down's syndrome. BJOG 115:689–696.

Boyd PA, Haussler M, Barisic I, et al. 2011. Paper 1: The EUROCAT network–organization and processes. Birth Defects Res A Clin Mol Teratol 91(Suppl 1):S2–S15.

Czeizel AE, Kovacs M, Kiss P, et al. 1988. A Nationwide evaluation of multiple congenital abnormalities in Hungary. Genetic Epidemiol 5:183–202.

de Jong G, Kirby PA. 2000. Defects of blastogenesis: counselling dilemmas in two families. Am J Med Genet 91:175–179.

Garne E, Dolk H, Loane M, Boyd PA. 2010. EUROCAT website data on prenatal detection rates of congenital anomalies. J Med Screen 17:97–98.

Garne E, Dolk H, Loane M, et al. 2011. Paper 5: Surveillance of multiple congenital anomalies: implementation of a computer algorithm in European registers for classification of cases. Birth Defects Res A Clin Mol Teratol 91(Suppl 1):S44–S50.

Gilbert S. 2004. Mechanisms for the environmental regulation of gene expression. Birth Defects Res C Embryo Today 72:291–299.

Greenlees R, Neville A, Addor M-C, et al. 2011. EUROCAT member registries: organization and activities. Birth Defects Research (Part A), 2011;91:S51–S100.

Hales BF, Grenier L, Lalancette C, Robaire B. 2011. Epigenetici programming: from gametes to blastocyst. Birth Defects Res A Clin Mol Teratol 91:652–666.

ICBD - EUROCAT. 1998. World atlas of birth defect - 1st edition. Geneva: World Health Organization.

Kalter H. 1998. Congenital malformations: an inquiry into classification and nomenclature. J Med Genet 35:661–665.

Källén KB, Castilla EE, da Graca Dutra M, et al. 1999. A modified method for the epidemiological analysis of registry data on infants with multiple malformations. Int J Epidemiol 28:701–710.

Khoury MJ, Adams MM, Rhodes P, Erickson JD. 1987. Monitoring for multiple malformations in the detection of epidemics of birth defects. Teratology 36:345–353.

Khoury MJ, Botto L, Waters GD, et al. 1993. Monitoring for new multiple congenital anomalies in the search for human teratogens. Am J Med Genet 46:460–466.

Khoury MJ, Botto L, Mastroiacovo P, et al. 1994. Monitoring for multiple congenital anomalies: an international perspective. Epidemiol Rev 16:335–350.

Khoury MJ, Waters GD, Erickson JD. 1991. Patterns and trends in multiple congenital anomalies in birth defects surveillances systems. Teratology 44:57–64.

Kubota T. 2008. Epigenetics in congenital diseases and pervasive disorders. Enivron Health Prev Med 13:3–7.

Martinez-Frías ML, Frías JL, Salvador J. 1990. Clinical/epidemiological analysis of malformations. Am J Med Genet 35:121–125.

Martínez-Frías ML, Frías JL, Rodríguez-Pinilla E, et al. 1991. Value of clinical analysis in epidemiological research: the Spanish registry experience. Am J Med Genet 41:192–195.

Martínez-Frías ML, Frías JL. 1997. Primary developmental field. III: Clinical and epidemiological study of blastogenetic anomalies and their relationship to different MCA patterns. Am J Med Genet. 70:11–15.

Martínez-Frías ML. 2001. Approaches to the analysis of infants with multiple congenital anomalies. Am J Med Genet 101:33–35.

Martínez-Frías ML. 2010. Can our understanding of epigenetics assist with primary prevention of congenital defects? J Med Genet 47:73–80.

Opitz JM. 1994. Associations and syndromes: terminology in clinical genetics and birth defects epidemiology: comments on Khoury, Moore, and Evans. Am J Med Genet 49:14–20.

Rosenthal ET, Biesecker LG, Biesecker BB. 2001. Parental attitudes toward a diagnosis in children with unidentified multiple congenital anomaly syndromes. Am J Med Genet 103:106–114.

Waddington CH. 1940. Organisers and Genes, Cambridge University Press.

Zhu H, Kartiko S, Finnell RH. 2009. Importance of gene-environment interactions in the etiology of selected birth defects. Clin Genet 75:409–423.