Surveillance of multiple congenital anomalies

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Surveillance of multiple congenital anomalies in EUROCAT

Text from WP5 in Joint Action 2011-2013:

5.3 A computer algorithm has been developed to filter multiply malformed cases needing geneticist review. This algorithm and a website review tool will be implemented to enable separate surveillance of isolated and multiply malformed cases (for WP4, WP6, WP9).

Short background

The EUROCAT multiple congenital anomaly algorithm has been continuously developed and improved since 2004. A paper published in 2011 describes the methodology (Garne, Birth Defects Research). The aim of the algorithm is to classify congenital anomaly cases into isolated and multiple congenital anomalies. This classification has been used in many EUROCAT studies and publications on specific congenital anomalies. The long-term aim is to implement routine surveillance of isolated and multiple congenital anomalies separately.

The computer algorithm allocates 90% of all cases into a classification group. Approx. 10% of cases are potential multiple cases and these cases are manually reviewed by three EUROCAT geneticists to reach agreement for classification as true multiple congenital anomaly cases or allocation to another group. In the beginning, this review was done manually with the output being available for specific studies, but not transferred back to the EUROCAT central database.

Web based review

A web based system for review of cases has been developed by James Demsen, which allows easy and fast review of many cases and transfer of the final decision back to the central database. Cases for review are uploaded to website by Maria Loane. The three geneticists (Diana Wellesley, Ingeborg Barisic and Elisa Calzolari) review the cases on the website. If two geneticists agree on a case classification, this will be the final decision. If all three geneticists disagree or one of them classify the case for query, the moderator (Ester Garne) takes the final decision.

Three years of EUROCAT data (2009, 2010 and 2011) have now been reviewed and classified through the web based system with final decisions on individual cases taken at the coding meeting in Zagreb in June 2013. A total of 3946 cases are now available for analysis and surveillance.

How to do surveillance of multiples?

The main aim is to detect new associations/combinations of anomalies, detect increasing trends of overall or specific combinations of multiple anomalies and detect other changes in the overall multiple congenital anomaly population.

Surveillance of multiple congenital anomalies can be done in many ways: over time, by geographical differences, by subgroup combinations, by combination of ICD10 codes, search for new associations. As multiple congenital anomalies are rare and specific combinations of anomalies are very rare, the surveillance needs to be done using the pan-European data and not individual registry data.

The first preliminary data output for surveillance was presented by Joan Morris at the coding meeting in Berlin February 2013. This first output was a cluster analysis based on ICD10 codes in the Q-chapter. Looking at the data it became clear that using individual ICD10 codes raised issues related to use of unspecified codes, short codes and codes often used to describe minor anomalies.

From July 2013 Joan Morris and Ester Garne have worked together on the final dataset to find the best way of defining the output of data for the multiple congenital anomaly surveillance. The second data output included all EUROCAT subgroups, live and stillbirths only, males and females and combined and described combinations of 2 or 3 subgroups (email Joan Morris July 12.th). The main problem in this data output was the frequent occurrence of the sequence subgroups in combinations more frequent than expected, the respiratory subgroup occurring with congenital anomalies with secondary lung hypoplasia, and CHD combined with situs inversus. The number of less frequent associations was higher than the number of more frequent associations.

As all TOPFA in the multiple dataset are known to have at least two anomalies, as TOPFA for structural congenital anomalies takes places later than TOPFA for chromosomal defects and as some very severe anomalies would be kept outside the surveillance, we decided to include all birth types in the multiple surveillance. A table with mainly subgroups based on organ systems was prepared in August 2013 by Ester (21 subgroups) and used for the third data output (Table 1). This step reduced the number of combinations occurring together more frequently than expected very much for both 2 and 3 anomalies combined (Table 2). Most of these combinations are known associations. The number of subgroups included seems to be too small. A new extended list was prepared during a meeting in London (Joan and Ester) on October 1.st with 60 subgroups (Table 3). The output (excel document November 2013) is for discussion at the coding meeting in London November 20.th. Number of “less frequent” associations is still higher than the number of “more frequent” associations and most “more frequent” associations are well-known.

Text from Joan for the 4.th data output November 2013:

I have done the analyses in several ways …
I have redone the analysis on the data set Maria sent – so you have a spreadsheet with several pages.

