ARTICLE

Prevalence, prenatal diagnosis and clinical features of oculo-auriculo-vertebral spectrum: a registry-based study in Europe

Ingeborg Barisic[*,1], Ljubica Odak[1], Maria Loane[2], Ester Garne[3], Diana Wellesley[4], Elisa Calzolari[5], Helen Dolk[2], Marie-Claude Addor[6], Larraitz Arriola[7], Jorieke Bergman[8], Sebastiano Bianca[9], Berenice Doray[10], Babak Khoshnood[11], Kari Klungsoyr[12], Bob McDonnell[13], Anna Pierini[14], Judith Rankin[15], Anke Rissmann[16], Catherine Rounding[17], Annette Queisser-Luft[18], Gioacchino Scarano[19] and David Tucker[20]

Oculo-auriculo-vertebral spectrum is a complex developmental disorder characterised mainly by anomalies of the ear, hemifacial microsomia, epibulbar dermoids and vertebral anomalies. The aetiology is largely unknown, and the epidemiological data are limited and inconsistent. We present the largest population-based epidemiological study to date, using data provided by the large network of congenital anomalies registries in Europe. The study population included infants diagnosed with oculo-auriculo-vertebral spectrum during the 1990–2009 period from 34 registries active in 16 European countries. Of the 355 infants diagnosed with oculo-auriculo-vertebral spectrum, there were 95.8% (340/355) live born, 0.8% (3/355) fetal deaths, 3.4% (12/355) terminations of pregnancy for fetal anomaly and 1.5% (5/340) neonatal deaths. In 18.9%, there was prenatal detection of anomaly/anomalies associated with oculo-auriculo-vertebral spectrum, 69.7% were diagnosed at birth, 3.9% in the first week of life and 6.1% within 1 year of life. Microtia (88.8%), hemifacial microsomia (49.0%) and ear tags (44.4%) were the most frequent anomalies, followed by atresia/stenosis of external auditory canal (25.1%), diverse vertebral (24.3%) and eye (24.3%) anomalies. There was a high rate (69.5%) of associated anomalies of other organs/systems. The most common were congenital heart defects present in 27.8% of patients. The prevalence of oculo-auriculo-vertebral spectrum, defined as microtia/ear anomalies and at least one major characteristic anomaly, was 3.8 per 100 000 births. Twinning, assisted reproductive techniques and maternal pre-pregnancy diabetes were confirmed as risk factors. The high rate of different associated anomalies points to the need of performing an early ultrasound screening in all infants born with this disorder.
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INTRODUCTION

Oculo-auriculo-vertebral spectrum (OAVS) (OMIM 164210, OMIM 141400) is a complex developmental disorder that mainly affects head and neck structures derived from the first and second branchial arches and the intervening first pharyngeal pouch and branchial cleft. It is characterised by anomalies of the ear, hemifacial microsomia, epibulbar dermoids and vertebral anomalies.[1–3] Other terms, such as Goldenhar syndrome, hemifacial microsomia, lateral facial dysplasia, oculo-auriculo-vertebral dysplasia, facio-auriculo-vertebral spectrum/sequence and first and second branchial arch syndrome are also used, but it is now accepted that these conditions are part of the same clinical spectrum that varies from mild-to-severe phenotype.[3–5]

The causes of OAVS are unknown but undoubtedly complex and heterogeneous. Genetic as well as environmental causative factors have been proposed. Different chromosomal anomalies have been identified by standard karyotyping or array comparative genomic hybridisation in OAVS patients.[6,7] The association with chromosomes 5, 9, 18, 22 and X was observed on several occasions.[3] There are three reports that link OAVS with 14q22.3-q23.3 region. One patient and his father both had branchio-oto-renal syndrome and OAVS associated with an 11.79-Mb duplication of chromosome

