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Prevalence at birth of congenital abnormalities of external ears in Hungary

Research Article

László Paput[1*], Ferenc Bánhidy[2], Andrew E. Czeizel[3]

[1] *Department of Oto-Rhino-Laryngologic and Head/Neck Surgical Department, National Center for Healthcare Audit and Improvement, H-1062 Budapest, Hungary*

[2] *Second Department of Obstetrics and Gynecology, Semmelweis University, School of Medicine, H-1082 Budapest, Hungary*

[3] *Foundation for the Community Control of Hereditary Diseases, H-1148 Budapest, Hungary*

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Abstract: The objective of the study was to estimate the prevalence at birth and epidemiologic characteristics of patients/cases with both isolated and multiple "syndromic" external ear congenital abnormalities (CAs) in Hungary. The Hungarian Congenital Abnormality Registry, 1980-1996, included 649 cases with isolated external ear CAs, while the number of cases with unclassified multiple CA, including ear CAs, was 331. Thus the prevalence at birth of cases with isolated external ear CAs and unclassified multiple CAs was 0.30 and 0.15, respectively, for a total 0.46 per 1000 births. After reevaluation of reported 354 cases with isolated external ears CAs in the Hungarian Case-Control Surveillance of Congenital Abnormalities, 74 (20.9%) and 236 (66.7%) were affected with mild and severe microtia, while 24 (6.8%) had anotia. The fourth group included 20 cases with the combination of anotia/microtia and external/middle ear CAs. Isolated ear CAs showed a slight male excess (54.0%) and strong predominance of unilateral manifestation (93.4%). Multiple ear CAs showed a stronger male excess (65.4%) and less frequent unilateral affection (62.2%). In conclusion, ear CAs had a low diagnostic validity; thus it was necessary to reassess the data and to reclassify several cases.

Keywords: *Ear congenital abnormalities • microtia/anotia • isolated and multiple/syndromic manifestation • prevalence at birth • sex ratio • laterality*

1. Introduction

The ear is composed of three parts: the internal, middle, and external portions. The external portion of the ear comprises the auricle, the external auditory meatus/canal, and the external layer of the eardrum. Structural birth defects, i.e., congenital abnormalities (CAs) of external ears are visible, therefore easily diagnosed in newborn infants by routine inspection. Among CAs of external ears, microtia (the external portion of the auricle is malformed with or without narrowing of absence of the external auditory canal/meatus) is more frequent, while anotia (the total absence of auricle most often with narrowing of absence of the external auditory meatus) is less frequent [1].

The aim of this population-based study was to describe the ascertainment procedure, diagnostic criteria, and classification of external ear CAs to determine their prevalence at birth in the Hungarian Congenital Abnormality Registry (HCAR) [2], and their main characteristics in the Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA) [3].

* *E-mail: barabas.ev@gmail.com*

2. Material and Methods

2.1. The Hungarian Congenital Abnormality Registry

Patients, i.e. *cases* with different CAs, are recorded in the data set of the HCAR. In Hungary, reporting cases with CA to the HCAR is mandatory, from birth until the end of the first postnatal year. Most cases are reported by obstetricians and pediatricians. In Hungary, practically all deliveries take place in inpatient obstetric clinics, and the birth attendants are obstetricians. Pediatricians work in the neonatal units of inpatient obstetric clinics, or in various general and specialized (cardiologic, orthopaedic, surgical, oto-rhino-laringologic, etc) inpatient and outpatient pediatric clinics. Autopsy was mandatory for all infant deaths, and commonly done (about 80%) for stillborn fetuses during the study period. Pathologists send a copy of the autopsy report to the HCAR if defects are identified in stillbirths and infant deaths. Since 1984, fetal defects diagnosed in prenatal diagnostic centers, with or without termination of pregnancy, have also been included into the HCAR.

CAs were differentiated into three groups: lethal (if defects caused stillbirth or infant death or pregnancies were terminated due to fetal defect in more than 50% of cases), severe (without medical intervention CAs caused handicap or death), and mild (CAs required medical intervention but life expectancy was good) [4]. Lethal and severe CAs together constitutes major CAs. Minor anomalies or morphological variants without serious medical or cosmetic consequences are recorded in the HCAR; these cases are excluded from the estimate of different CA rates, but were considered for the evaluation of multiple CAs.