1. *All males & females compared*
    a. *with all babies with at least two or more anomalies ie multiples data set*
    b. *With all babies with one anomaly ie EUROCAT data set*
2. *Males compared*
    a. *with all babies with at least two or more anomalies*
    b. *With all babies with one anomaly*
3. *Females compared*
    a. *with all babies with at least two or more anomalies*
    b. *With all babies with one anomaly*

4. *Occurrence of three anomalies compared with babies with at least two or more anomalies*
    a. *Females only*
    b. *Males only*
    c. *Males & Females combined*

I have been a bit more inclusive and have listed the anomalies with P < 0.01 as well as the FDR criteria – it perhaps gives us more to discuss.

I have also rerun the analysis excluding all the times situs inversus occurs with any cardiac anomaly – it does not make much difference to any of the analysis

Agenda and Minutes of the Multiple Surveillance Discussion in London November 20.th 2013:

Black: agenda questions

Red: minutes

We will ask Maria to upload 2008 potential multiple data for review together with the 2012 dataset in spring 2014

Agree on final list of subgroups to use

Respiratory subgroup, situs inversus and others

We will not include the respiratory subgroup (Joan will delete from the output tables)

We will keep the situs inversus in the subgroup list for multiple surveillance

Compare with prevalence in the multiple data set or use prevalence from all non-chromosomal anomalies?

We will do both and look manually at the output for associations we have not heard of previously. Until we have a larger dataset we will look at 2 anomalies occurring together and not 3.

Whenever we have reviewed another year we will look at the output tables together at a coding meeting.

We expect that the surveillance of multiples will continue to be manually reviewed and not an automated process

We will only look at more frequently observed observations, not less frequently observed

Male – female grouping – hypospadia in or out of male genital subgroup

We agree to analyse males and females separately and have hypospadia and male genitals as two separate subgroups

Conclusions from manual surveillance output for the dataset 2009-2011:

Duodenal atresia/common AV canal: (karyotype performed for the six cases? Ester check in Belfast) then check literature

Hydrocephalus and common arterial truncus –Ester check hydrocephalus info – then check literature

Male: Tetralogy of Fallot and anorectal atresia/stenosis: Ester check in Belfast for VATER - then check literature

How to do geographical surveillance and surveillance over time? Much more years of data is needed before we can do this

Use for pharmacovigilance? Results from the multiple surveillance may be used when we have the 5 year dataset.

Add more years backwards? 2008

January 2014: revision of methodology by Michiel and Joan after the London meeting:

Decision points

- Following discussion with Prof. Joan Morris late 2013, it was decided not to proceed with the 3-way comparison since the 3-way comparison essentially is three 2-way comparisons and adds to multiple testing. Any association detected by 3-way comparison will also be detected by the 2-way comparisons. Additionally, 3-way comparison leads to a large number of associations based on 1 or 2 cases.
- Following discussion with Joan Morris on January 8th 2014, it was decided to test the multiple CA control group versus the any CA (isolated and multiple) control group. It was also decided to remove all negative associations before utilizing the multiple testing procedure because 1) negative associations are generally artifacts (e.g. anencephaly and various CHD), 2) negative associations have no clinical relevance and 3) negative associations distort the multiple testing procedure by adding a large amount of very low p-values. As a result, Simes tests the p-values of positive correlations to much less stringent thresholds.

Table A: Dataset – Multiple CA controls only

N of H0 rejected for positive correlations

Male + Female		Male		Female	
FDR 10%	FDR 5%	FDR 10%	FDR 5%	FDR 10%	FDR 5%
20	18	3	1	11	2

Table B: Dataset – Any CA controls only

N of H0 rejected for positive correlations

Male + Female		Male		Female	
FDR 10%	FDR 5%	FDR 10%	FDR 5%	FDR 10%	FDR 5%
17	17	8	6	13	8

Table 4 and 5 present the results of the multiple surveillance after revision of the methodology in January 2014.

The three associations taken out for further individual review of cases are still significant (female duodenal atresia + AV canal, female hydrocephalus + truncus arteriosus and male Tetralogy of Fallot + anal atresia).

Many associations in the tables are already known and described in the literature, example NTD and omphalocele. Other examples are the anomalies in VATER/VACTERL, limb-body-wall complex, OEIS, amniotic band sequence and other sequences.