[1]Children's Hospital Zagreb, Medical School University of Zagreb, Zagreb, Croatia; [2]EUROCAT Central Registry, Room 12L09, University of Ulster, Ulster, Northern Ireland, UK; [3]Pediatric Department, Hospital Lillebaelt, Kolding, Denmark; [4]Wessex Clinical Genetics Service, Princess Anne Hospital, Southampton, UK; [5]Registro IMER, Azienda Ospedaliero–Unifersitaria di Ferrara, Ferrara, Italy; [6]Autonome de Genetique Medicale, Lausanne, Switzerland; [7]Registro Anomalias Congenitas CAV, Direccion de Salud Publica, Donostia San Sebastian, Spain; [8]Eurocat Registration Northern Netherlands, Department of Genetics, University Medical Center Groningen, Groningen, The Netherlands; [9]Genetica Medica, ARNAS Garibaldi, ARNAS Garibaldi, Catania, Italy; [10]Service de genetique Medicale, Hopitale de Hautepierre, Strasbourg Cedex, France; [11]Paris Registry of Congenital Malformations, INSERM U953, Maternite de Port-Royal, Paris, France; [12]Medical Birth Registry of Norway, Norwegian Institute of Public Health, and Department of Public Global Health and Primary Health Care, University of Bergen, Bergen, Norway; [13]Health Information Unit, Health Service Executive, Dr Steevens Hospital, Dublin, Ireland; [14]CNR Institute of Clinical Physiology, Pisa, Italy; [15]Institute of Health and Society Newcastle University, Newcastle upon Tyne, UK; [16]Malformation Monitoring Centre Saxony-Anhalt, Medical Faculty Otto-von-Guericke University, Magdeburg, Germany; [17]National Perinatal Epidemiology Unit, University of Oxford, Oxford, UK; [18]Universitatskinderklinik Mainz, Mainz, Germany; [19]Registro Campano Difetti Congeniti, Azienda Ospedaliera "G Rummo", Benevento, Italy; [20]Congenital Anomaly Register and Info Service Public Health Level 3 West Wing, Singleton Hospital, Wales, UK
*Correspondence: Dr I Barisic, Department of Paediatrics, Children's Hospital Zagreb, Medical School University of Zagreb, Klaiceva 16, Zagreb 10 000, Croatia. Tel: +385 1 4600 107; Fax: +385 1 4600 160; E-mail: ingeborg.barisic@kdb.hr
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14q22.3-q23.3 and a 4.38-Mb deletion in 13q21.31-q21.32.[8] Northrup et al[9] have described a patient with per inv(14)(p11.2q22.3) inherited from his phenotypically normal mother. Recent publication describes a new familial 14q23.1 duplication, 1.34 Mb in size, which segregates with the OAVS phenotype in an autosomal dominant manner.[10] These findings indicate that disruption of potential candidate gene/genes in 14q22.3–q23.3 region could be a causative factor in at least some of the OAVS cases. A genome-wide linkage analysis in one family identified *Goosecoid* mapped at 14q32.1 as a possible candidate gene, but no pathogenetic mutation was found.[11] A more recent genome-wide association study also failed to identify a clear causative variant.[12] Fischer et al[13] found abnormal expression of *BAPX1* gene (mapped at 4p15.3) in a significant number of OAVS patients and suggested that epigenetic disregulation of *BPAX1* and possibly other genes might have a role in the aetiology of OAVS. The epigenetic changes could explain the higher incidence of twinning, high proportion of discordant monozygotic twins and high correlation of use of *in vitro* fertilisation in OAVS.[14]

The condition usually occurs sporadically, but familial cases compatible with autosomal dominant[15,16] and autosomal recessive[2,17] types of inheritance have been described. The possibility of germinal mosaicism has also been considered.[18] The low empiric recurrence risk of 2–3% and the rarity of reports of concordance in twins support the multifactorial type of inheritance in most cases.[3]

The OAVS has been linked with intrauterine exposure to many different drugs. In particular, maternal use of vasoactive medications in combination with cigarette smoking in the first trimester was found to be associated with an increased risk of OAVS.[19] Vasoactive medications reported more often in OAVS pregnancies compared with controls include pseudoephedrine, phenylpropanolamine, aspirin, and ibuprofen, but clear association was demonstrated only for pseudoephedrine.[19] Severe manifestations of OAVS were also observed in a cocaine-exposed infant.[20]

In fact, it was previously suggested that disturbance in vascular supply to cephalic neural crest cells could hinder embryonic development in the branchial arches and cause OAV spectrum.[21]

Twin pregnancies[19,22,23] and the use of artificial reproductive techniques (ART)[14,24] have been observed more often than expected among OAVS patients. The relationship with maternal diabetes contributes additionally to the heterogeneity of environmental causes associated with OAVS.[25] As the aetiology is largely unknown, data on the possible environmental risk factors from epidemiological studies are needed.

Although several large clinical series of OAVS patients have been published discussing the classification, clinical presentation, diagnostic criteria and associated findings,[2,4,5] population-based epidemiological studies on OAVS are lacking, because they demand large populations, standardised data collection and genetic expertise. There has been considerable discrepancy in the reported prevalence rates that range from 1 per 5642[2] to 1 per 45 000.[26] Most data are based on live born (LB) children, while little is known about fetal deaths (FDs) and terminations of pregnancy for fetal anomaly (TOPFA) after prenatal ultrasound diagnosis. In addition, hospital-based series of patients from specialised centres bring ascertainment biases in prevalence data and frequency of associated abnormalities.