In addition, two main categories of cases with CAs were differentiated: isolated CAs (only one organ is affected) and multiple CAs (concurrence of two or more CAs in the same person affecting at least two different organ systems). Thus the diagnosis of multiple CAs was accepted if patients/cases had 2 or more component CAs with or without minor anomalies [5].

The total (birth + fetal) prevalence of cases with CA diagnosed from the second trimester of pregnancy through the age of one year was 35 per 1000 offspring (live-born infants, stillborn fetuses and electively terminated malformed fetuses) recorded in the HCAR, 1980-1996, and about 90% of major CAs were recorded in the HCAR during the 17-year study period.

At the establishment of the HCAR in 1970, the classification of ear CAs was based on the International Classification of Diseases (ICD), World Health Organization (WHO) 1975 revision [6]. According to the ICD, "Congenital anomalies of ears" were coded by 4 sub-codes within the major code 744 in the XIVth Chapter of ICD: 744.0, Anomalies of ear causing impairment of hearing; 744.1, Accessory auricle; 744.2, Other specified anomalies of ear; and 744.3, Unspecified anomalies of ear (Table 1). However, the sub-code 744.0 was completed "with anotia/microtia", and only anotia/microtia without aural atresia/stenosis was coded in the sub-code 744.2. As mentioned previously, we use the term CA for structural/morphologic/anatomic birth defects/congenital anomalies; thus, functional anomalies such as deafness were excluded. There was a strict differentiation of isolated and multiple (the so-called syndromic) ear CAs in the HCAR, and only isolated ear CAs were coded in the sub-codes of 744, whereas ear CAs as component CAs of multiple CAs were coded in 759.7 using a special own classification system [5].

However, the category of *isolated CAs* includes 3 groups: (i) single (e.g., microtia without narrowing stenosis, or absence, atresia/agenesis of external auditory canal/meatus); (ii) complex (e.g., anotia with the absence of external auditory canal); and (iii) sequence (e.g. ear deformity as the secondary consequence of renal agenesis in the Potter oligohydramnios sequence). The category of *multiple CAs* is also differentiated theoretically into three groups: (i) CA-syndromes, i.e., recognizable patterns of component CAs (e.g., Franceschetti-Treacher Collins syndrome); (ii) CA-associations, i.e., recognizable pattern of component CAs currently without the knowledge of causes (e.g. CHARGE association); and (iii) random combination of component CAs, e.g. microtia with postaxial polydactyly in hands. However, the majority of multiple CAs have not been delineated and/or identified in the clinical workup, thus it is not possible to differentiate them from random combinations. The term unclassified multiple CA is used for this group of cases with multiple CA [7].

The diagnosis of ear CAs was checked in the HCAR and modified if necessary by two steps:

(1) If cases with unspecified ear CAs were reported to the HCAR since 1988, an extra effort was made by the assistant of the HCAR to contact the medical doctors who reported these cases to specify the diagnosis.

(2) For the request of parents the co-workers of the HCAR organized the so-called parental meetings for the families of cases with the different main groups of CAs. The parents of children with isolated ear CAs were invited for a parental meeting twice, in 1988 and 1996. These meetings had three aims: (i) information for parents regarding the ear CAs and replies to their questions; (ii) an exchange of experiences among parents; and (iii) the

examination of these cases by experts. Thus we were able to examine personally about one-third of cases with isolated ear CAs.

2.2. The Hungarian Case-Control Surveillance of Congenital Abnormalities

However, the detailed analysis of cases with isolated and multiple ear CAs was based on the data set of the HCCSCA in this study. There were three exclusion criteria of cases with CAs at their selection from the HCAR for the data set of the HCCSCA: (i) Cases reported after three months of birth or pregnancy termination (77% of cases were reported during the first three-month time window, the rest included mainly mild CAs); (ii) Cases with three mild CAs (congenital dysplasia of hip and inguinal hernia, large haemangioma); and (iii) CA syndromes caused by major mutant genes or chromosomal aberrations with preconception origin were also excluded.