Table 1

EUROCAT Subgroups	exclude
Nervous system	Excluding NTD
Neural Tube Defects	
Eye	
Ear, face and neck	
Less severe CHD	CHD subgroup excluding severe CHD
Severe CHD	
Respiratory	
Cleft lip with or without cleft palate	
Cleft palate	
Digestive system	Excluding diaphragmatic hernia
Diaphragmatic hernia	
Gastroschisis	
Omphalocele	
Urinary	
Genital	Excluding hypospadia
Hypospadia	
Limb	Excluding limb reduction
Limb reduction	
Craniosynostosis	
Situs inversus	
Congenital skin disorders	

Table 2

Results from subgroups in table 1

Anomaly 1	Anomaly 2	Anomaly 3	Observed/expected	P value
nervousexclntd	earfaceneck	resp	5.2	0.0002
severeschd	resp	dhernia	4.1	0.0010
nervousexclntd	eye	resp	3.7	0.0001
severeschd	digestexclhern	sinvers	3.4	0.0030
ntd	omphalo	urinary	3.1	0.0013
nervousexclntd	eye	cleftlip	3.0	0.0093
ntd	urinary	genitalexclhypospad	2.7	0.0030
digestexclhern	genitalexclhypospad	limbred	2.6	0.0101
digestexclhern	urinary	genitalexclhypospad	2.5	0.0000

Anomaly 1	Anomaly 2	Observed/expected	Pvalue	Male – female significance
severeschd	sinvers	4.14	0.0000	M and F
ntd	omphalo	3.69	0.0000	
ntd	gstro	2.99	0.0011	
nervousexclntd	eye	2.07	0.0000	M and F
resp	dhernia	1.94	0.0010	
urinary	genitalexclhypospad	1.58	0.0000	F
digestexclhern	genitalexclhypospad	1.46	0.0006	F

Table 3

List of subgroups used for the 4.th data output – numbering according to Joan's programming

Z1 Nervous system (excl z2-z7)
Z2 Anencephalus and similar
Z3 Encephalocele
Z4 Spina Bifida
Z5 Hydrocephalus
Z6 Microcephaly
Z7 Arhinencephaly / holoprosencephaly
Z8 Anophthalmos / microphthalmos
Z9 Congenital cataract
Z10 Congenital glaucoma
Z11 Anotia
Z12 Common arterial truncus
Z13 Transposition of great vessels
Z14 Single ventricle
Z15 VSD
Z16 ASD
Z17 AVSD
Z18 Tetralogy of Fallot
Z19 Tricuspid atresia and stenosis
Z20 Ebstein's anomaly
Z21 Pulmonary valve stenosis
Z22 Pulmonary valve atresia
Z23 Aortic valve atresia/stenosis
Z24 Hypoplastic left heart
Z25 Hypoplastic right heart
Z26 Coarctation of aorta

Z27	Total anomalous pulm venous return
Z28	PDA as **only** CHD in term infants (GA +37 weeks)
Z30	Choanal atresia
Z31	Cystic adenomatous malf of lung
Z32	Cleft lip with or without cleft palate
Z33	Cleft palate
Z34	Oesophageal atresia with or without tracheo-oesophageal fistula
Z35	Duodenal atresia or stenosis
Z36	Atresia or stenosis of other parts of small intestine
Z37	Ano-rectal atresia and stenosis
Z38	Hirschsprung's disease
Z39	Atresia of bile ducts
Z40	Annular pancreas
Z41	Diaphragmatic hernia
Z42	Gastroschisis
Z43	Omphalocele
Z44	Bilateral renal agenesis including Potter syndrome
Z45	Renal Dysplasia
Z46	Congenital hydronephrosis
Z47	Bladder exstrophy and/or epispadia
Z48	Posterior urethral valve and/or prune belly
Genital	Z59 female Z60 Male
Z61	Hypospadia
Z62	Indeterminate sex
Z49	Limb reduction
Z50	Club foot - talipes equinovarus
Z51	Hip dislocation and/or dysplasia
Z52	Polydactyly

Z53	Syndactyly
Z54	Skeletal dysplasias
Z55	Craniosynostosis
Z56	Congenital constriction bands/amniotic band
Z57	Situs inversus
Z58	Congenital skin disorders