In this study, we used data from EUROCAT, a large network of population-based congenital anomaly registries in Europe, to provide population-based information on OAVS patients, including the total prevalence and birth outcomes (proportion of LB, FD at gestational age (GA) ≥ 20 weeks, TOPFA), time of diagnosis, sex, GA and weight at birth, associated anomalies, family history, consanguinity and possible risk factors. To our knowledge, this is the largest series of OAVS patients published so far.

MATERIAL AND METHODS

The EUROCAT congenital anomaly registries are surveying > 1.7 million births per year (30% of the annual European birth population). They collect data on all major structural congenital anomalies, chromosomal abnormalities and genetic syndromes for all birth outcomes. The registries are based on multiple sources of information that include hospital records, birth and death certificates, cytogenetic reports and *post mortem* examinations. A detailed description of registries, methods of case ascertainment, data collection and processing is available elsewhere[27] (http://www.eurocat-network.eu/content/DQI-2010.pdf). For the purpose of this study, we used data provided by 34 registries from 16 European countries for the 1990–2009 period. Data was extracted from the central database in January 2013.The central EUROCAT database was searched for ICD9/BPA (756060, 75606), ICD10/BPA (Q8704) and OMIM (164210, 141400) codes assigned to cases of OAVS/Goldenhar/hemifacial microsomia. For the inclusion in the study or minimal diagnostic criteria, we used arbitrary definition of the presence of microtia/ear anomalies and at least one major anomaly of the OAV spectrum. Isolated cases of microtia or other minor craniofacial anomalies specified in the Minor Anomalies for Exclusion list in the EUROCAT classification guidelines (www.eurocat-network.eu/content/EUROCAT-Guide-1.3.pdf) were not included. EUROCAT registries do not collect data on laterality of malformations or zygosity, thus we were not able to analyse our data set in this respect. An associated anomaly was defined as a major structural anomaly other than craniofacial and vertebral anomalies, which are usually considered to be part of the classical OAVS. In 20/30 (66.6%) of EUROCAT registries, clinical geneticists take part in the examination of most or all patients with dysmorphic features and multiple anomalies, and in the remaining registries clinical geneticists participate in the examination of selected cases. Medical geneticist (IB) reviewed all records. Textual description was also analysed in order to ensure all relevant clinical information. Local registries were occasionally contacted for supplying additional information. All phenotype and epidemiological data will be available to all phenotypic databases (eg, OMIM or GeneReviews).

Statistical analysis

Descriptive data are presented as counts and percentages for categorical data, and mean and 95% confidence interval based on Poisson's distribution is used for prevalence. Statistical testing was performed at $P = 0.05$ level of statistical significance. Generalised Linear/Nonlinear model based on Poisson's distribution was used for statistical testing of time trends in prevalence, Fisher's exact test for testing difference between categorical data and difference between two proportions' test for statistical testing between prenatal diagnosed and non-diagnosed patients. Chi-squared test was performed in order to determine differences in maternal age distribution between OAVS and other EUROCAT cases.

RESULTS

We recorded a total of 355 cases of OAVS during the 20 years of study period. There were 95.8% (340/355) LB, 0.8% (3/355) FDs, 3.4% (12/355) TOPFA and 1.5% (5/340) neonatal deaths (Table 1). Of the 307 patients with a known time of diagnosis, 69.7% were diagnosed at birth, 3.9% in the first week of life and 6.1% within 1 year of life. In 18.9%, there was a prenatal detection of congenital anomaly/anomalies, followed by the diagnosis of OAVS later on. The number of prenatally detected cases increased to some extent from 1990–1999 to 2000–2009 period, although not significantly ($P = 0.27$) (Table 1). The mean GA at discovery of an anomaly by prenatal ultrasound was 21.3 ± 4.1 (range 11–40) gestational weeks. Of the 58 prenatally detected patients, there were 45 LB, 1 FD and 12 (20.7%) pregnancies were terminated at 22.1 ± 4.8 (range 17–36) gestational weeks.

Table 1 Prenatal detection rate and outcome of pregnancies with oculo-auriculo-vertebral spectrum (OAVS) in the EUROCAT registries, 1990–2009

Monitored period	Total births	Total no. of patients	Prenatally detected/number of patients with available data	Prenatal detection rate, (%) 95% CI	LB	FD	TOPFA
1990–1999	4 639 123	125	18/113	15.9 (10.0–24.3)	119	2	4
2000–2009	9 114 383	230	40/194	20.6 (15.3–27.1)	221	1	8
1990–2009	13 753 506	355	58/307	18.9 (14.8–23.8)	340	3	12

Abbreviations: FD, fetal death; LB, live born; TOPFA, terminations of pregnancy for fetal anomaly.