The diagnosis of ear CAs was further checked and/or modified if necessary by three approaches in the HCCSCA:

(1) Mothers of cases were asked in an explanatory letter to send us all medical records of the CA in their child particularly the discharge summaries of their hospitalization. The mean $\pm$ S.D. time elapsed between the birth and the return of these documents in our prepaid envelope was 3.5 $\pm$ 2.1 months. An informed consent form was signed by 98% of mothers; names and addresses were deleted in the remaining 2%.

(2) There was a supplementary data collection in the HCCSCA as well, because regional nurses were asked to visit all non-respondent mothers at home to obtain the necessary data of their children affected with CAs, and to observe and describe their CAs.

(3) There was a special approach for the evaluation of children with ear CAs due to the scientific interest of a specialist (L.P) for his PhD thesis research. The parents of all children with severe ear CAs were invited for a special otological examination. In addition, familial cases with ear CAs were invited to our genetic counselling clinic (A. E. C). Finally, upon evaluation of total dataset of ear CAs, some special cases were also invited or visited at home by the specialist (L.P).

2.3. Classification of congenital abnormalities of external ears

For classification of isolated ear CAs in the HCCSCA, we used the previously suggested different classifications [8–10] with some modifications, because the ICD classification was not appropriate for research purpose. Thus the classification of cases with external ear CAs was as follows in the study:

Type I or minor microtia: The external ear is small and the auricle retains most of its normal structure. The external auditory meatus is present. However, type I microtia is considered a minor anomaly, and minor anomalies were excluded from the category of CAs including ear CAs. A similar approach has been used in some other studies [11]. However, type I microtia was evaluated in the analysis of unclassified multiple ear CAs.

Type II or mild microtia: The external ear is moderately anomalous. The auricle can be hook-, S- or question-mark–shaped in appearance; the external auditory meatus is usually present.

Type III or severe microtia. The external ear is rudimentary, does not have a normal appearance. The structure of auricle does not include cartilage, only soft tissue, and there is no external auditory meatus.

Anotia, i.e., all external ear structures are absent, thus there is no external auditory meatus/canal.

Other ear CAs included bilateral cases with anotia and microtia, and the combination of middle ear CAs with anotia/microtia.

Low-set ears, preauricular tag/pit/sinus and lobule anomalies without other ear CAs were also classified as minor anomalies. However, preauricular anomalies frequently associated with microtia/anotia; these cases were evaluated.

In the present study, 17 years' data from the HCCSCA between 1980 and 1996 are evaluated because the data collection has been changed since 1997 after the retirement of the founder of the HCCSCA (A. E. C) and all mothers are visited by regional nurses, but the recent data had not been validated at the time of the present analysis.

2.4. Statistical analysis

We used SAS version 8.02 (SAS Institute Inc., Cary, North Carolina, USA) for statistical analysis.

3. Results

There were 649 cases with isolated ear CAs and 331 cases with unclassified multiple ear CAs in the HCAR, 1980-1996 (Table 1). There was no time cluster of these cases according to the yearly number of cases. Thus the prevalence at birth of cases with isolated ear CAs was 0.30 per 1000 births during the study period.