For the first analysis using subgroups from Table 3 – see excel document from London meeting

Table 4 and 5 includes the results after the methodology revision in January 2014

Table 4: Associations considered statistically significant using "any" control (both isolated and multiple CA)

Sex	Anomaly 1	Anomaly2	p-value	Risk Ratio	Controls	CA1 no CA2	CA2 no CA1	CA1 + CA2	FDR 10	FDR 5
Combined	AnorectalAtr	RenalDysplasia	6.19E-13	3.44	44672	620	882	46	1	1
Combined	Omphalocele	BladderExtrophy	1.17E-10	9.24	45608	451	146	15	1	1
Male	AnorectalAtr	RenalDysplasia	8.32E-10	3.72	24904	346	523	30	1	1
Female	AnorectalAtr	BladderExtrophy	6.68E-09	14.92	18086	255	33	9	1	1
Combined	AnorectalAtr	BladderExtrophy	1.46E-08	6.47	45408	651	146	15	1	1
Female	Omphalocele	BladderExtrophy	1.28E-06	17.05	18193	148	36	6	1	1
Male	AnorectalAtr	BilateralRenalAgenesis	2.67E-06	5.94	25311	365	116	11	1	1
Combined	AnorectalAtr	BilateralRenalAgenesis	0.000011	4.08	45330	652	224	14	1	1
Combined	AnorectalAtr	LimbReduction	1.16E-05	2.33	44633	634	921	32	1	1
Combined	AnorectalAtr	Omphalocele	1.84E-05	2.98	45108	646	446	20	1	1
Combined	ArinencephalyHolo	AnophMicroph	6.24E-05	8.94	45872	189	153	6	1	1
Combined	Omphalocele	CompleteAbsLimb	6.38E-05	11.81	45717	461	37	5	1	1
Combined	Hydrocephalus	AnophMicroph	0.000177	3.30	44930	1131	146	13	1	1
Female	Omphalocele	CompleteAbsLimb	0.000196	25.58	18218	151	11	3	1	1
Combined	Anencephaly	Omphalocele	0.000272	2.44	44961	793	446	20	1	1
Combined	AnorectalAtr	CompleteAbsLimb	0.000335	8.26	45517	661	37	5	1	1
Female	AnorectalAtr	Omphalocele	0.000393	4.07	17974	255	145	9	1	1
Combined	NTD	Omphalocele	0.000488	1.78	43675	2079	428	38	1	1
Male	TetralogyFallot	AnorectalAtr	0.000776	2.60	25046	381	361	15	1	1
Combined	Microcephaly	AnophMicroph	0.000827	4.67	45632	429	152	7	1	1
Female	AnorectalAtr	CompleteAbsLimb	0.000948	14.92	18108	261	11	3	1	1
Male	AnorectalAtr	LimbReduction	0.001148	2.34	24945	359	482	17	1	1
Combined	Encephalocele	AnophMicroph	0.0012	6.37	45838	223	154	5	1	1
Male	Omphalocele	BladderExtrophy	0.001579	5.95	25501	192	105	5	1	1
Female	Hydrocephalus	AnophMicroph	0.001663	4.05	17861	453	62	7	1	1

Male	ArinencephalyHolo	AnophMicroph	0.001806	12.50	25648	69	83	3	1	1
Female	AVSD	DuodenalAtr	0.002582	4.37	18058	206	113	6	1	1
Combined	TetralogyFallot	OesophagealAtresia	0.002708	2.16	45025	654	524	17	1	1
Male	BilateralRenalAgenesis	CompleteAbsLimb	0.002757	25.40	25662	125	14	2	1	0
Female	AnorectalAtr	RenalDysplasia	0.00283	2.56	17804	252	315	12	1	1
Male	Microcephaly	AnophMicroph	0.003438	6.49	25536	181	82	4	1	0
Female	SevereCHD	CompleteAbsLimb	0.003938	4.35	16866	1503	9	5	1	0
Combined	AVSD	DuodenalAtr	0.004421	3.47	45582	419	212	7	1	1
Combined	TetralogyFallot	AnorectalAtr	0.004505	1.97	44902	652	647	19	1	1
Female	SitusInversus	AtresiaBileDucts	0.005366	18.24	18290	61	30	2	1	0
Female	Hydrocephalus	CommonArtTrunc	0.008644	3.38	17858	454	65	6	1	0
Female	AnorectalAtr	LimbReduction	0.010033	2.17	17746	252	373	12	1	0
Female	AnophMicroph	CleftLip	0.010668	2.88	17673	62	641	7	1	0