The diagnosis was confirmed by *post mortem* examination in 13 cases. Prenatally suspected cases had a higher frequency of central nervous system ($P = 0.001$), congenital heart ($P = 0.009$), genitourinary ($P = 0.001$) and spine ($P = 0.02$) anomalies compared with those who had negative prenatal ultrasound scan. In addition, there were significantly more cases with two or more major congenital anomalies compared with patients who were detected after birth ($P = 0.004$). In 16/108 (14.8%) cases, a major structural anomaly was detected postnatally following a negative prenatal ultrasound result.

Detailed clinical description was available for 259 patients, and the frequencies of observed anomalies are presented in Table 2. Microtia (88.8%), hemifacial microsomia (49.0%) and ear tags (44.4%) were most frequent, followed by atresia/stenosis of external auditory canal (25.1%), diverse vertebral (24.3%) and eye (24.3%) anomalies and orofacial clefts (17.8%).

There were 180 (69.5%) OAVS patients with anomalies other than craniofacial and vertebral anomalies, which are usually considered to be part of classical OAVS. One associated major anomaly was present in 111 (61.7%), two anomalies in 54 (30%) and three or more associated anomalies in 15 (8.3%) patients. The most common anomaly was congenital heart defect present in 72 (27.8%) patients. The frequency of a particular type of cardiac anomalies did not differ from the frequency in the general population of the EUROCAT registries included in the study for the same period, with the exception of conotruncal defects ($P = 0.02$). Congenital heart defects were not significantly associated with pulmonary ($P = 0.68$) or renal ($P = 0.34$) abnormalities.

Epidemiological data

Prevalence was calculated based on data from 16 registries with non-chromosomal syndrome prevalence above the EUROCAT average of 7.8 per 1000 in order to secure a high rate of ascertainment of cases (http://www.eurocat-network.eu/content/DQI-2010.pdf). In the period from January 1990 to December 2009 in these registries, we recorded 161 cases in the population of 4 245 519 births. The estimated prevalence is thus 1 per 26 370 or 3.8 per 100 000 births. The prevalence rates for 1990–1999 and 2000–2009 were 2.8 and 4.3 per 100 000 ($P = 0.008$), respectively (Table 3).

The characteristics of OAVS patients observed in all 34 registries are shown in Table 4. The male-to-female ratio was 1.4:1. The mean GA in live births was 38.1 ± 6.2 in females and 38.9 ± 4.1 in males, while the mean birth weight was 2971 ± 769 g in females and 2940 ± 769 g in males.

The mean maternal age was 29.9 ± 4.8 years and the mean paternal age 32.1 ± 6.4 years. Comparison of the maternal age distribution with the maternal age distribution in the total EUROCAT population (data known for 67.6% of the EUROCAT total birth population) yielded a significant difference ($P = 0.04$), mothers of OAVS patients being more represented in the ≥ 30-year-old group compared with the rest of EUROCAT population.

There were 11 confirmed familial OAVS cases, 3 of these among sibs and 8 cases where one of the parents was affected. No phenotypic differences between familial and sporadic cases were observed. Parental consanguinity was recorded in two cases.

Karyotyping was performed in 54.8% (155/283) of cases and yielded two abnormal findings (47,XXY and 45,X/46,XY). Data on FISH analyis for del22q11.2 were not available.

No evidence of exposure to consistent teratogenic agents was noted, including data on medications that were available for 70 patients. The use of vasoactive drugs was recorded in six cases. Multiple pregnancies of undetermined zygosity were recorded in 25 (7.2%) cases (in all cases, only one affected of twins/triplets), and 15/172 (8.7%) patients were conceived by one of the methods of ART. Maternal diabetes was present in 3.9% (6/152) of the affected pregnancies (Table 4).

DISCUSSION

Prevalence

The usually cited prevalence of OAVS is 1 per 5600,[2] although others have suggested much lower figures in the range of 1 per 10 000,[30] 1 per 19 500,[31] 1 per 26 550[32] to 1 per 45 000.[26] The prevalence of 1 per 26 370 found in our study is more in line with these results. The observed significant increase in the prevalence observed comparing 1990–1999 and 2000–2009 may be due to the better ascertainment of cases or to the true increase in prevalence of this condition and should be investigated further.