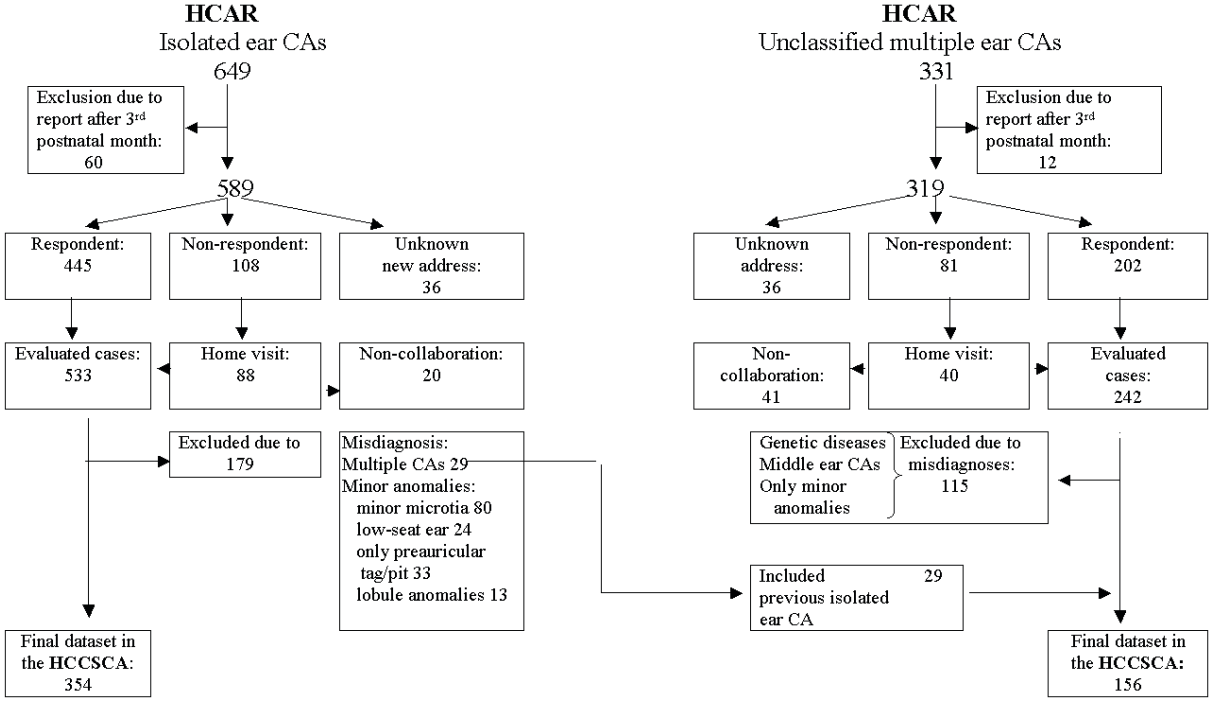
The prevalence at birth of cases with unclassified multiple ear CAs was 0.15 per 1000 births; however, there is an obvious underascertainment of these cases. Cases affected with chromosomal aberrations were reported in general only by names (e.g. trisomy 21 or

Table 1. Number of cases with different isolated external ear CAs according to the codes of ICD, WHO, and unclassified multiple CAs, including ear CAs and their prevalence at birth per 1000 in the HCAR 1980-1996, when the total number of births was 2,147,109 in Hungary.

Isolated external CAs	No.	%	Prevalence at birthper 1000 births
744.0	257	39.6	0.11
744.1	171	26.3	0.08
744.2	108	16.6	0.05
744.3	113*	17.4	0.05
Total	649	99.9	0.30
Multiple CA including ear CAs			
Unclassified multiple CAs	331	100.0	0.15

**before 1988*

Figure 1. Flowchart of cases with isolated and unclassified multiple ear CAs from the HCAR to the HCCSCA.



Down syndrome and trisomy 13 or Patau syndrome) without mentioning the component CAs and minor anomalies. The number of recorded cases with trisomy 21, 13, 18 and other chromosomal aberrations was 2,840, 68, 77, 131, respectively, in the HCAR during the study period. Ear CAs and anomalies were mentioned very rarely, even though small ears in cases with trisomy 21, abnormal helices with or without low-set ear in cases with trisomy 13, or low-set malformed auricle in cases with trisomy 18 are characteristics. There was a similar problem in the report of CA syndromes caused by mutant major genes. Of 344 cases with CA syndromes in the HCAR, 1980-1996, 11 and 4 were affected with Franceschetti-Treacher Collins and Goldenhar syndrome, respectively, but ear CAs were mentioned only in 3 and 2 cases. Of 136 CA syndromes due to teratogens, 24 cases had diabetic embryopathy and 2 were affected with fetal varicella disease, without mentioning ear CAs. Thus we excluded specified CA syndromes, including ear CAs, from this analysis because of their drastic underascertainment; therefore, these cases are not included in Table 1.