Table 5: Associations considered statistically significant using "multi" controls

Sex	Anomaly 1	Anomaly2	p-value	Risk Ratio	Controls	CA1 no CA2	CA2 no CA1	CA1 + CA2	FDR 10	FDR 5
Combined	NTD	Omphalocele	1.43E-11	3.70	3557	215	142	38	1	1
Combined	Anencephaly	Omphalocele	6.11E-11	7.48	3716	56	160	20	1	1
Combined	Omphalocele	BladderExtrophy	4.39E-10	7.89	3742	165	30	15	1	1
Combined	AnorectalAtr	RenalDysplasia	1.22E-09	2.74	3436	317	153	46	1	1
Male	AnorectalAtr	RenalDysplasia	1.71E-07	2.93	1887	190	82	30	1	1
Female	AnorectalAtr	BladderExtrophy	3.03E-06	6.56	1393	115	9	9	1	1
Combined	AnorectalAtr	BladderExtrophy	5.54E-06	3.74	3559	348	30	15	1	1
Female	Omphalocele	BladderExtrophy	3.35E-05	9.48	1455	53	12	6	1	1
Combined	PDAonlyCHDatTERM	DiaphragmaticHernia	8.23E-05	3.55	3702	100	136	14	1	1
Combined	SpinaBifida	Omphalocele	0.000115	3.13	3665	107	164	16	1	1
Combined	SevereCHD	DuodenalAtr	0.000287	2.23	3345	539	47	21	1	1
Combined	Hydrocephalus	AnophMicroph	0.000322	3.05	3632	255	52	13	1	1
Combined	ArinencephalyHolo	AnophMicroph	0.000391	6.64	3833	54	59	6	1	1
Male	Omphalocele	BladderExtrophy	0.000456	7.64	2098	71	15	5	1	0
Combined	AnorectalAtr	BilateralRenalAgenesis	0.000808	2.60	3543	349	46	14	1	1
Combined	AnophMicroph	CleftLip	0.000857	3.23	3640	53	247	12	1	1
Female	PDAonlyCHDatTERM	DiaphragmaticHernia	0.000908	4.22	1420	48	50	8	1	0
Combined	NTD	Gastroschisis	0.001062	3.00	3651	242	48	11	1	1
Male	AnorectalAtr	BilateralRenalAgenesis	0.001083	2.90	1941	209	28	11	1	0
Female	SevereCHD	DuodenalAtr	0.001377	2.50	1289	198	26	13	1	0
Combined	Encephalocele	AnophMicroph	0.00175	6.10	3838	49	60	5	1	1
Combined	Hydrocephalus	ConGlaucoma	0.001985	6.64	3679	264	5	4	1	1
Combined	Omphalocele	CompleteAbsLimb	0.002593	5.10	3755	175	17	5	1	1
Female	Hydrocephalus	CommonArtTrunc	0.00284	4.07	1395	111	14	6	1	0
Female	AVSD	DuodenalAtr	0.002853	4.40	1435	52	33	6	1	0

Combined	TetralogyFallot	OesophagealAtresia	0.002893	2.24	3587	110	238	17	1	1
Female	Encephalocele	CleftPalate	0.003053	4.28	1386	19	114	7	1	0
Combined	AVSD	DuodenalAtr	0.00313	3.74	3777	107	61	7	1	1
Female	Microcephaly	CleftPalate	0.003212	2.56	1346	59	108	13	1	0
Female	AnophMicroph	CleftLip	0.003459	4.01	1404	26	89	7	1	0
Female	NTD	Gastroschisis	0.00373	3.87	1394	111	15	6	1	0
Female	NTD	Omphalocele	0.003983	2.58	1361	106	48	11	1	0
Combined	Microcephaly	AtresiaStenOtherIntestine	0.005243	4.47	3789	129	29	5	1	0
Combined	Microcephaly	AnophMicroph	0.005946	3.30	3760	127	58	7	1	0