There is no universal agreement upon minimal diagnostic criteria for OAVS, but an ear anomaly has been suggested by some authors as the mildest form.[2–5,19] As EUROCAT registries do not record cases with isolated minor anomalies of the head and neck, our series of OAVS patients did not include the possible mild cases presenting only as microtia or some other minor/cosmetic ear defect. According to our case definition, only patients with ear anomaly and at least one major craniofacial and/or vertebral feature involved in OAVS were included in the study. Therefore, the prevalence of 1 per 26 370 in EUROCAT registries represents a minimum figure and refers to a clinically relevant/serious group of patients. In addition, OAVS patients who are diagnosed at a later age will be missed, as some registries only register cases with anomalies discovered in the neonatal period.

Clinical features

Premature birth, low birth weight and failure to thrive have been often reported in infants with OAVS. In a demographic study of OAVS, Werler *et al*[23] found that 20% of cases weighed <2500 g at birth, compared with only 5% of controls. In our patient series, 20.8% of males and 36.7% of females weighed <2500 g. More than two-thirds of both sexes had normal GA at birth. The observed male preponderance is in accordance with observations from previous studies.[3–5,19]

The diagnosis of OAVS relies on the recognition of the characteristic craniofacial, ear, eye and vertebral defects and in most cases is

Table 2 Type and frequency of anomalies among patients with oculo-auriculo-vertebral spectrum (OAVS)

Type of anomaly	Patients N = 259 (%)	Rollnick et al,[4] N = 294	Vento et al,[28] N = 154	Tasse et al,[5] N = 53	Toulitaou et al,[29] N = 17
Ear	259 (100)	294 (100)		53 (100)	17 (100)
Microtia/misshapen/dysplastic/rudimentary ear[a]	230 (88.8)				16 (94)
Preauricular skin tag[a]	115 (44.4)		61 (39.6)		10 (59)
Atresia/stenosis of external auditory canal	65 (25.1)				9 (53)
Absence of auricle	24 (9.3)				
Accessory auricle	23 (8.9)				
Anotia	17 (6.6)				
Preauricular pits/sinus[a]	6 (2.3)				
Other	17 (6.6)				
Eye	63 (24.3)	52 (18)		13 (24.5)[b]	11 (65)
Epibulbar dermoids	20 (7.7)	9 (4.4)	32 (20.7)	11 (20.7)	2 (12)
Epicanthus[a]	14 (5.4)				12 (75)
Microphthalmia	14 (5.4)			5 (9.4)	6 (35)
Coloboma of eyelid	10 (3.9)			4 (7.5)	2 (12)
Coloboma of iris	4 (1.5)				1 (6)
Anophthalmia	4 (1.5)			2 (3.7)	
Aniridia	1 (0.4)				
Absence of lens	1 (0.4)				
Other	8 (3.1)				
Orofacial clefts	46 (17.8)	66 (22)		21 (40)	5 (29)
Cleft lip and palate	21 (8.1)	21 (7)		5 (9.4)	
Cleft palate	17 (6.6)	45 (15)		5 (9.4)	
Cleft lip	7 (2.7)			2 (3.7)	
Orofacial clefts, other	11 (4.2)			9 (16.9)	
Face and neck	145 (56.0)				13 (76)
Hemifacial microsomia, including asymmetry of the face[a], micrognathia, mandibular hypoplasia, and anomalies of jaw size	127 (49.0)	202 (68.7)		44 (83)	10 (59)
Anomalies of the nose	9 (3.5)				1 (6)
Facial palsy	9 (3.5)		24 (45)		
Branchial cyst[a]	9 (3.5)				
Macrostomia[a]	6 (2.3)		95 (61.6)		
Tongue anomaly	4 (1.5)				
Vertebral	63 (24.3)	55 (18.7)	29 (18.8)	10 (19)	3 (18%)
Cervical	17 (6.6)				
Cervical anomaly NOS	10 (3.9)				
Hemivertebre cervical	4 (1.5)				
Split cervical vertebrae	1 (0.4)				
Fussed cervical vertebrae	2 (0.8)				
Thoracic/lumbar/sacral	13 (5.0)				
Thoracic vertebrae anomaly NOS	8 (3.1)				
Lumbar vertebrae anomaly NOS	2 (0.8)				
Accessory lumbar vertebrae	1 (0.4)				
Agenesis lumbar vertebrae	1 (0.4)				
Sacral agenesis	1 (0.4)				
Hemivertebrae NOS	14 (5.4)				
Spine scoliosis	8 (3.1)				
Spine NOS	18 (6.9)				
Rib anomalies	18 (6.9)		12 (7.8)		
Congenital heart defects	72 (27.8)	14 (5)		8 (15)	3 (18)
Ventricular septal defect	31 (12.0)			5 (9.4)	
Atrial septal defect	13 (5.0)				