The total number of cases with isolated and unclassified multiple ear CAs was 980, thus their prevalence at birth was 0.46 per 1000 in Hungary between 1980 and 1996.

The detailed analysis of cases with isolated and unclassified multiple ear CAs was based on the data set of the HCCSCA. The flowchart of cases with inclusion and exclusion criteria, as well as the causes of dropouts, is shown in Figure 1. Thus of 649 cases with isolated ear CAs, 354 cases were evaluated; all were diagnosed

Table 2. Number of cases with different isolated external ear CAs: microtia/anotia and their association with other ear CAs.

Isolated ear CA groups	Total		Aural atresia/stenosis		Preauricular tag/pit/sinus	
	No.	%	No.	%	No.	%
Mild microtia	74	20.9	0	0.0	9	12.2
Severe microtia	236	66.7	212	89.8	69	29.2
Anotia	24	6.8	24	100.0	8	33.3
Others	20	5.6	15	75.0	2	10.0
Total	354	100.0	251	70.9	88	24.0

Table 3. Sex ratio and side distribution of isolated external ear CAs and unclassified multiple CAs.

Ear CA groups	Total	Sex ratio(male)		Side								
				Right		Left		Together		Bilateral		Unknown
	No.	No.	%	No.	%	No.	%	No.	%	No.	%	No.
Mild microtia	74	40	54.1	39	60.9	23	35.9	62	96.9	2	3.1	10
Severe microtia	236	125	53.0	138	61.1	82	36.3	220	97.3	6	2.7	10
Anotia	24	12	50.0	12	50.0	10	41.7	22	91.7	2	8.3	0
Others	20	14	70.0	4	21.1	3	15.8	7	36.8	12	63.2	1
Total	354	191	54.0	193	57.9	118	35.4	311	93.4	22	6.6	21
Multiple	156	102	65.4	47	56.0	37	44.0	84	62.2	52	38.2	20

in live-born infants. The two groups of misdiagnoses included unclassified multiple CAs and minor anomalies. Of 331 cases with unclassified multiple ear CAs, 156 cases were analyzed in detail.

The major findings of cases with isolated ear CAs in the dataset of the HCCSCA are shown in Table 2. Of 354 cases, 74 and 236 had mild and severe microtia, respectively. Cases of mild microtia were not associated with the stenosis or atresia of external auditory canal; however, association with preauricular tag/pit/sinus sometimes occurred. Nearly 30% of cases with severe microtia were associated with preauricular tag/pit/sinus, and 90% with aural stenosis or atresia. Anotia occurred rarely: it was diagnosed only on 24 cases. There is an obvious correlation between the severity of microtia/anotia and the above-associated CAs. The fourth group of “Others” included 20 cases with isolated ear CAs, and of these 20 cases, 18 were personally examined by the principal investigation of the study. Five cases had middle ear CAs (atresia of auditory canal with fusion of ear ossicles in 4 cases, atresia of auditory canal with absent of membranous labyrinth in the middle ear and organ Corti in one case) and anotia/microtia; 12 cases were affected with anotia in one side and microtia on the other side, and one case was affected with polyotia. Two cases had only medically recorded diagnosis of ear CAs without personal examination (inner ear CA with anotia in one case, and absence of Eustachian tube with microtia in another case). Thus, of 354 cases with external ear CA, 353 had microtia or anotia with or without other ear CAs.

The sex ratio (i.e. the proportion of males) shows a slight male preponderance (Table 3), but the male excess was strong in the group of “Other ear CAs”. Laterality of ear CAs was also planned to evaluate, but we were not able to clarify the side manifestation on the basis of medical records in some cases. Microtia/anotia had an obvious predominance of unilateral manifestation, with some excess of ride side in cases with microtia. However, this trend does not exist in the fourth group of “Other ear CAs”, because nearly two-thirds of these cases had bilateral manifestation of ear CAs.

Of 156 cases with unclassified multiple CA, including ear CAs as component CAs, 4 occurred in stillborn fetuses. These cases showed a more drastic male predominance with a less frequent occurrence of unilateral ear CA. Unclassified multiple ear CAs will be evaluated in detail in another study.

4. Discussion

The major—and disappointing—finding of the study is that the ear CAs in the HCAR had a low diagnostic validity even though these diagnoses were based on the reports of medical doctors. These misdiagnoses can be explained by three main problems.

First, a major part of reported diagnoses of ear CAs did not correspond to the true clinical manifestation of CAs. The explanation is that most ear CAs were reported by obstetricians and pediatricians after the birth of cases and they were not able to differentiate among ear CA entities. Of 536 reported cases with isolated external ear CAs and without unspecified ear CAs, 257 (47.9%) had a diagnosis of absence or atresia/stricture/stenosis of external auditory canal with anotia/microtia. However, of 354 cases with a detailed analysis, 251 (70.9%) were affected with aural atresia/stenosis. A similar problem has been recognized in the diagnosis of different types of limb deficiencies in the HCAR [12]. Of 555 cases with isolated congenital limb deficiency, 210 (37.8%) were reported as phocomelia; however, the personal examination of these children confirmed phocomelia in only 2 cases.

Second, some clinicians cannot differentiate between the minor anomalies and CAs of external ears, in addition to isolated and multiple CAs. In the HCAR, 168 cases had the diagnosis of microtia, but 80 were classified as a minor anomaly (type I), therefore were excluded from the study. Other 29 cases had ear CA but it associated with other CAs, thus, they were in fact multiple CAs.

Third, some cases of ear CAs was reported as unspecified. The coworkers of the HCAR did their best to minimize the proportion of unspecified ear CAs; therefore, cases with unspecified ear CA did not occur after 1988. This is an important benefit, because unspecified ear CAs cannot be evaluated.

In conclusion, reporting of external ear CAs by obstetricians and neonatologist/pediatricians after birth without appropriate expertise to examine ear and to diagnose ear CA was biased with serious diagnostic problems. Therefore, it was a difficult, sometimes impossible, task to correctly evaluate ear CAs in the HCAR. We suppose it is true for Hungary, but is a general problem in other countries as well. This unfortunate situation needs modification. On the one hand, some specialized education regarding the diagnostic criteria for external ear CAs among obstetricians and pediatricians may be useful. On the other hand, it would be necessary to organize the consultation of otologists after the diagnosis of ear CA by obstetricians or neonatologist in these children, at least in the leading medical institutions.

Thus the reliability of the Hungarian prevalence at births of external ear CAs is questionable based on the HCAR dataset. The prevalence of isolated ear CAs, mainly microtia, was 0.30 per 1000 Hungarian newborn infants; this figure is within the spectrum of rates from different countries [13]. However, the marked variation in the prevalence of cases with microtia/anotia, ranging from 0.083 in Central-East France [11] to 1.74 in Quito, Ecuador [14] per 1000 births, can be explained partly by methodological differences, partly by population characteristics. Among methodological differences, the classification—whether only isolated or isolated and unclassified multiple or isolated, unclassified multiple and specified CA syndromes of microtia/anotia are evaluated—and ascertainment—whether type I/minor microtia or Facio-Auriculo-Vertebral Spectrum: FAVS is included to the group of isolated microtia/anotia—problems need to be mentioned, beyond the differences in the completeness of ascertainment and the quality of diagnoses. However, population characteristics are also important: microtia/anotia is relatively rare in white and black people, more frequent in Hispanics, mainly in children born in Mexico [15] and particularly in regions within special geographical clusters of microtia/anitia as in Quito, Ecuador [14] and the Navajo Indians in the USA state of New Mexico [16], in addition to populations living in high altitudes [17]. Nevertheless, differences in ascertainment and diagnostic criteria are probably the major source of great variations in the rate of external ear CAs, mainly microtia/anotia; therefore, their comparison demands caution among interpreting data for different populations/registries/studies.

The mild male excess of cases with isolated ear CAs in the study was in agreement with the results of some previous studies [11,13,15,18-23], though the cases with isolated microtia/anotia in the Italian registry did not show a male predominance [24]. The strong male excess in cases with unclassified multiple ear CA is worth mentioning, because in general previous studies did not have strict differentiation between cases with isolated and multiple ear CAs.