Table 2 (Continued)

Type of anomaly	Patients N = 259 (%)	Rollnick et al,[4] N = 294	Vento et al,[28] N = 154	Tasse et al,[5] N = 53	Toulitaou et al,[29] N = 17
Pulmonary valve stenosis	8 (3.1)				
Atrioventricular septal defect	6 (2.3)			1 (1.8)	
Dextrocardia	6 (2.3)			1 (1.8)	
Transposition of great arteries	4 (1.5)				
Tetralogy of Fallot	4 (1.5)				
Aortic valve stenosis	3 (1.2)			1 (1.8)	
Coarctation of aorta	3 (1.2)			1 (1.8)	
Hypoplastic aorta	3 (1.2)				
Double outlet right ventricle	2 (0.8)				
Hypoplastic left heart syndrome	1 (0.4)				
Aortopulmonary window	1 (0.4)				
Abnormal subclavian artery	1 (0.4)				
Congenital heart disease, NOS	4 (1.5)				
Respiratory system	13 (5.0)	2 (0.6)			-
Choanal atresia	4 (1.5)				
Lobar anomaly of the lungs	4 (1.5)				
Lung hypoplasia	4 (1.5)				
Tracheomalacia[a]	1 (0.4)				
Laryngomalacia[a]	1 (0.4)				
Digestive system	20 (7.7)	6 (2)			2 (12)
Oesophageal atresia with tracheo-oesophageal fistula	7 (2.7)				
Anorectal stenosis/atresia	4 (1.5)				
Imperforate anus	3 (1.2)				
Diaphragmatic hernia	2 (0.8)				
Pyloric stenosis[a]	2 (0.8)				
Annular pancreas	1 (0.4)				
Small intestine stenosis	1 (0.4)				
Hirschsprung's disease	1 (0.4)				
Genitourinary	41 (15.8)	16 (5)		9 (16.9)	4 (23)
Renal agenesis, unilateral	12 (4.6)			2 (3.7)	
Anomalies of ureter	9 (3.5)				
Congenital hydronephrosis	8 (3.1)			1 (18)	
Renal hypoplasia/dysplasia	7 (2.7)			1 (1.8)	
Hypospadias	7 (2.7)			2 (3.7)	
Cystic kidney	3 (1.2)				
Horseshoe kidney	2 (0.8)				
Duplex kidney	1 (0.4)				
Cyst of urachus	1 (0.4)				
Limb defects	30 (11.6)	33 (11)	26 (16.8)	6 (11.3)	4 (23)
Polydactyly	7 (2.7)				
Radial defects of hands	6 (2.3)				
Congenital hip dislocation	5 (1.9)				
Pes equinovarus	4 (1.5)				
Syndactyly	4 (1.5)				
Bifid thumb	3 (1.2)				
Camptodactyly	2 (0.8)				
Low set thumbs[a]	2 (0.8)				
Pes calcaneovalgus	1 (0.4)				
Forearm anomalies NOS	3 (1.2)				
Nervous system	27 (10.4)	38 (13)		8 (15)	5 (29)[c]
Neural tube defects (including encephalocele)	6 (2.3)				
Hydrocephaly	5 (1.9)			1 (1.8)	
Ventriculomegaly	5 (1.9)			1 (1.8)	

Table 2 (Continued)

Type of anomaly	Patients N = 259 (%)	Rollnick et al,[4] N = 294	Vento et al,[28] N = 154	Tasse et al,[5] N = 53	Toulitaou et al,[29] N = 17
Agenesis of corpus callosum	5 (1.9)				
Agenesis/hypoplasia of cerebellum	4 (1.5)				
Cerebral cyst	2 (0.8)				
Aqueductus stenosis	1 (0.4)				
Cerebral anomaly NOS	4 (1.5)				
Situs viscerum inversus	1 (0.4)				

Abbreviation: NOS, not otherwise specified; individuals with more than one anomaly within a category were counted only once.
[a]These anomalies are considered minor according to the EUROCAT criteria and not are not systematically recorded in some registries.
[b]Epibulbar dermoids excluded.
[c]Facial nerve palsy included.

Table 3 Prevalence of oculo-auriculo-vertebral spectrum (OAVS) in 16 selected EUROCAT registries, 1990–2009

Monitored period	Total births	Total no. of patients	Birth prevalence per 100 000 (95% CI)
1990–1999	1 775 132	49	2.8 (2.1–3.7)
2000–2009	2 596 179	112	4.3 (3.6–5.2)
1990–2009	4 245 519	161	3.8 (3.2–4.4)

quite straightforward in spite of the clinical variability and possible overlap with other entities (eg, CHARGE syndrome, Treacher Collins syndrome, VACTERL association). Ear anomalies were present in all recorded patients, ranging from mild deformities in the size and shape of the external ear, preauricular tags and pits to anotia. The frequency and type of ear anomalies, facial asymmetry and eye anomalies are similar to data reported by others.[4,5]

Vertebral defects were reported in 18–60% of patients with OAVS.[2,4,5,28,29,33] The frequency of spine anomalies in previously published OAVS cohorts depends on the sample size, patient selection and the level of spine investigation. We recorded spinal anomalies in 24.3% of cases. Vertebral anomalies occurred at all levels of spinal column, although slightly more frequently in the cervical region. The association of ocular and vertebral anomalies reported by Gibson et al[33] was not observed.

Associated anomalies
We found 69.4% of OAVS patients to have associated anomalies. This is the highest rate of anomalies not involving the head, neck and vertebral column reported in OAVS so far. The high rate of associated anomalies can be explained by the fact that we were able to present data on all types of birth, including TOPFA, FD and early deaths. In addition, existing studies have been small and/or from specialised centres, which can cause ascertainment bias towards a specific group of anomalies. There are only two detailed clinical reports with a large number of patients. Grabb[2] has reported seven associated anomalies among 102 patients. Here the under-reporting could be due to the limited diagnostic possibilities in those times. Rollnick et al[4] found 44% of associated anomalies in a large series of 294 patients, but the study included mild cases, with isolated microtia being present in 31% of cases. Excluding these, the proportion of associated anomalies would be in line with our findings.

We observed not only a high rate but also a vast range of defects of different organs and systems. The most frequent associated anomalies

were congenital heart defects present in almost one-third of patients. The reported prevalence of congenital heart defects among OAVS patients ranges from 1 to 58%.[2,4,26,29,34] These differences are related to the sample size and different methodology of respective studies. Grabb[2] found only one heart anomaly among 102 patients. Rollnick et al[4] included mild cases and found that only 4 and 5% of cases had a congenital heart defect, respectively. On the other hand, heart defects were found in a half of patients in the series coming from cardiac department.[35] In our study, the conotruncal anomalies were significantly associated with OAVS as observed previously by some authors,[34,36] while the prevalence of other types of congenital heart defects did not differ from the EUROCAT general population. The congenital heart defects were not associated with pulmonary and renal abnormalities, as observed by Kumar et al.[36]

Genitourinary malformations were the second most common group of anomalies in our cohort (15.8%), with renal agenesis and ureteral anomalies being most frequent. The presence of genitourinary defects reported in OAVS patients ranges from 2–5%[2,4] to 50% in a small study where 14 urinary tract anomalies (of these five cases of renal agenesis) were diagnosed in 28 children with OAVS by performing imaging of the urinary tract.[37] This indicates that a more detailed investigation may reveal that genitourinary anomalies are more common than expected.

The frequency of central nervous system anomalies found in our study (10.4%) is lower than that described in the literature, where frequencies were reported that range between 13 and 47%.[4,5,38] The highest frequency was found by Rosa et al[38] who included only subjects undergoing neuroimaging and detected anomalies in 47% of patients. We did not confirm the association between central nervous system anomalies and ophthalmologic anomalies observed previously.[5,38]

OAVS with radial defect (OMIM 141400), which is considered a separate entity among OAVS, was present in only six patients. In our data set, we did not find cases that were diagnosed as oculo-auriculo-fronto-nasal syndrome (OMIM %601452), a rare developmental field defect that combines abnormal development of the first and second branchial arches with abnormal morphogenesis of the frontonasal and maxillary processes.[39,40]

The broad spectrum of associated major anomalies reinforces the heterogeneity of OAVS supporting the hypothesis that OAVS could be part of the axial mesodermal dysplasia spectrum.[41]

Prenatal diagnosis
In order to delineate the pattern of anomalies detected prenatally in OAVS, Castori et al[42] reviewed prenatal ultrasound findings in 20 previously reported cases. They found asymmetric facial defects

Table 4 Descriptive epidemiological data on patients with oculo-auriculo-vertebral spectrum (OAVS) in the EUROCAT registries, 1990–2009