The obvious predominance of unilateral cases and among them a slight right side excess in cases with isolated microtia/anotia in our study corresponded to the previous observations in other studies/countries [11,13,15,18-25].

In general microtia/anotia is unilateral, however, microtia and anotia were combined in 12 cases in the fourth group of “Other ear CAs” in our dataset. Similar findings were found in other studies, e.g. 13%–22% of bilateral cases had the combination of microtia and anotia in the Italian registry [24] and in the international collaborative study based on CA registries [11] indicating their common origin. On the other hand it is worth mentioning the significant difference between the predominance of unilateral cases with isolated and multiple ear CAs (93.4% vs. 62.2%) in our study.

Previously a high correlation was found between the degree/type of microtia/anotia and the frequency

of middle ear anomalies [26], and this association was confirmed in our study because the degree/type of microtia/anotia and frequency of atresia/stenosis of the auditory canal showed correlation. Most forms of these complex ear CAs are associated with conductive hearing loss: the middle ear may be functional, but will only pick up low tones and vibrations. In addition, the association of mild/severe microtia and anotia with preauricular tag/pit/sinus showed also a "dose": severity – "effect": frequency relation.

However, our study stressed the importance of the checking of reported and registered diagnoses of ear CAs in the CA-registries; in addition, it would be necessary to introduce a scientific classification of ear CAs on the basis of international consensus. The external ear is developed from the first and second branchial arches [27], while the auricle is formed by a series of auricular hillocks that surround the first pharyngeal groove during the sixth postconceptional week [28]. Thus this CA is a typical developmental field defect [29] or complex CA [5] including – beyond microtia/anotia – sometimes atresia/stenosis of external auditory meatus/canal and/or preauricular tag/pit/sinus. On the other hand, this complex CA may include the so-called facia-auriculo-vertebral spectrum (FAVS) [30] or oculo-auriculo-vertebral spectrum (OAVS) [31,10] because this developmental field is the derivative of the first and second branchial arches. Thus external ear CAs cover a wide spectrum from the minor manifestation of this developmental field defect to the most severe manifestations involving unilateral (i) type I microtia as minor anomaly, (ii) type II microtia as mild CA, (iii) type III microtia as severe CAs, (iv) anotia as more severe CA, (v) microtia/anotia with hemifacial (malar) microsomia, (vi) Goldenhar syndrome, i.e. unilateral microtia, small malformed mandible and CA of the cervical spine and (vii) OAVS or dysplasia, i.e. unilateral microtia, small malformed mandible, CA of cervical vertebras and CA of eye, mainly epibulbar dermoid, but notch in upper lid and microphthalmia as complex CAs [1,10,32].

The strength of our material is the population-based data set of the HCAR and HCCSCA in an ethnically homogeneous Hungarian (Caucasian) population. Additional strength is the good validity of final ear CA diagnoses because these diagnoses were based on medically report but checked in the HCAR and later modified, if necessary, on the basis of the results of recent medical examinations in the HCCSCA and frequently completed by the personal examination of cases by a specialist.

However, this data set also has limitations. (i) The reported/registered diagnoses of ear CAs is unreliable in the HCAR. (ii) There was a considerable loss of cases from the data set of the HCAR to the data set of the HCCSCA but partly it was connected with the data cleaning partly there was no significant selection bias according to the validation study [33]. (iii) In addition ear CAs could not be evaluated in specified CA syndromes because in general only their names were reported or recorded without the complete list of component CAs.

In conclusion unfortunately the reported/recorded cases with external ear CAs in the HCAR could be evaluated only after an intensive data cleaning and using a new classification system. Of 354 cases with isolated ear CAs, 74 (20.9%) and 236 (66.7%) were affected with mild and severe microtia, respectively, while 24 (6.8%) had anotia. The evaluation of these cases showed a slight male excess and strong predominance of unilateral manifestation in isolated ear CAs; however, there was a strong male excess and more frequent bilateral manifestation in cases with multiple ear CAs.

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