Characteristics	Number of OAVS patients (%)	
Sex		
Male	205	
Female	148	
Unknown	2	
	n = 321 (live births with known	
Gestational age, week	gestational age and sex)	
	M	F
	n = 188	n = 133
<37	33 (17.5%)	21 (15.8%)
37–41	147 (78.2%)	105 (78.9%)
≥42	8 (4.3%)	7 (5.3%)
	n = 320 (live births with known	
Birth weight (g)	gestational age and sex)	
	M	F
	n = 192	n = 128
<1500	9 (4.7%)	13 (10.1%)
1500–1999	13 (6.8%)	7 (5.5%)
2000–2499	18 (9.3%)	27 (21.1%)
2500–2999	39 (20.3%)	28 (21.9%)
3000–3499	71 (37%)	41 (32%)
>3500	42 (21.9%)	12 (9.4%)
Positive family history	11/196 (5.6%)	
Consanguinity	2/202 (1%)	
Singleton pregnancies	322/347 (92.8%)	
ART	10/158 (6.3%)	
Multiple pregnancies	25/347 (23 twins, 2 triplets) (7.2%)	
ART	5/14 (35.7%)	
Maternal pregestational diabetes	6/152 (3.9%)	

Abbreviation: ART, assisted reproductive technology.

and central nervous system anomalies to be the most common findings. In our group of OAVS patients, prenatally observed anomalies were rather heterogeneous, affecting not only craniofacial structures but also other organs and systems. In more severe cases, the prenatal diagnosis is possible as early as from 11 weeks of gestation.

Possible aetiology and risk factors

The aetiological heterogeneity and complexity of OAVS has been suggested in many reports. Previous studies have occasionally identified chromosomal abnormalities associated with OAVS. We identified one patient with 47,XXY and one with 45,X/46,XY. Sex chromosome aneuploidies have been described on several occasions in patients with OAVS[5,43,44] but as these aneuploidies are quite frequent, the association with OAVS is possibly due to chance.

Although most cases were sporadic, 5.6% cases were familial, confirming the existence of a small proportion of families with a high recurrence risk.

Twin pregnancies were, on average, five times more common in OAVS patients compared with the incidence of twin pregnancies in European countries who participated in the study (the mean rate of twin pregnancies was 14.9 per 1000 births, ranging from 11.2 in Italy to 18.0 in Denmark).[45] Several studies have reported an increased rate of twinning in pregnancies with OAVS with and without infertility treatment. Different possible mechanisms, including basic common embryological, disruptive or epigenetic events, were discussed.[14,22,23,26] Because multiple gestations occur commonly in couples treated for infertility, we also examined the use of ART. Couples who had children with OAVS were treated more for infertility than the general European population (15/172 or 8.7% compared with the mean use of ART of 2.7%; range 1.2–4.9% in European countries under study).[46] An excess of patients with OAVS conceived by ART has been also described before.[14,47–49] At present, it is not known whether the observed increased risk is due to the technique itself or to the fertility problems in parents.[14] Our data confirm the observation that twinning and treatment for infertility are associated with an increased risk of congenital anomalies in general[50] and in particular with OAVS, as proposed previously.[14,23,24] The higher maternal age observed among mothers of OAVS patients could be also related to the higher rate of reproductive difficulties.

It was suggested that maternal diabetes may also be associated with OAVS.[25] It is estimated that 0.3% of all pregnant women have pre-pregnancy diabetes.[51] We found the number of mothers with pre-pregnancy diabetes in OAVS pregnancies to be more than 10 times higher, supporting the hypothesis that diabetes is a risk factor for this developmental disorder.

Study strengths and limitations

This epidemiological population-based study is the largest to date and the only one in which data on all types of birth outcomes is included. The greatest strengths of this study are the large series of OAVS patients and the use of multiple sources of ascertainment, which made possible avoiding ascertainment bias found in the reports from specialised centres.

However, in spite of the use of the same methodology, the possible differences due to case ascertainment methods, data-coding practices and true differences in the risk of OAVS among different populations must be taken into consideration when combining epidemiological data from many different registries. For example, the average age at diagnosis varies according to the prenatal and early neonatal screening and follow-up practices in each region. The different prenatal ultrasound policies and possible differences in operators' skill and equipment can account for differences in prenatal detection rates among different registries. Few registries report only cases up to 1 week of life and could miss patients diagnosed later on with milder clinical presentation. Furthermore, there are differences in the completeness and accuracy of case description and in the level of genetic expertise. As registries are collecting limited set of routine data, we were not able to consider all possible aetiological factors.

Another limitation is that mild cases of isolated microtia and other minor ear anomalies are not included, which hampers comparison with some of the studies. However, caution should be exercised when comparing with other studies due to differences in methodology, sample size, biases in patient selection and level of investigations of internal organs/systems.

The high rate of associated anomalies points to the need to perform an early screening of the heart, kidneys and spine in all infants born with this disorder. Early diagnosis, long-term multi-disciplinary follow-up and genetic counselling of affected families are needed for optimal patient management.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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